BENIGN PAROXYSMAL POSITIONAL VERTIGO

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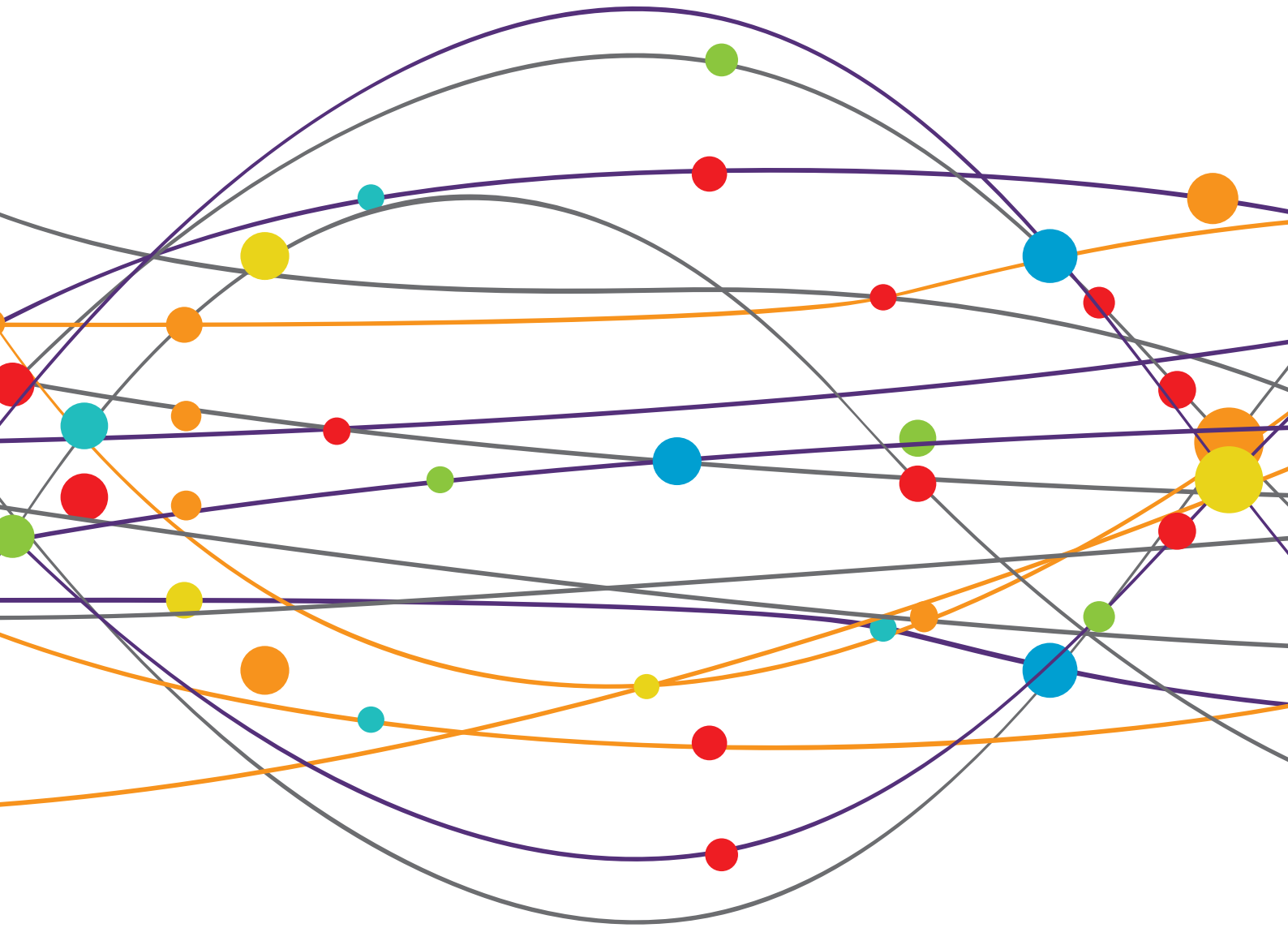

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BENIGN PAROXYSMAL POSITIONAL VERTIGO

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Seasonality and Cardio-Cerebrovascular Risk Factors for Benign Paroxysmal Positional Vertigo

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Background: Benign paroxysmal positional vertigo (BPPV) is the most common cause of vertigo, especially in the elderly. Several studies have revealed a possible seasonality to BPPV. However, whether the seasonality of BPPV also exists in China is unclear. The characteristics of cardio-cerebrovascular risk factors for BPPV in the cold season have not yet been investigated.

Objectives: (1) To investigate the seasonality of BPPV; (2) To explore the relationship between cardio-cerebrovascular risk factors and seasonality of BPPV.

Methods: A retrospective observational study was performed in Beijing Tiantan Hospital from Jan 2016 to Dec 2018. The study included 1,409 new-onset BPPV patients aged 18–88 years. The demographic data, onset time, and medical history of BPPV were collected. The meteorological data, including temperature, atmospheric pressure, rainfall, and insolation, was obtained from Beijing Meteorological service. The x^2 goodness of fit test was used to evaluate whether BPPV patients' numbers were significantly different among different months of the year. The Spearman correlation was used to detect the correlation between numbers of BPPV patients diagnosed monthly with each climatic parameter. The chi-square test for linear-by-linear association were used to investigate the relationship between cardio-cerebrovascular risk factor and seasonality of BPPV.

Results: November to next March is the top 5 months with higher BPPV patient numbers ($P < 0.001$). The numbers of BPPV diagnosed monthly were conversely correlated with temperature and rainfall ($r = -0.736$, $P = 0.010$; $r = -0.650$, $P = 0.022$, respectively), positively correlated with atmospheric pressure ($r = 0.708$, $P = 0.010$), but no significant correlated with insolation. BPPV in the cold season (including January, February, March, November, and December) had a higher proportion, accounting for 54.2% of all BPPV patients. Among BPPV patients with ≥2, 1, and none cardio-cerebrovascular risk factors, the cold season accounted for 57.0, 56.0, 49.8%, respectively. As the number of cardio-cerebrovascular risk factors increased, the proportion of patients in the cold season of BPPV increased ($P = 0.025$).

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Conclusions: BPPV patients are seen more in the months with low temperature, low rainfall, and high atmospheric pressure. Compared with the non-cold season, BPPV patients have more risk factors for cardio-cerebrovascular diseases in the cold season.

Keywords: benign paroxysmal positional vertigo, seasonality, cold season, temperature, cerebrovascular risk factors

INTRODUCTION

Vertigo, a high frequency disease, imposes a rising burden on the health care system, aggravated by the aging of the population (1). Benign paroxysmal positional vertigo (BPPV) is the most common type of peripheral vestibular vertigo. It was caused by otoconia that migrate from the utricle to the semicircular canal or cupula. The clinical symptom is characterized by recurrent bouts of positionally triggered spinning vertigo. The lifetime prevalence of BPPV was estimated at 2.4%, the 1 year prevalence at 1.6% (2). At present, canalith repositioning maneuvers (CRM) are the primary treatment for BPPV, through the movement of the otoconia back into the utricle. Nevertheless, the recurrence rate of BPPV was high, a third to a half of patients have recurrences at 3 years, with most recurrences occurring in the first year (3). Due to the high recurrence, the quality of life, ability to perform activities of daily life have severely decreased. Meanwhile, it brings several complications, such as emotional disorder, sleep disorder, fall risk, and even death (4). Therefore, understanding the risk factors for BPPV is necessary for relieving symptoms and preventing recurrence.

Seasonality of patients with BPPV has been investigated. Whitman and Baloh (5) reported that the incidence of BPPV was significantly higher in the early spring months (March, April, May) in Boston. In Brazil, Pereira et al. found vertigo was more frequent in late winter- spring (6), but Zuma et al. showed more patients with BPPV are seen in consultation in the months with low solar radiation (March–September) (7). Korpon et al. demonstrated a association between barometric pressure and BPPV (8). Whether the seasonality of BPPV also exists in Chinese patients is unclear.

In addition to seasonality, the cardio-cerebrovascular risk factors (hypertension, diabetes, and hyperlipidemia) were associated with BPPV because of possible vascular damage to the inner ear (9). BPPV patients with hypertension and hyperlipidemia were at a higher risk of symptom recurrence (4). Patients with BPPV had a higher prevalence of coronary artery disease (10). Moreover, hyperglycemia and hyperinsulinemia are risk factors for the recurrence of BPPV (11). Cardiovascular and cerebrovascular diseases have a high incidence in the cold season. However, the relationship between cardio-cerebrovascular risk factors and seasonality of BPPV has not yet been investigated.

Therefore, we aimed to investigate the seasonality of BPPV in Chinese patients and to explore the relationship between cardio-cerebrovascular risk factors and seasonality of BPPV.

MATERIALS AND METHODS

Meteorological Index

The study was conducted in Beijing Tiantan Hospital in China from January 2016 to December 2018. Beijing is located at latitude 39°56′N and longitude 116°20′E. It displays a typical temperate and monsoonal climate with four distinct seasons. The climate indexes included temperature, atmospheric pressure, rainfall, and insolation of the study period were retrieved from Beijing Meteorological service. Averages were calculated for each month across the 3 years study period. According to the temperature in Beijing, considering that from November to next March was recognized as the cold season. The meteorological indexes were documented to correlate these events with disease occurrence.

Participants

The study was performed according to the Declaration of Helsinki guidelines, and written informed consent was obtained from all participants. The patients in our study only underwent standard treatment without additional interventions for research purposes, so no formal ethics approval was required. This study is a retrospective and exploratory study. The sample size of the previous study about seasonality and BPPV was ∼207 (12) patients over the 3 years, 339 (13) patients over the 4 years, 956 (5) patients over the 5 years. About the cardiovascular risk factors and BPPV, the sample size of previous study was about 314 (14) patients over 4 years. At the same time, about 30–40 BPPV patients visited to our hospital every month. We retrospectively analyzed the data of 1,409 new-onset BPPV patients registered in the BPPV diagnosis and treatment registration database of Beijing Tiantan Hospital from Jan 2016 to Dec 2018. The diagnosis of BPPV met the criteria of BPPV established by the Barany Society (15). The all patients were first episode, received the definite diagnosis and canalith repositioning maneuvers (CRM). In order to describe the baseline clinical characteristics in detail, the patients were divided into five groups (aged 18–30 years, 31–44 years, 45–59 years, 60–80 years, ≥80 years) according to the age.

Measurement Index

All patients underwent evaluations including demographic variables, potential risk factors, and neurological examination. The cardio-cerebrovascular risk factors included age ≥ 60 years, hypertension, hyperlipidemia, diabetes, coronary heart disease, migraine (16), and stroke. During the assessment, hypertension, hyperlipemia, diabetes, stroke, and coronary heart disease were

TABLE 1 | Demographic information and clinical characteristics.

Risk factors *n* (%)	18–30 y (*n* = 73)	31–44 y (*n* = 225)	45–59 y (*n* = 542)	60–79 y (*n* = 546)	≥80 y (*n* = 23)	*P*-value
Male	15 (20.5)	68 (30.2)	185 (34.1)	184 (33.7)	10 (43.5)	0.113
Hypertension	1 (1.4)	17 (7.6)	171 (31.5)	171 (31.3)	15 (65.2)	<0.0001
Hyperlipemia	0 (0)	9 (4.0)	99 (18.3)	110 (20.1)	6 (26.1)	<0.0001
Diabetes	0 (0)	1 (0.4)	27 (5.0)	59 (10.8)	6 (26.1)	<0.0001
Coronary heart disease	0 (0)	2 (0.9)	28 (5.2)	35 (6.4)	2 (8.7)	0.004
Stroke	0 (0)	2 (0.9)	9 (1.7)	24 (4.4)	1 (4.3)	0.008
Sudden deafness	5 (6.8)	9 (4.0)	16 (3.0)	27 (4.9)	1 (4.3)	0.256
Migraine	3 (4.1)	19 (8.4)	49 (9.0)	50 (9.2)	3 (13)	0.615
Meniere disease	0 (0)	0 (0)	2 (0.4)	4 (0.7)	0 (0)	0.622

defined according to International Classification of Diseases 10. Migraine was diagnosed on the basis of the International Headache Society (IHS) criteria (17). Sudden deafness was defined as a history of unilateral sensorineural hearing loss with sudden onset, without other prior otological histories (18). Probable Meniere's disease was defined according to the criteria defined by consensus among Barany Society, Japan Society for Equilibrium Research, EAONO, AAO-HNS, and Korean Balance Society (19).

Statistical Analysis

Patients were divided into five different age groups (aged 18–30 years; 31–44 years; 45–59 years; 60–79 years; ≥80 years). All categorical variables are presented as frequency and percentage. Statistical significance between five groups was determined using a chi-squared test or Fisher's exact test. To evaluate whether patients' numbers were significantly different among different months of the year, the number of patients presented monthly was compared with the assumption of the equal number of patients diagnosed monthly. The comparison was analyzed by the x^2 goodness of fit test. The Spearman's Rank Correlation Coefficient was used to study the correlation between overall numbers of patients diagnosed monthly with each climate parameter (temperature, atmospheric pressure, rainfall, and insolation) of each month of the year pooled from the years 2016–2018. The chi-square test for linear by linear association were used to determine the correlation between cardio-cerebrovascular risk factor and seasonality of BPPV. Statistical analysis was performed in SPSS 24.0 (IBM, Chicago, IL, USA). Graphs were delineated by using Prism 7.0 (GraphPad software, La Jolla, CA, USA). Values with $P < 0.05$ were regarded as statistically significant.

RESULTS

Demographic Profiles of Participants

We collected 1,409 new-onset BPPV patients accepted definitive diagnosis in the Department of Neurology, Beijing Tiantan Hospital from Jan 2016 to Dec 2018. BPPV was found to be more frequent in female patients-947 (67.2%) against 462 (32.8%) males. The age varied from 18 to 88 years, with a median of 57.00 years (standard deviation = 12.91). The patients were divided into the five groups. Among groups, there was statistical difference in the common cardio-cerebrovascular risk factors, including hypertension, hyperlipemia, diabetes, coronary heart disease, and stroke. But no significant difference in the numbers with Meniere's disease, sudden deafness, and migraine was found (**Table 1**).

TABLE 2 | Overall monthly patients' distribution with percentage.

Month	Overall number of patients in the years 2016, 2017, and 2018 *n* = 1,409
Jan	121 (8.6%)
Feb	126 (8.9%)
Mar	136 (9.7%)
Apr	80 (5.7%)
May	89 (6.3%)
Jun	93 (6.6%)
Jul	87 (6.2%)
Aug	106 (7.5%)
Sep	82 (5.8%)
Oct	109 (7.7)
Nov	119 (8.4)
Dec	261 (18.5)
P-value	<0.001

Seasonality of BPPV in Chinese Patients

As shown in **Table 2**, the distribution of patients is not equal in several months of the years. The overall monthly numbers of BPPV over the 3 years were significantly different ($P < 0.001$). The highest number of BPPV patients is in December, and the lowest number of BPPV is in April (**Table 2**, **Figure 1**).

The climatic indexes that were studied in relation to BPPV were the temperature, atmospheric pressure, rainfall, and insolation. **Table 3** showed the mean values of these parameters. As shown in **Table 3**, the lower temperatures were in November-December and January-March (the cold season), and the higher were in April- October (**Figure 1A**). The atmospheric pressure was high in the cold season (November–December,

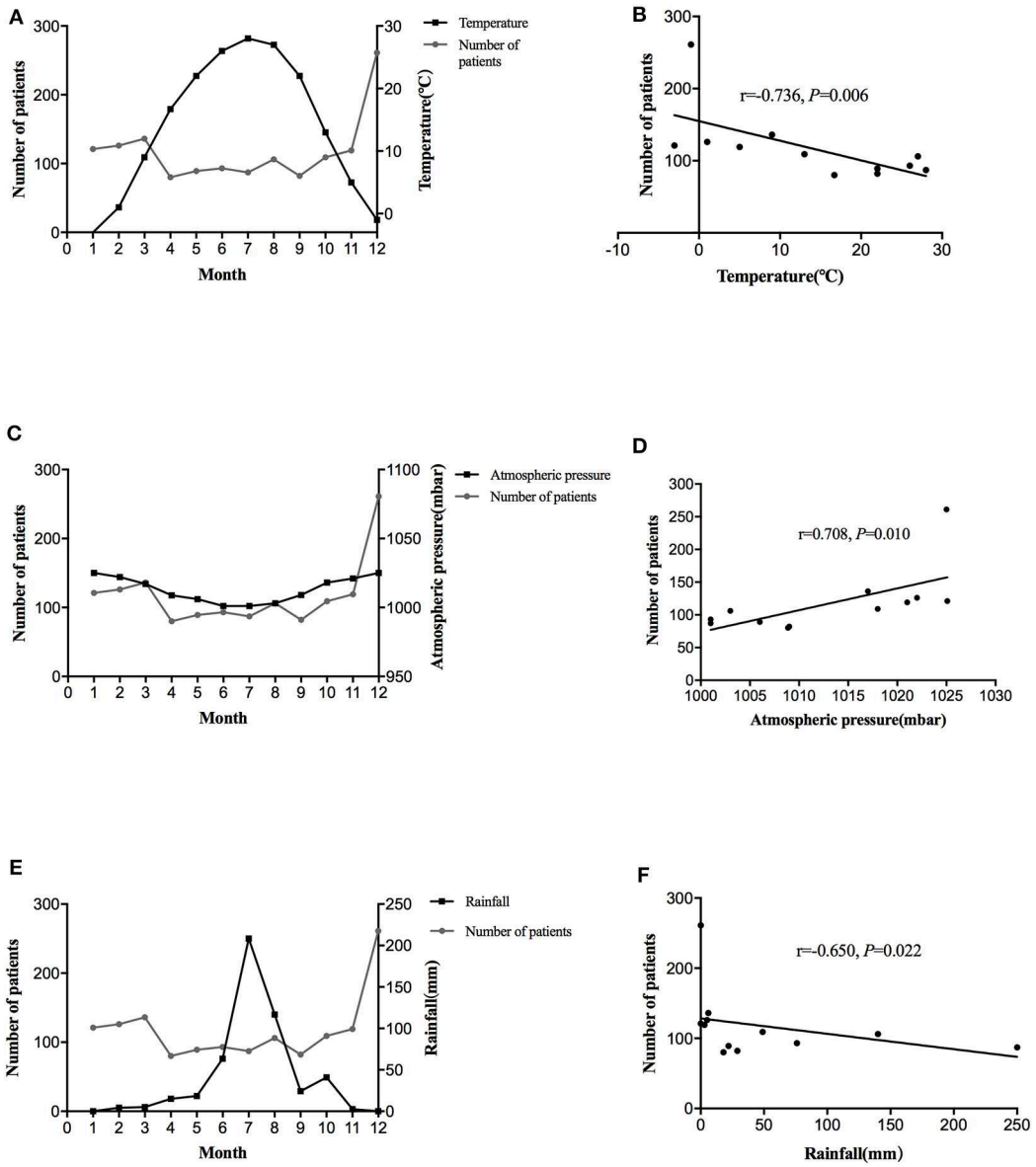

FIGURE 1 | The distribution of average monthly diagnoses of BPPV and temperature over the 3 year period **(A)**. Association between the number of BPPV patients with temperature **(B)**. The distribution of average monthly diagnoses of BPPV and atmospheric pressure over the 3 year period **(C)**. Association between the number of BPPV patients with atmospheric pressure **(D)**. The distribution of average monthly diagnoses of BPPV and rainfall over the 3 year period **(E)**. Association between the number of BPPV patients with rainfall **(F)**.

January–March), less in the warm and hot months (**Figure 1C**). Similarly, the rainfall and insolation were low in the cold season (**Figure 1E**). The number of BPPV patients was conversely correlated with temperature and rainfall ($r = -0.736$, $P = 0.006$, **Figure 1B**; $r = -0.650$, $P = 0.022$; **Figure 1F**, respectively) and positively correlated with the atmospheric pressure ($r = 0.708$, $P = 0.010$; **Figure 1D**). Regarding the insolation, it was found to be conversely correlated to BPPV, yet this correlation was not significant ($r = -0.203$, $P = 0.527$).

Relationship Between Cardio-Cerebrovascular Risk Factors and Seasonality of BPPV

BPPV in the cold season (including January, February, March, November, and December) had a high proportion, accounting for 54.2% of all BPPV patients. As shown in **Table 4**, among BPPV patients with ≥2, 1, and none cardio-cerebrovascular risk factors, the cold season accounted for 57.0, 56.0, 49.8%, respectively. As the number of cardio-cerebrovascular risk factors increased, the

TABLE 3 | Average climatic indexes by months of the year in Beijing, China, 2016–2018.

Month	Atmospheric pressure (mbar)	Average temperature (°C)	Rainfall (mm)	Insolation (h)
Jan	1025.10	−3.03	0.10	197.13
Feb	1022.00	1.00	5.00	217.00
Mar	1017.00	9.00	6.00	238.00
Apr	1008.87	16.70	18.00	251.67
May	1006.00	22.00	22.00	269.00
Jun	1001.00	26.00	76.00	234.00
Jul	1001.00	28.00	250.00	164.00
Aug	1003.00	27.00	140.00	204.00
Sep	1009.00	22.00	29.00	210.00
Oct	1018.00	13.00	49.00	168.00
Nov	1021.00	5.00	3.00	187.00
Dec	1025.00	−1.00	0.07	188.00

TABLE 4 | Relationship between cardio-cerebrovascular risk factors and seasonality of BPPV.

The number of risk factors	Cold season ($n = 763$)	Non-cold season ($n = 646$)	x^2	*P*-value
0	246 (49.8%)	248 (50.2%)		
1	255 (56.0%)	200 (44.0%)	5.000	0.025
≥2	262 (57.0%)	198 (43.0%)		

proportion of patients in the cold season of BPPV increased ($P = 0.025$).

DISCUSSION

Our study showed that there is a seasonality to BPPV in China. The numbers of BPPV diagnosed monthly demonstrated a statistically significant converse correlation with temperature and rainfall, positive correlation with atmospheric pressure. As the number of cardio-cerebrovascular risk factors increased, the proportion of BPPV in the cold season increased.

In accordance with the present results, previous studies have revealed that the incidence of BPPV presents climatic variations in USA (5), UK (13), Iraq (12), and Brazil (7). Our results also showed in the cold season, namely in winter-spring (January, February, March, November, and December), had a high incidence in China. The numbers of BPPV diagnosed monthly had a statistically significant converse correlation with temperature. There were many possible explanations: (1) As we known, BPPV attacks when otoconia of the utricular macula become dislodged and freely floating otolithic debris moves into 1 or more of the semicircular canals. Calcium is the main component of otoconia crystals and Vitamin D is required for its regulation (20). A series of clinical observational studies showed that vitamin D levels were decreased in BPPV (13, 21, 22). Compared with the non-cold season, there is less sunlight time and a lower ultraviolet index, leading to decreased vitamin D levels in the cold season. Therefore, low vitamin D levels could cause the formation of calcium carbonate in endolymph. (2) At the same time, in the cold season, many people like the sedentary lifestyle rather than outdoor activities. The sedentary life may increase the incidence of bone demineralization and osteoporosis with possible increase in BPPV. (3) Other possible reasons for increased cases of BPPV shouldn't be neglected. Medical conditions that affect the inner ear, such as upper respiratory infections and allergies, have a higher occurrence of BPPV in winter and spring. Korpon et al. found an association between allergens and BPPV (8). Gacek et al. showed BPPV is associated with positive viral serology, particularly during certain months of the year, mainly in spring and autumn (23). These may also explain the relatively high incidence of BPPV in the cold season (winter-spring).

BPPV is the most common vestibular disease in females and the aged population. Women have doubled risk for BPPV than men (4, 24). Similarly, in the present study, there is a predominance of female sex, accounting for about 67.2% of BPPV patients. This female preponderance may be linked to hormonal factors (25). Estrogen deficiency has been shown to disturb the internal structure of the otoconia and their interconnection and attachment to the matrix (26). Oghalai et al. (27) carried out a study of unrecognized BPPV in elderly patients with the age of onset 45 to 60 years. The mean age is about 54.9 years, median age is about 57.00 years in this study. The semicircular canal function, as well as the otolith one, declines with age (28). Cardio-cerebrovascular risk factors, including hypertension, hyperlipidemia, diabetes, coronary artery disease, migraine, are considered as independent risk factors for the occurrence and recurrence of BPPV (9, 11, 29). The older patients have more cardio-cerebrovascular risk factors in our study. The possible reason was that the function of otolith got worse with organic changes caused by hypertension or diabetes which promote a diffuse vascular damage resulting in the atherosclerotic disease (29). An inner ear vascular damage caused by atherosclerosis can generate a progressive detachment of otoconia from the otolithic membrane. Especially in the cold season, accompanied by sympathetic nerve excitement and increased adrenaline secretion, people predisposed to faster heart rate, vasoconstriction, and higher blood pressure. Additionally, platelets, triglycerides, plasma fibrinogen, CRP, and other concentrations would also increase. These factors leading to an increase in the occurrence of ischemic vascular events caused the circulation disorder of inner ear. Our study also showed that the proportion of BPPV in the cold season is higher than that in the non-cold season. Furthermore, as the number of cardio-cerebrovascular risk factors increased, the proportion of BPPV in the cold season increased. Effective measures in the cold season including keeping warm and cardio-cerebrovascular risk factors control, may be helpful for prevention of BPPV.

In addition to the temperature, our study also showed that the number of BPPV patients was positively correlated with atmospheric pressure. Such findings confirm the association

reported by Saeed and Omari (12) and Korpon et al. (8). The previous studies have demonstrated the pressure-sensitive nature of vestibular receptors and the presence of a valve-like structure that regulates endolymphatic pressure in the inner ear (30). The function of this valve was to regulate inner ear pressure with changes in atmospheric pressure (31). Transmission of this increased pressure by the inner ear space may lead to dislodgement of otoconia crystals leading to symptomatic BPPV. Also, there are studies that revealed that vestibular migraine (32) (VM) and Meniere's disease (33) (MD) have association with atmospheric pressure. Our study suggested a possible pathophysiologic link between the clinically observed coincidence of BPPV and VM or MD. The present study also showed that the number of BPPV patients was conversely correlated with rainfall and no significant correlation with insolation. The study about seasonality of vertigo (6) also demonstrated the above findings. The potential mechanism was not clear and warrant further evaluations.

Limitations of our study should be paid attention to: firstly, climatic variations may appear from year to year. This study endeavored to avert this by investigating 3 years of data. Secondly, it's a retrospective study based on clinical record and there was no follow-up information in this database. The specific and disease-related information was not available in this study. Therefore, further validated prospective studies are necessary to confirm our results. At last, some other cardio-cerebrovascular risk factors, such as behavior factors, were not available in this database. At present, this is the initial finding about the relationship between cardio-cerebrovascular risk factors and seasonality of BPPV in the cold season. Further prospective study is needed.

CONCLUSIONS

BPPV patients are seen more in the months with low temperature, low rainfall and high atmospheric pressure. Compared with the non-cold season, BPPV patients have more risk factors for cardio-cerebrovascular diseases in the cold season.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The study was performed according to the Declaration of Helsinki guidelines, and written informed consent was obtained from all participants. The patients in our study only underwent standard treatment without additional interventions for research purposes, so no formal ethics approval was required. Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

ZC conceived the study and design, conducted the experiment, and wrote the manuscript. XZ provided the data analysis and revised this manuscript. YJ conceived the study and design and edited the manuscript. YW and MC conducted acquisition of subjects and interpretation of data.

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Short-Term Central Adaptation in Benign Paroxysmal Positional Vertigo

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Objective: To elucidate the frequency, underlying mechanisms, and clinical implications of spontaneous reversal of positional nystagmus (SRPN) in benign paroxysmal positional vertigo (BPPV).

Methods: We prospectively recruited 182 patients with posterior canal (PC, $n = 119$) and horizontal canal (HC) BPPV ($n = 63$) canalolithiasis. We analyzed the maximal slow phase velocity (maxSPV), duration, and time constant (Tc) of positional nystagmus, and compared the measures between groups with and without SRPN. We also compared the treatment outcome between two groups.

Results: The frequency of SRPN in PC- and HC-BPPV was 47 and 68%, respectively. The maxSPVs were greater in BPPV with SRPN than without, larger in HC-BPPV than PC-BPPV (114.3 ± 56.8 vs. 57.1 ± 38.1°/s, $p < 0.001$). The reversed nystagmus last longer in HC-BPPV than PC-BPPV. The Tc of positional nystagmus got shorter in PC-BPPV with SRPN (3.7 ± 1.8 s) than without SRPN (4.5 ± 2.0 s, $p = 0.034$), while it was longer during contralesional head turning in HC-BPPV with SRPN (14.8 ± 7.5 s) than that of ipsilesional side (7.3 ±2.8 s, $p < 0.001$). The treatment response did not significantly differ between groups with and without SRPN in both PC- and HC-BPPV ($p = 0.378$ and $p = 0.737$, respectively).

Conclusion: The SRPN is common in both PC- and HC-BPPV canalolithiasis. The intensity of rotational stimuli may be a major determinant for the development of short-term central adaptation which utilizes the velocity-storage system below a certain velocity limit. The presence of SRPN is not related to treatment outcome in BPPV.

Keywords: benign paroxysmal positional vertigo, nystagmus, spontaneous reversal, adaptation, velocity storage system

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is characterized by brief spinning sensations, which are generally induced by a change in head position with respect to gravity (1–6). Because the free-floating or cupula-attached otolith debris induce abnormal lymph flow within the semicircular canals (SCCs), the sense of rotation is induced depending on the head position (5). According to the fundamental pathophysiology based on abnormal endolymph flow due to the free-floating debris,

the positional nystagmus in canalilithiasis type of BPPV should be stopped when the head kept at the final position during positioning maneuvers, since the otolith debris would be at standstill. However, spontaneous reversal of positional nystagmus (SRPN), which is defined as spontaneous reversal of initial geotropic nystagmus without any head movement in horizontal canal (HC) BPPV (**Figure 1**, **Supplementary Video 1**), has been occasionally reported (4, 7–11). A few studies have described high frequency (73%) of SRPN in HC-BPPV canalolithiasis, whereas the frequency was significantly low (4%) in PC-BPPV (11). They also reported clinical significance of SRPN that patients presenting with SRPN had a trend to require more repositioning maneuver sessions (11). A spontaneous reflux of endolymph with the elastic force of cupula or the gravitational forces of otoconia debris, coexistence of canalo- and cupulolithiasis, and short-term adaptation of the

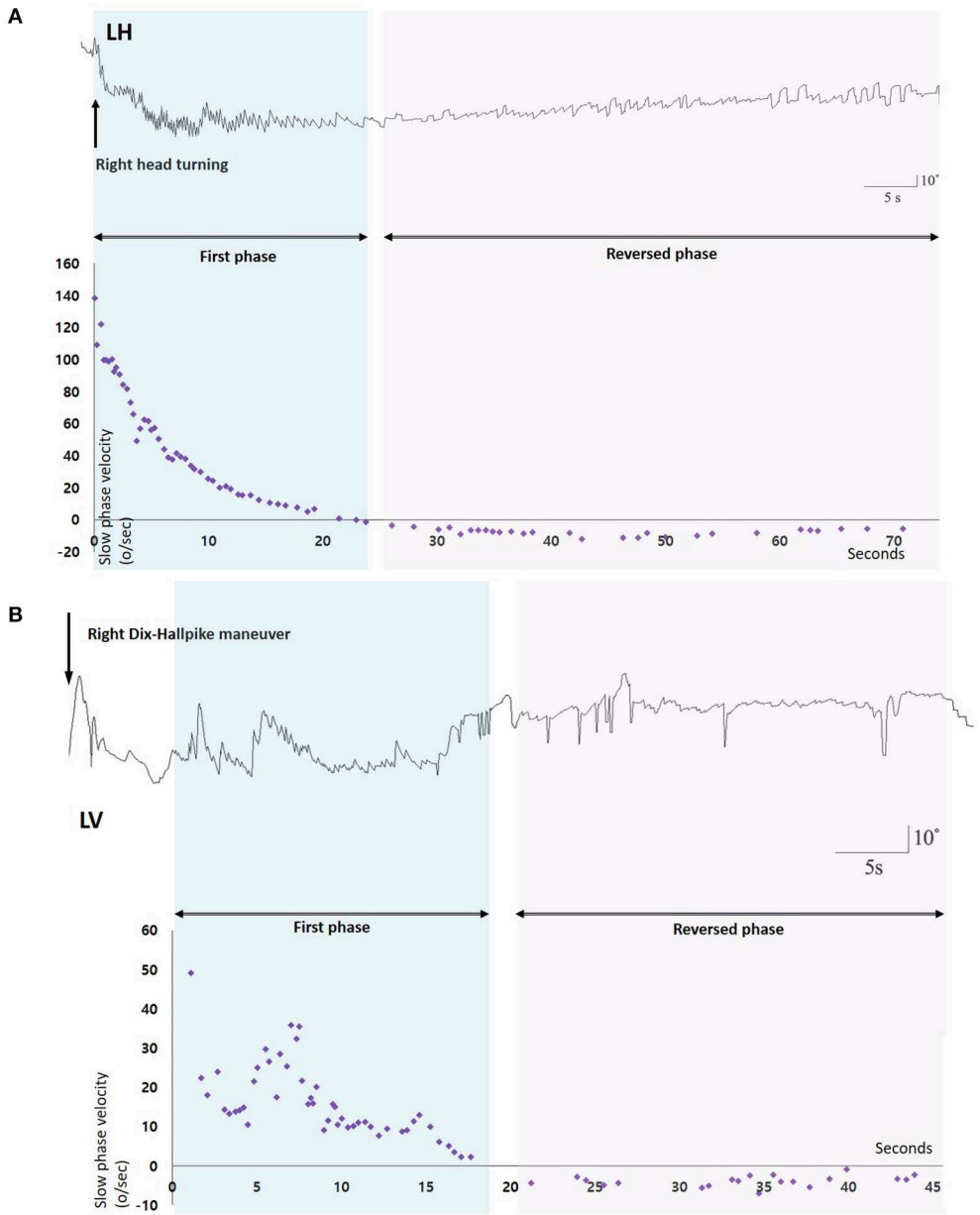

FIGURE 1 | Nystagmus response profiles of two patients with benign paroxysmal positional vertigo and spontaneous reversal of positional nystagmus. **(A)** After head turning to the right, 3D-video oculography shows vigorous right-beating nystagmus with maximal slow phase velocities of about 140°/s which decays during 20 s, and then is followed by small left-beating nystagmus lasting more than 60 s. **(B)** Right Dix-Hallpike maneuver induces upbeat nystagmus with maxSPVs of 50°/s and rapidly decays during 15 s. Small downbeat nystagmus immediately follows and lasts for 25 s. LH, Horizontal position of the left eye; LV, Vertical position of the left eye.

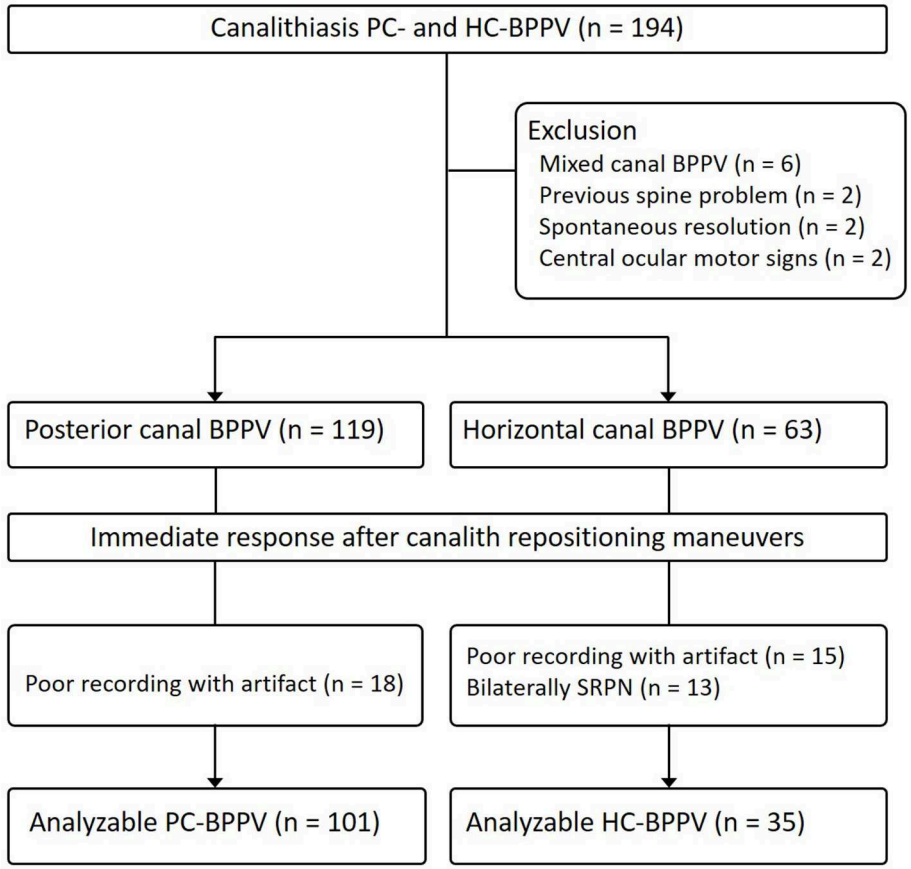

FIGURE 2 | Study flow diagram. BPPV, benign paroxysmal positional vertigo; SRPN, spontaneous reversal of positional nystagmus.

vestibulo-ocular reflex (VOR) are proposed mechanisms for the development of SRPN in BPPV (4, 7–11). To date, there have been no prospective studies that investigated the frequency, underlying mechanisms, and clinical implications of SRPN in BPPV.

We hypothesized that if short-term central adaptation of VOR is the main mechanism of SRPN in BPPV, initial reversed nystagmus would disappear immediately after treatment of canalolithiasis. To determine major factors associated with the generation of SRPN, we analyzed various measures including the maximal slow phase velocity (maxSPV), duration, and time constant (Tc) of positional nystagmus, and compared them between groups with and without SRPN. In addition, we attempted to investigate clinical application of SRPN by comparison of treatment outcome between two groups.

MATERIALS AND METHODS

Subjects and Evaluations

We prospectively recruited 182 patients with canalolithiasis type of PC- (n = 119) and HC-BPPV (n = 63) (men = 64, mean age ± SD = 63.9 ± 13.9) at the Dizziness Clinic of Pusan National University Hospital between January 2017 and December 2018. The inclusion criteria for this study were (1) a history of brief episodes of positional vertigo, (2) torsional–upbeat nystagmus with the upper pole of the eye beating toward the affected ear (PC-BPPV) during Dix-Hallpike maneuver or direction changing horizontal nystagmus beating toward the undermost ear (geotropic nystagmus) during supine head-roll tests (HC-BPPV) which was detected with Frenzel glasses or video-oculography (3) positional nystagmus not lasting more than 1 min (4) no persistent spontaneous nystagmus during the sitting positions, (5) absence of identifiable central nervous system disorders that could explain the positional vertigo and nystagmus. We excluded 12 patients with simultaneous involvement of other SCCs (n = 6), spine problems that did not permit repositioning maneuvers (n = 2), spontaneous resolution of BPPV after a diagnostic positioning maneuver (n = 2), and central ocular motor signs (n = 2) (**Figure 2**).

To exclude the patients with central positional nystagmus, all patients received neurotological examinations including spontaneous and gaze-evoked nystagmus, ocular motor tests including saccades and smooth pursuit, bedside head impulse tests, limb ataxia, and balance function in addition to routine neurological examinations. Patients with central ocular motor signs, limb ataxia, and severe imbalance had MRIs. Severe

TABLE 1 | Analysis of positional nystagmus during the first phase.

	PC-BPPV			HC-BPPV		
	maxSPV (°/s, mean ± SD)	**Duration (s, mean ± SD)**	**Tc (s, mean ± SD)**	**max SPV (°/s, mean ± SD)**	**Duration (s, mean ± SD)**	**Tc (s, mean ± SD)**
SRPN (–)	40.2 ± 34.4	13.6 ± 5.3	4.5 ± 2.0	59.3 ± 41.8	21.8 ± 10.5	5.8 ± 2.5
SRPN (+)	57.1 ± 38.1	11.1 ± 5.2	3.7 ± 1.8	114.3 ± 56.8	24.2 ± 6.6	7.3 ± 2.8
p-value	0.032	0.016	0.034	0.003	0.485	0.125

All of p-values are estimated by t-test.
PC, posterior canal; HC, horizontal canal; BPPV, benign paroxysmal positional vertigo; maxSPV, maximal slow phase velocity; SRPN, spontaneous reversal of positional nystagmus; Tc, time constant.

TABLE 2 | Comparison of clinical characteristics.

	Total (*n* = 182)	**PC-BPPV**				**HC-BPPV**				
		Total (*n* = 119)	**SPRN (+) (*n* = 56)**	**SPRN (–) (*n* = 63)**	***p*-value**	**Total (*n* = 63)**	**SPRN (+) (*n* = 43)**	**SPRN (+) (*n* = 20)**	***p*-value**	***p*-value**
Age, y, mean (SD)	63.0 (12.8)	62.6 (12.9)	63.7 (12.5)	61.7 (13.4)	0.414	63.7 (12.7)	62.7 (12.5)	65.7 (13.3)	0.401	0.587
Male, *n* (%)	67 (36.8)	49 (41.2)	22 (39.3)	26 (41.3)	0.770	18 (28.6)	11 (25.6)	7 (35.0)	0.398	0.145
Lesion side, left, *n* (%)	66 (36.3)	44 (37.0)	17 (30.4)	27 (42.9)	0.121	22 (35.0)	16 (37.2)	6 (30.0)	0.774	0.935
Symptom duration, day, mean (SD)	5.5 (6.9)	6.9 (7.8)	6.8 (7.5)	7.1 (8.1)	0.810	2.5 (3.2)	2.6 (3.2)	2.5 (3.5)	0.891	<0.001

PC, posterior canal; HC, horizontal canal; BPPV, benign paroxysmal positional vertigo; SRPN, spontaneous reversal of positional nystagmus.

imbalance was defined when the patients were unable to stand or sit without support.

Nystagmus was recorded binocularly without fixation at a sampling rate of 120 Hz using a 3D video-oculography (SLMED, Seoul, Korea). To induce positional nystagmus, the patients lay supine from sitting (lying-down nystagmus) and turned their heads to either side while in the supine position (supine head-roll test). Then the patients were moved from a supine to a sitting position, and the head was bent down (head-bending nystagmus). Patients were also subjected to right and left Hallpike maneuvers. At each step during the test, the examiners kept the head position and observed the nystagmus at least for 1 min and then, transited to the next step. Digitized eye position data were analyzed by MATLAB software (version R2013b, MathWorks, Natick, MA).

We attempted to determine the immediate therapeutic efficacy of the barbecue or Gufoni maneuver for HC-BPPV and Epley maneuver for PC-BPPV. In HC-BPPV, the affected ear was determined by intensity of the nystagmus with an assumption that the induced nystagmus is more intense when the head is rotated to the affected side. When the decision was inconclusive because of symmetric nystagmus, the affected ear was determined by the direction of lying-down or head-bending nystagmus. Each maneuver was performed by a trained physiotherapist. The resolution was defined when vertigo and positional nystagmus disappeared within 1 h after a maximum of two applications of each maneuver.

Analyses and Measures

We analyzed the vertical components of positional nystagmus during Dix-Hallpike test in PC-BPPV, and the horizontal ones during supine head roll test in HC-BPPV. We divided positional nystagmus into the first and reversed phases (**Figure 1**). The presence of SRPN was defined when there was the following direction-changing nystagmus after initial positional nystagmus (the first phase nystagmus) without change of a head position (**Figure 1**, **Supplementary Video 1**). The direction of SRPN was determined as downward in PC-BPPV, and apogeotropic in HC-BPPV.

The measures of positional nystagmus for analysis were the maximal slow phase velocity (maxSPV), duration, and time constant (Tc). The Tc of positional nystagmus was calculated with a non-linear regression test (12). Since the SPVs of positional nystagmus exponentially decreased, we use a non-linear regression equation, which is SPVs $= A * e^{-t/\tau} + C$ (12), the A is amplitude of maxSPV, t is time, C is offset indicating the constant SPVs, and τ is Tc. The value of A and C were arranged to 1 and 0 (12).

Statistical Analysis

Student or paried t-tests were used to compare the continuous variables, and Fisher's exact test or χ^2-tests were applied for the categorical variables. Pearson's correlation coefficient was used to correlate SPRN with nystagmus measures between in the first and reverse phases. All statistical procedures were performed using SPSS statistical software (version 18.0; SPSS, Chicago, IL, USA) and $p < 0.05$ were considered significant.

RESULTS

Clinical Characteristics and Prevalence of SRPN in BPPV

Of the 182 patients enrolled in the study, 67 (63.8%) were male and 66 (36.3%) had involvement of left semicircular canals. The mean (SD) age was 63.0 (12.8) year, and mean (SD) duration from symptom onset to enrollment was 5.5 (6.9) days. There were no significant differences in the sex ratio, lesion side, and age between groups with PC- and HC-BPPV, or groups with and without SRPN. The duration from symptom onset to enrollment was longer in PC-BPPV than HC-BPPV ($p < 0.001$), but it did not differ between groups with and without SRPN (**Table 2**). None of the patients showed catch-up saccades during bedside head impulse tests or had a history of recurrent vertigo compatible to endolymphatic hydrops.

The frequency of SRPN was 47% (56/119) in PC-BPPV and 68% (43/63) in HC-BPPV canalolithiasis, which was not significantly different between two groups (47 vs. 68%, $p = 0.213$).

PC-BPPV

We analyzed 101 of 119 patients with PC-BPPV after excluding 11 due to poor recording with artifact by video-oculography, and 51 of them developed SRPN. The frequency of SRPN was similar to that of initial population with PC-BPPV (47 vs. 51%, χ^2-test, $p = 0.611$).

In the first phase of positional nystagmus, the maxSPV was greater in patients with SRPN than without (57 ± 38 vs. 40 ± 34°/s, $p = 0.032$, **Table 1**). The duration and Tc of positional nystagmus were shorter in patients with SRPN than without ($p = 0.016$ and 0.034, respectively, **Table 1**).

The SRPN disappeared within 1 min in 22 patients (43%), and the maxSPV of SRPN was lower than that of the first phase nystagmus (6 vs. 56°/s, $p < 0.001$). There was no correlation in the maxSPVs between the first and reversed phases (Pearson's correlation coefficient = 0.173, $p = 0.255$).

HC-BPPV

We analyzed 35 of 63 patients with HC-BPPV after excluding 15 with poor recording with artifacts by video-oculography and 13 with bilateral SRPN. We found SRPN in 66% (23/35) which was not significantly different to the frequency of initial population with HC-BPPV (68 vs. 66%, χ^2-test, $p = 0.797$).

In the first phase of positional nystagmus, the maxSPV was greater in patients with SRPN than without (114 ± 57 vs. 59 ± 42°/s, $p = 0.003$, **Table 1**). The duration and Tc of the first phase nystagmus did not differ between groups with and without SRPN ($p = 0.485$ and 0.125, **Table 1**).

The SRPN persisted more than 1 min in most of patients (96%), and the maxSPV of SRPN was lower than that of the first phase nystagmus (12 ± 6.7 vs. 114 ± 57°/s, $p < 0.001$). Any correlation was not found in the maxSPVs between the first and reversed phases (Pearson's correlation coefficient = 0.239, $p = 0.285$).

We compared various measures of positional nystagmus during ipsilesional and contralesional head turning in patients with and without SRPN (**Figure 3**). The maxSPV is greater during ipsilesional head turning than contralesional turning in both groups ($p = 0.004$ and < 0.001, respectively, **Figures 3A,B**). In patients with SRPN, the duration and Tc of the first phase nystagmus were significantly longer during contralesional than ipsilesional head turning (**Figures 3D,F**), whereas those were not significantly different in patients without SRPN (**Figures 3C,E**, paired t-test, $p = 0.923$ and 0.925).

The maxSPVs were greater in HC-BPPV with SRPN than PC-BPPV with SRPN (114 ± 57 vs. 57 ± 3°/s, $p < 0.001$).

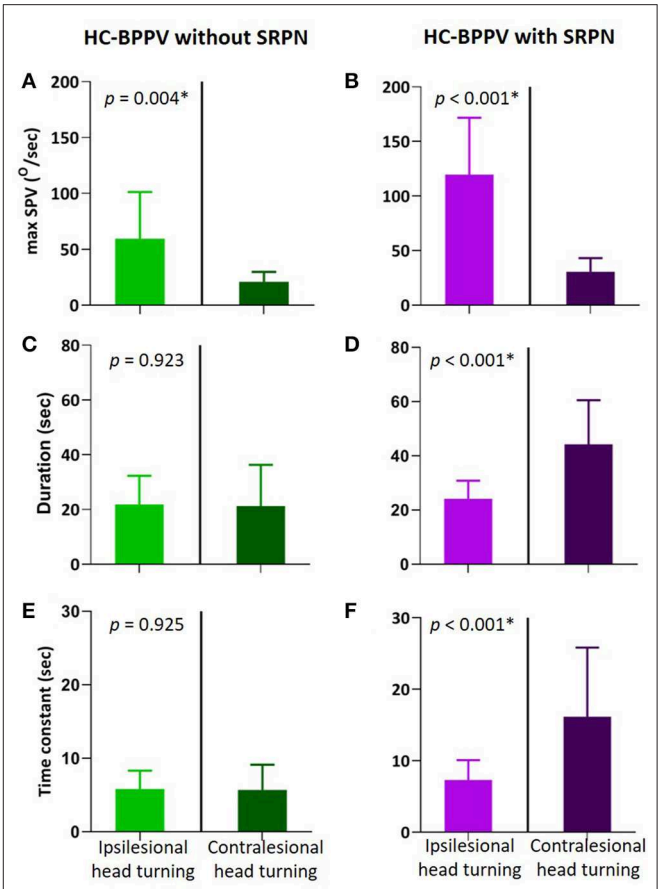

FIGURE 3 | Comparison of positional nystagmus between during ipsilesional and contralesional head turning in the first phase of horizontal canal benign paroxysmal positional vertigo (HC-BPPV) without and with spontaneous reversal of positional nystagmus (SRPN). **(A,B)** Maximal slow phase velocity (maxSPV) of positional nystagmus. The maxSPV is greater during ipsilesional than contralesional head turning in both of HC-BPPV with and without SRPN. Light green and purple columns are the mean of maxSPV during ipsilesional head turning, Dark green and purple columns are that during contralesional head turning. Their bars mean standard deviation. **(C,D)** Duration of the contralesional positional nystagmus (Dark purple) is significantly longer than the ipsilesional one in HC-BPPV with SRPN. **(E,F)** Time constant of positional nystagmus is also greater in contralesional than ipsilesional side of HC-BPPV with SRPN.

Treatment Responses Depending on the Presence of SRPN

The majority of patients with PC- (78%) and HC-BPPV (81%) immediately improved by repositioning maneuvers. The treatment response did not differ between patients with

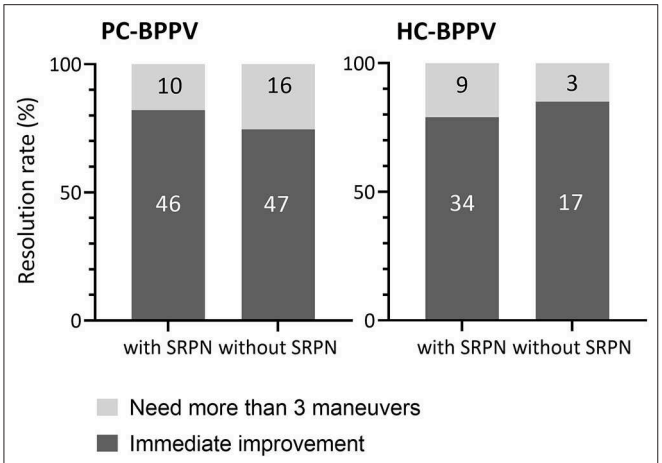

FIGURE 4 | Comparison of treatment outcome between patients with and without spontaneous reversal of positional nystagmus in benign paroxysmal positional vertigo. The number inside boxes means the number of patients. PC-BPPV, posterior canal benign paroxysmal positional vertigo; HC-BPPV, horizontal canal benign paroxysmal positional vertigo; SRPN, spontaneous reversal of positional nystagmus.

and without SRPN in both PC- and HC-BPPV ($p = 0.378$ and $p = 0.737$, respectively, Fisher's exact test, **Figure 4**). Except for only one patient with PC-BPPV, there was no remaining reversed positional nystagmus after the resolution of canalolith.

DISCUSSION

Our prospective data demonstrates that SRPN is common in both PC- and HC-BPPV canalolithiasis. Compared to previous retrospective analysis (9, 11), the frequency of SRPN in HC-BPPV was similar, but it was significantly higher in PC-BPPV (47 vs. 4%) (**Table 3**). The maxSPVs of positional nystagmus may be a major determinant for the development of SRPN in BPPV. The maxSPVs of positional nystagmus in both PC- and HC-BPPV were considerably greater in patients with SRPN than without. These results support earlier assumption that the presence of short-term reversal of positional nystagmus in BPPV and post-rotatory nystagmus in normal subjects may be determined by a certain velocity threshold from rotatory stimuli (4, 13). A small study reported that the maxSPV in the first phase should be over 50°/s to make the spontaneous reversal appeared in HC-BPPV (4). In post-rotatory nystagmus following horizontal rotation with earth vertical axis in normal human subjects, the initial rotatory stimuli (velocity) should be also stronger than about 70°/s for producing the secondary phase after-nystagmus (13).

For the explanation of SRPN in BPPV, several hypotheses have been previously proposed, which included the elastic force of cupula or the gravitational forces of otoconia debris, coexistence of cupulolithiasis, and short-term adaptation of VOR (4, 7, 9–11, 14). In our study, given long duration of the reversed phase of positional nystagmus, no significant correlation between nystagmus intensities in the first and reversed phases, and immediate disappearance of reversed nystagmus after treatment of canalolithiasis in most patients, the SRPN in BPPV may be ascribed to short-term central adaptation rather than peripheral mechanical forces or coexistence of cupulolithiasis. This type of adaptive phenomenon for the rotational VOR could be observed in normal human subjects using constant acceleration stimuli in rotatory chairs and the strong magnetic fields of MRI machines (6, 15–17). Using controlled step and ramp angular velocity stimuli with earth-vertical axis, after 100 s, a under 10°/s may develop with slow phases in the opposite direction (6, 15). Independence of the initial rotation velocity with the time reaching after post-rotatory nystagmus to maximal velocity or Tc of nystagmus in reversal phase reflects central adaptation, not simply pendulum model, neither physical factor such as canal size or endolymphatic viscosity as a mechanism for the phenomenon (13). Likewise, during the sustained magnetic vestibular stimulation (MVS), slow-phase velocity slowly decays back toward a new, but non-zero, baseline (16, 17). When the adaptive stimulus is abruptly removed, an after-effect appears, revealing the prior adaptation with oppositely directed slow phases that slowly fade away. A recent study identified a process that occurred over multiple time courses and simulations suggested that three adaptation integrators of varying dynamic properties could account for it (18). Our data also showed dynamic modulation of Tc of positional nystagmus in BPPV depending on the presence of SRPN. When the SRPN developed, Tc of positional nystagmus in PC-BPPV got shorter, while it became longer during contralesional head turning in HC-BPPV. And, the reversed nystagmus of HC-BPPV last longer than that of PC-BPPV. Although neural substrates responsible for short-term adaptive mechanism of VOR are not established yet, our finding suggests that the velocity-storage integrator could be a conduit for instant rebalancing activity. Disparity in the adaptive strategies between PC- and HC-BPPV would be attributed to difference in the intensity of rotational stimuli. The maxSPVs of positional nystagmus in PC-BPPV with SPRN were significantly lower than those of HC-BPPV with SRPN, indicating that immediate adaptive shortening of the velocity-storage mechanism, which would finally decrease the duration of reversed nystagmus, is probably effective only below a certain velocity limit. However, once the rotational stimuli exceed the velocity limit, central nervous system cannot utilize the strategy any more, and let the reversed nystagmus to be prolonged. Resultant adaptive property with oppositely directed bias may extend the vestibular response during contralesional head turning in HC-BPPV with SRPN. Similar extension of positional nystagmus was previously observed during contralesional head turning in HC-BPPV with SRPN (11). Set-point adaptation was implemented by adaptation operators, representing mathematical integrators of varying fidelity that feedback their output to be subtracted from the input signal (18). The greater the integrator time constant, the slower the pace of learning toward the new set-point but the reversal nystagmus (the after-effect) lasts longer (18).

The clinical implications of SRPN in BPPV remained to be elucidated. Earlier retrospective study stated that patients with BPPV and SRPN required more repositioning maneuver sessions, although not statistically significant (11). The authors assumed that the vigorous first phase nystagmus can be induced by the clustered large amount of otolith particles within SCCs

TABLE 3 | Summary of previous and our studies.

References	Canalolithiasis HC-BPPV						Canalolithiasis PC-BPPV				
	Age, year, mean (SD)	Sex, male, *n* (%)	unilateral SRPN	bilateral SRPN	without SRPN	Treatment response	Age, year	Sex, male, *n* (%)	with SRPN	without SRPN	Treatment response
Baloh et al. (4)	30–82 (range)	7 (54)	38.5% (5/13)	0% (0/13)	61.5% (8/13)	NA	NA	NA	NA	NA	NA
Lee et al. (9)	64 (8.3)	8 (38)	76.2% (16/21)	23.8% (5/21)	NA	Resolution SRPN (+) = 95.2% (20/21)	NA	NA	NA	NA	NA
Jeong et al. (11)	19–79 (range)	19 (30)	42.9% (27/63)	30.2% (19/63)	30.0% (17/63)	Resolution after one CRM unilateral SRPN (+) = 55.6% (15/27) bilateral SRPN (+) = 57.9% (11/19) SRPN (–) = 82.4% (14/17)	19–82 (range)	33 (36)	4.3% (4/92)	95.7% (88/92)	NA
Present study	63.7 (12.7)	18 (29)	47.6% (30/63)	20.6% (13/63)	31.7% (20/63)	Immediate resolution unilateral SRPN (+) = 80.0% (24/30) bilateral SRPN (+) = 76.9% (10/13) SRPN (–) = 85.0% (17/20)	62.6 ± 12.9 (mean ± SD)	49 (41)	47.1% (56/119)	52.9% (63/119)	Immediate resolution SRPN (+) = 82.1% (46/56) SRPN (–) = 74.6% (47/63)

PC, posterior canal; HC, horizontal canal; NA, not applicable; CRM, canalith repositioning maneuver; BPPV, benign paroxysmal positional vertigo; SRPN, spontaneous reversal of positional nystagmus.

which have left behind some particles at the end of repositioning maneuver requiring another repeated therapy (11). However, our study contradicts the prior supposition. We did not find any difference in the treatment outcome of BPPV canalolithiasis between groups with and without SRPN.

Our study has potential limitations. Since this study was based on the data from tertiary referral centers, the results from this study may not be applied to the community hospitals or the ambulatory care units. Our study included the small sample size of HC-BPPV with SRPN and consequent underpowered analysis, particularly for the various measures of positional nystagmus and treatment outcome. We eliminated patients with bilateral SRPN in HC-BPPV from the analysis because it was not clear which side more contributed to adaptation process. A selection bias is also possible because we analyzed positional nystagmus only in patients with clear tracing. PC-BPPV stimulate ipsilateral superior oblique muscle of which primary action is cyclotorsion, and torsional component of positional nystagmus may be well-correlated with the degree of excitation (1, 6, 19). However, due to poor recording with artifact in torsional tracing in the majority of patients with PC-BPPV, we could analyze vertical component of positional nystagmus only.

DATA AVAILABILITY STATEMENT

Anonymized data will be shared by request from any qualified investigator.

ETHICS STATEMENT

Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article. All experiments followed the tenets of the Declaration of Helsinki, and this study was approved by Institutional Review Board of Pusan National University Hospital (1402-003-014).

AUTHOR CONTRIBUTIONS

S-YC conducted the experiments, analyzed and interpreted the data, and wrote the manuscript. M-JL, EO, and J-HC conducted the experiments, and analyzed and interpreted the data. K-DC conducted the design and conceptualization of the study, interpretation of the data, and revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00260/full#supplementary-material

Video S1 | The first patient with right horizontal canal benign paroxysmal positional vertigo shows left-beating nystagmus lasting 50 s after head turning to

the left. When the patient's head is turned to right, vigorous right-beating nystagmus develops, and rapidly decays for 20 s, and then is followed by small left-beating nystagmus lasting more than 60 s. In the second patient with right posterior canal benign paroxysmal positional vertigo, right Dix-Hallpike maneuver provokes torsional-upbeating nystagmus lasting 10 s which spontaneously reverses its direction downward.

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Increased Otolin-1 in Serum as a Potential Biomarker for Idiopathic Benign Paroxysmal Positional Vertigo Episodes

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Objective: Otolin-1, a main specific otoconia matrix protein, passes through the labyrinth-blood barrier and is detectable in peripheral blood. Serum otolin-1 levels differ between patients with benign paroxysmal positional vertigo (BPPV) and healthy controls and are significantly age-related, increasing in healthy controls with age, suggesting that serum otolin-1 levels reflect otolith status. The aim of this study was to determine whether otolin-1 levels change during vertigo episodes in patients with BPPV and whether any change is specific and sensitive enough for BPPV episodes.

Method: Patients diagnosed with *de novo* idiopathic BPPV during an acute episode were included in the study from May 2017 to May 2018. Blood samples were drawn before patients were treated with canalith-repositioning maneuvers. Serum otolin-1 levels were compared between 78 patients and 121 age- and sex-matched healthy individuals.

Results: There were no significant differences between the groups in the age distribution, sex ratio, body mass index, clinical history, routine blood parameters, or total protein, albumin, uric acid, creatinine, blood urea nitrogen and lipid profiles ($P > 0.05$). Serum levels of otolin-1 were significantly higher in BPPV patients than in healthy controls ($P < 0.001$). Receiver operating characteristic analysis revealed that a serum otolin-1 value of 299.45 pg/ml was the optimal cut-off value to discriminate patients with BPPV from healthy controls (area under the curve 0.757, 95% CI 0.687∼0.826) with a sensitivity of 67.9% and a specificity of 72.7%.

Conclusion: Serum levels of otolin-1 may be a potential biomarker for BPPV episodes.

Keywords: otoconia, otolin-1, biomarker, vertigo, benign paroxysmal positional vertigo

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is one of the most common otoconia-related balance disorders, accounting for 36.5% of all dizziness complaints in the Chinese population (1, 2). BPPV is characterized by transient vertigo, nausea and nystagmus provoked by head position changes. BPPV diagnosis mainly relies on a typical history and positive provocative maneuvers (1, 3).

However, the diagnosis and management of nearly 30% of BPPV cases remain challenging, especially in subjective BPPV or cases with multiple canal involvement, and performing diagnostic positional maneuvers (e.g., in small children or frail elderly patients) can be difficult (4, 5). According to clinical practice guidelines, canalith repositioning maneuvers are recommended as the first approach to treat BPPV. Observation or "watchful waiting" is also a therapeutic option for BPPV (1, 6). Thus, the unnecessary examination and test of BPPV may result in increased costs for patients. Considering the high incidence of BPPV, it places a heavy burden on health care systems and society. Given these properties of BPPV, it is principally important to clarify its diagnosis. However, no laboratory indicators are currently available for establishing the diagnosis of BPPV.

Currently, it is widely accepted that the pathogenesis of BPPV involves the displacement of otoconia, which float into the semicircular canals or attach to the cupula of the semicircular canals, making them sensitive to gravity (7). Otoconia, as bone, are composed of Ca carbonate arranged as calcite crystals and are predominantly composed of the glycoproteins otolin-1 and otoconin 90, which make an organic core synthesized primarily during embryonic development, with calcification essentially completed by the seventh postnatal day (8–11). Otoconia are a dynamic calcium reservoir, and their repair and regeneration may occur throughout life (12–14). Dislodged otoconia can be dissolved in the endolymph, and matrix proteins are likely to be reabsorbed from the endolymph and released into circulation; however, little is known about these processes (15, 16). If proteins corresponding to inner ear diseases can be identified and tested with non-invasive techniques, then they have the potential to serve as biomarkers of inner ear health.

Otolin-1 is a secreted glycoprotein present mainly in otoconial crystals and fibrous membranes (17). It serves as a scaffolding protein that connects otoliths and otoconial core matrix proteins to the inner ear sensory epithelial and acellular gel matrix. Recently, studies reported that otolin-1 can be detected in serum and that its levels significantly increase with age, consistent with the age-related degeneration of otoconia (18–20). A preliminary study found that only one-third of patients with BPPV had higher serum otolin-1 values than those found in healthy controls because some of the enrolled BPPV patients were not in the acute stage (21). This promising result suggests that otolin-1 might have the potential to serve as a biomarker for acute episodes of BPPV.

The aim of this study was, therefore, to explore whether serum levels of otolin-1 can serve as a biomarker for distinguishing between acute episodes of BPPV and matched healthy controls without vertigo symptoms.

METHODS

All consecutive patients with a final diagnosis of *de novo* idiopathic BPPV during the attacks of vertigo at the Department of Neurology and Emergency, Hwa Mei Hospital, University of Chinese Academy of Science between May 2017 and May 2018 were included in this study. The diagnosis of BPPV was based on a typical history of recurrent, brief positional vertigo and clinical observation of characterized nystagmus during provocative maneuvers. The details of the diagnosis of BPPV were obtained according to the criteria established by the Barany Society (1, 3).

Some patients with persistent untreatable dizziness underwent head imaging, and other examinations were performed to exclude central nervous system disease. Patients with any history of head trauma, migraine, vestibular neuritis, Meniere's disease, sudden hearing loss, otitis media, ear surgery, severe organ dysfunction (e.g., chronic renal failure or liver or bile duct disease), malignant tumor or hormonal disorders were excluded. In addition, patients previously diagnosed with BPPV or multiple canal involvement were also excluded. The healthy control group included 121 volunteers with age and gender distributions similar to those of the study group; these individuals without a history of vertigo or dizziness were selected from the health check-up center of our hospital. We recorded all of the following data: age, sex, lifestyle habits, ongoing health problems, medication history, affected semicircular canal, onset time, initial assessment time and laboratory indicators.

This study was approved by our institutional review board (protocol number KY-2017-014-03) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects or his or her legal representative.

Measurement of Otolin-1 and Other Parameters

Morning fasting blood samples were collected from all subjects and centrifuged at 3000 rpm for 10 min at 4°C. Serum was then separated and frozen at −80°C until assays were performed.

Otolin-1 was measured using a human otolin-1 enzyme linked immunosorbent assay (ELISA) kit (QAYEEBIO, Shanghai, China) as described in the manufacturer's instruction manual, and each sample was tested in triplicate. Absorbance was measured using a microplate reader (Molecular Devices Spectra Max Plus 384) at a wavelength of 450 nm. Other parameters consisted of hematological and biochemical analyses were measured using an automated machine at the laboratory of our hospital. The laboratory staff who analyzed the samples were blinded to the group assignment of the study participants.

Statistical Analysis

SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA) was used to analyse all the data. The Kolmogorov-Smirnov test was used to test the data distribution. Quantitative values following normal distributions are expressed as the mean ± SD; if not, they are presented as the median and interquartile range (IQR). Qualitative variables are described as numbers and percentages. A *T*-test, chi-square test, Fisher's test or non-parametric Mann–Whitney *U*-test was used to compare the differences between groups. Receiver operating characteristic (ROC) analysis was performed to determine the sensitivity and specificity of serum otolin-1 for distinguishing patients with BPPV from healthy controls. All P-values < 0.05 were considered statistically significant.

RESULT

Demographics and Clinical Characteristics of the Subjects

A total of 78 patients diagnosed with *de novo* idiopathic BPPV at our institution were included during the study period. After excluding 14 patients who were diagnosed with secondary BPPV, 10 patients who were previously diagnosed with BPPV, 4 patients who refused to participate in the study, 3 patients with severe organ dysfunction, and 1 patient in whom both the posterior and horizontal canals were affected, the final study group comprised 52 women and 26 men, resulting in a female to male ratio of 2:1. The patient ages ranged from 33 to 81 years (mean age 62.7 ± 10.7), and there was a significant difference between women and men (60.7 ± 12.0 vs. 66.7 ± 5.9, $p = 0.004$). In addition, the prevalences of smoking and drinking were significantly higher in men than in women (**Table 1**). However, there were no significant differences in the age distribution, sex ratio, body mass index, clinical history, lipid profiles, blood panels, or blood urea nitrogen levels between the BPPV patients and healthy controls (**Table 2**).

Of the 78 patients with BPPV, the most common finding was otoconia dislocated in the posterior canal ($n = 49$, 62.8%), followed by horizontal otoconia ($n = 29$, 37.2%), which included 20 cases of canalolithiasis and 9 of cupulolithiasis. The interval between the onset of symptoms and the initial evaluation varied from 6 h to 20 days (mean = 4.85 days, median = 3.00 days), and 79.5% of the patients were evaluated within a week from symptom onset. The time between blood collection and symptom onset varied from 18 h to 20.5 days (mean = 5.38 days, median = 3.65 days), and 74.4% of the blood samples were collected within 7 days of symptom onset.

TABLE 1 | Clinical characteristics of benign paroxysmal positional vertigo patients.

	Female (52)	Male (26)	*P*
Age (years)	60.7 ± 12.0	66.7 ± 5.9	0.004
BMI (kg/m^2)	23.68 ± 3.23	23.10 ± 3.23	0.462
Hypertension [*n*(%)]	22 (42.3%)	12 (46.153%)	0.747
Diabetes [*n*(%)]	8 (15.38%)	5 (19.23%)	0.667
Smoking[*n*(%)]	4 (7.69%)	11 (42.307%)	0.001*
Drinking [*n*(%)]	5 (9.615%)	9 (34.615%)	0.007
Symptom onset to initial evaluation (D)	3.00 (1.00–5.75)	5.00 (1.00–7.00)	0.419
Symptom onset to blood sampling (D)	3.52 (1.66-6.06)	5.30 (1.76–7.50)	0.504
Subtype of BPPV			
PSCC [*n*(%)]	34 (65.4%)	15 (57.7%)	
LSCC canalolithiasis[*n*(%)]	13 (25.0%)	7 (26.9%)	
LSCC cupulolithiasis[*n*(%)]	5 (9.6%)	4 (15.4%)	

*Values are expressed as n (%), mean ± SD or median (interquartile range). P-values were calculated using an independent t-test, chi-squared test, Fisher's test or non-parametric Mann–Whitney U-test. PSCC, posterior semicircular canal; LSCC, lateral semicircular canal. P-values < 0.05 were considered significant. *Fisher's test.*

Serum Otolin-1 Levels in Patients With BPPV and Healthy Controls

Serum levels of otolin-1 were significantly higher in BPPV patients [median 324.55 pg/ml (IQR 282.68–383.68)] than in healthy controls [median 259.54 pg/ml (IQR 215.50–305.07)] ($p < 0.001$, Mann–Whitney *U*-test) (**Figures 1**, **2**). To evaluate the potential for serum otolin-1 in the diagnosis of BPPV, ROC analysis was performed. A serum otolin-1 value of 299.45 pg/ml was the optimal cut-off value to discriminate patients with BPPV from healthy controls (area under the curve 0.757, 95% CI 0.687∼0.826); this value had a sensitivity of 67.9% and a specificity of 72.7% (**Figure 3**).

DISCUSSION

In this pilot study, we measured serum otolin-1 levels in *de novo* patients with idiopathic BPPV and demonstrated that serum otolin-1 levels were significantly higher in these patients than in healthy controls. Furthermore, we found that high levels of serum otolin-1 (>299.45 pg/ml) may serve as a biomarker to differentiate patients with BPPV from control subjects,

TABLE 2 | Demographic and biochemical characteristics of benign paroxysmal positional vertigo patients and healthy controls.

	BPPV ($n = 78$)	Control ($n = 121$)	*P*
Age (years)	62.7 ± 10.7	61.4 ± 11.9	0.434
Sex (M/F)	52/26	79/42	0.841
BMI (kg/m^2)	23.48 ± 3.22	23.76 ± 2.98	0.534
Hypertension [*n*(%)]	34 (43.589%)	63 (52.06%)	0.243
Diabetes [*n*(%)]	13 (16.667%)	24 (19.83%)	0.575
Smoking[*n*(%)]	15 (19.23%)	31 (25.61%)	0.297
Drinking [*n*(%)]	14 (17.948%)	28 (23.14)	0.381
White blood cells (10^9/L)	6.08 ± 1.85	6.04 ± 1.86	0.853
Hemoglobin (g/L)	129.4 ± 16.2	132.0 ± 15.7	0.252
Platelets (10^9/L)	203.1 ± 45.6	191.7 ± 47.7	0.096
Total protein (g/L)	68.5 ± 5.9	68.0 ± 6.6	0.601
Albumin (g/L)	42.0 ± 3.7	41.8 ± 4.0	0.699
Creatinine (umol/L)	62.82 ± 15.57	66.09 ± 24.5	0.294
Blood urea nitrogen (mmol/L)	5.02 ± 1.29	5.25 ± 2.15	0.406
Uric acid (mmol/L)	293.68 ± 67.59	314.92 ± 107.79	0.122
Total cholesterol (mmol/L)	4.61 ± 1.27	4.60 ± 1.17	0.952
HDL-C (mmol/L)	1.28 ± 0.32	1.30 ± 0.33	0.712
LDL-C (mmol/L)	2.56 ± 0.91	2.58 ± 0.96	0.872
Triglycerides (mmol/L)	1.65 ± 1.61	1.57 ± 1.02	0.682

BMI, body mass index was defined as weight in kilograms divided by the square of height in meters; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Values are expressed as n (%) or mean ± SD. P-values were calculated using an independent t-test or the chi-squared test. P-values < 0.05 were considered significant.

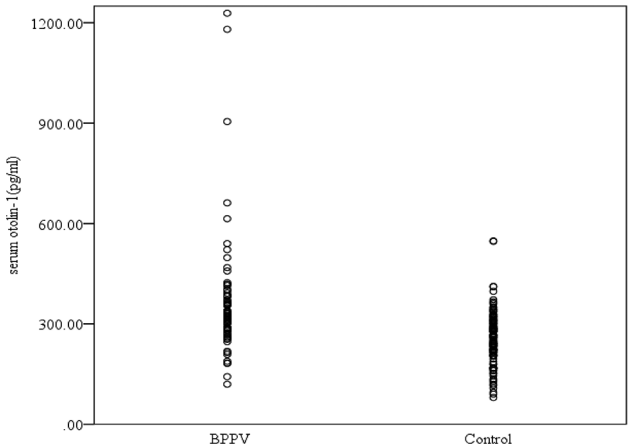

FIGURE 1 | Serum concentrations of otolin-1 in subjects with BPPV and healthy controls.

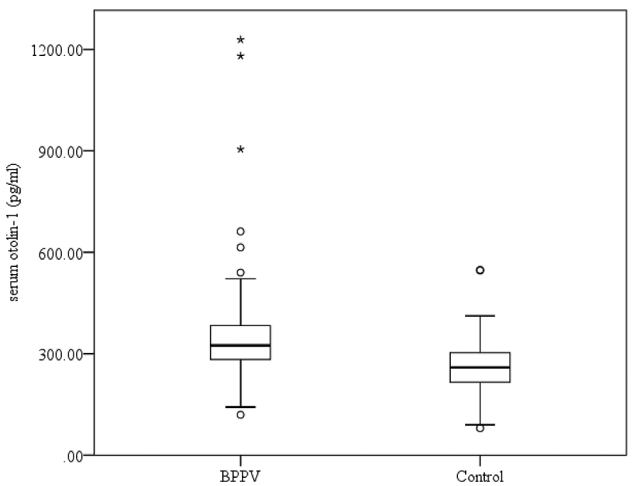

FIGURE 2 | Comparison of serum otolin-1 levels in subjects with BPPV and healthy controls.

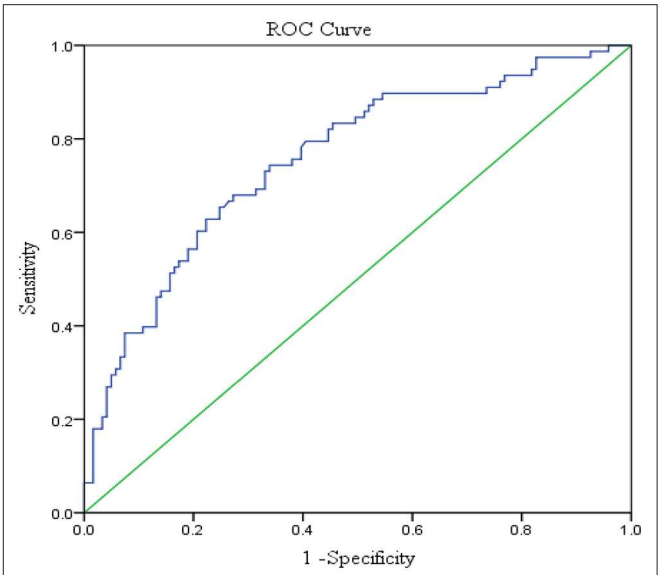

FIGURE 3 | Serum otolin-1 levels provided an area under the curve of 0.757, 95% CI (0.687∼0.826) (sensitivity = 67.9%, specificity = 72.7%) for BPPV patients vs. healthy controls.

suggesting the potential use of serum otolin-1 as a biomarker for BPPV episodes.

BPPV, an otoconia-related balance disorder, is the most common cause of vertigo in humans. The diagnosis of BPPV largely relies on a characterized clinical history and positional nystagmus during positive provocative maneuvers. However, this approach may be limited by the availability of trained specialists in view of the high incidence of vertigo. Importantly, in 30% of BPPV cases, management is challenging; this is especially true in patients with subjective BPPV or multiple canal involvement and in patients who find it difficult to perform diagnostic positional maneuvers, such as small children or frail elderly patients. In these cases, expensive and time-consuming investigations are required for inexperienced clinicians to diagnose and treat patients complaining of vertigo or dizziness, and delays in diagnosis or unreasonable treatment may result in increasing costs for patients. In Western countries, medical costs associated with the inappropriate diagnosis and treatment of BPPV can be as high as 2,684.74 US dollars per person (22). In studies from China, the missed or misdiagnosed rate of BPPV was as high as 60%, and the average expenditure was 1232.32 US dollars per patient. It has been estimated that the annual economic burden in Shanghai due to the unreasonable examination and treatment of BPPV was between 198.28 million and 1.14 billion US dollars (23, 24).

It is therefore necessary to explore laboratory markers as tools for achieving the quicker and more accurate diagnosis of BPPV. Various laboratory markers, such as neutrophil-lymphocyte ratios; serum vitamin D, C-reactive protein, DD dimer, fibrinogen, uric acid, and creatine kinase levels; or myocardial type and bone mineral density, have been investigated for the differential diagnosis and prediction of BPPV attacks, but some of these markers show no significant variation and may have no clinical application value (25–31).

Otoliths are dense crystals composed of calcium carbonate and an organic matrix and are primarily involved in gravity sensing by vestibular hair cells. Otoconia are synthesized primarily during embryonic development, and their calcification is essentially completed by the seventh postnatal day. The otoconial complex forms via a dynamic turnover process that occurs throughout an individual's lifetime. Otoconial degeneration and displaced otoconia falling into the canal are the leading causes of BPPV (1, 2, 7). It is known that most episodes of BPPV, even in untreated patients, recover spontaneously within 1–4 weeks because the dislodged otoconia can be dissolved in the endolymph (15, 18, 32). As we were not able to obtain inner ear tissue from the humans in real time, and there is currently no

suitable model to study this metabolic process, little is known about it.

Otolin-1 is an inner ear-specific collagen that forms a collagen-like scaffold that promotes optimal otoconia formation. It is a glycoprotein that is specifically secreted by the inner ear, and its messenger mRNA is strictly expressed in the support cells of vestibular maculae, semicircular canal cristae, the organ of Corti, and the marginal cells of the striavascularis (27, 28). Previous studies found that otolin-1 can pass through the labyrinth-blood barrier and enter the peripheral systemic blood circulation. Serum otolin-1 levels significantly increase with age, consistent with the finding that otoconia degeneration was age-related in a mouse model and data showing that the prevalence of BPPV increases with age. A pilot study measured serum otolin-1 levels in patients with BPPV and found that they were significantly higher in affected patients than in healthy controls, with only one-third of patients with BPPV having serum otolin-1 values higher than the control range (15). In addition, that study included only 14 patients with BPPV and 10 healthy controls, and some of the patients were not having an acute episode of vertigo; this may limit the valid generalization of their results. Recently, another clinical study reported that serum otolin-1 levels significantly increased in patients who underwent mastoidectomy due to chronic otitis media and were independently associated with the duration of drilling (33).

In our pilot study, we recruited 78 *de novo* idiopathic patients with BPPV during the attacks of vertigo, and most of these patients were evaluated within a week of symptom onset. We found that otolin-1 levels were significantly higher in the circulation of patients with BPPV than in that of healthy controls. ROC analysis showed that a cut-off value of 299.45 pg/ml of serum otolin-1 had a sensitivity of 67.9% and a specificity of 72.7% for suggestion of a BPPV episode.

These promising results suggested that serum otolin-1 levels may serve as a biomarker for BPPV episodes. However, serum otolin-1 levels cannot suggest which side semicircular canal is affected, and cannot distinguish the status of the displaced otoconia, such as canalithiasis or cupulolithiasis. Therefore, the marker serum otolin-1 has no guiding effect on which type of canalith repositioning maneuver can be used to treat BPPV.

This study, which represents the early phase of biomarker evaluation of BPPV, has some limitations. First, the sample size of the study was relatively small, and most of the study subjects were middle-aged or elderly individuals. No other subjects with vertigo or dizziness were selected as controls. The normal ranges of otolin-1 in healthy subjects and patients with vestibular migraine, vestibular paroxysmia, and neuritis vestibularis are still unknown. Indeed, it is unknown whether an increase in otolin-1 is clinically relevant to vestibular function. Second, the levels of otolin-1 differed among patients with BPPV, and the time between symptom onset and blood sample collection varied. We did not dynamically measure serum otolin-1 levels at different periods in patients with BPPV. It is unclear whether the serum levels of otolin-1 in patients with BPPV are correlated with the recurrence rate because the sample size was too small and the follow-up time was too short to draw specific conclusions. Third, the sensitivity and specificity of otolin-1 are not high. In the future, we will perform follow-ups to determine the otolin-1 levels or other possible biomarkers for otoconia, such as otoconin 90, at different stages of disease with a larger sample bigger study size to overcome the limitations of the current study.

CONCLUSION

Serum levels of the otolin-1 protein were significantly higher in patients with BPPV than in healthy controls and may serve as a potential biomarker for BPPV episodes and be used to promote better management of BPPV clinically. However, further studies should be conducted with larger patient cohorts and dynamic assessments of otolin-1 levels in different stages to establish its value.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this aricle are not publicly available. Requests to access the datasets should be directed to wu_yunqin@126.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Hwa Mei Hospital, University of Chinese Academy of Science (protocol number KY-2017-014-03). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YW and WH conceived and led the work. WH, WY, XL, MZ, LL, QG, and ZF acquired and checked medical records. YW and WH drafted and revised the manuscript with input from all co-authors.

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Correlation Between Benign Paroxysmal Positional Vertigo and 25-hydroxyvitamin D

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Objective: The correlation between benign paroxysmal positional vertigo (BPPV) and vitamin D levels was controversial. We explored age- and sex-related effects on 25-hydroxyvitamin D (25(OH)D) and correlation between 25(OH)D levels and BPPV.

Subjects and Methods: We recruited 380 patients with BPPV and collected 25(OH)D records of 3,125 control subjects who were further divided into age- and sex-based subgroups. We respectively investigated the effects of sex and age on 25(OH)D by comparing sex- or age-based subgroups. Then, we separately compared levels of 25(OH)D in sex-and age-based subgroups between the BPPV and control group.

Results: 25(OH)D levels in male subgroups were significant higher than those in female subgroup both in the BPPV and control group. With increasing age, 25(OH)D levels gradually increased, and there were significant between-subgroup differences for age in the control group. In males, the significant between-subgroup difference was observed only in the <40 year subgroup. Three female age-matched subgroups (<40, 40–49, and 60–69) showed significant between-subgroup differences.

Conclusions: There are sex and age differences in vitamin D levels. For both male and female patients with BPPV aged <40 years and female patients with BPPV aged 40–49 and 60–69 years, the lower vitamin D level is a risk factor for BPPV. In female patients with BPPV aged 50–59 and >70 years, and male patients with BPPV aged >40 years, the correlation between vitamin D and BPPV is non-existent.

Keywords: benign paroxysmal positional vertigo, 25-hydroxyvitamin D, otoconia, estrogen, lower, vitamin D

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common type of peripheral vestibular vertigo, with a lifetime prevalence of 2.4% and believed to be an otoconia-related balance disorder (1, 2). The pathophysiological processes of BPPV are well-established and involve falling into semicircular (canalolithiasis) or attaching to the cupula (cupulolithiasis) of otoconia debris which change the sensitivity of semicircular canals to gravity. Known predisposing factors for BPPV include advanced age, head trauma, vestibular neuritis, Meniere's disease, migraines, otologic surgery, and prolonged bed rest (3). However, there is little data on the underlying causes of otoconia degeneration and otoconial membrane detachments.

Vitamin D deficiency is a significant public health problem worldwide that affects almost all age groups. Approximately one billion people are affected by low vitamin D levels (4, 5). Besides modulating bone homeostasis, the use of vitamin D to prevent and treat non-skeletal health issues has gradually received significant media and research attention in recent years. In humans, observational data has suggested a link between poor vitamin D status and a large number of major human diseases including cancer, muscle weakness, falls, infections, autoimmune diseases, hypertension, cardiovascular disease, obesity, diabetes, metabolic syndrome, and other health problems (6, 7).

Previous studies have shown a link between seasonality variation, serum level of vitamin D and BPPV (8–13). However, some dissenting scholars believed that the correlation of vitamin D levels with BPPV cannot be proven by existing data and the observed coexistence of BPPV with vitamin D deficiency is coincidental (14, 15). Whether vitamin D levels is related to BPPV is still controversial. Furthermore, based on literatures quoted above, we found that almost all researchers did not seriously consider the possible effects of sex and age ratio differences (effect of sex and age differences on vitamin D status) on the results in their studies on the correlation between vitamin D and BPPV. In this study, we clarified if there were sex and age differences in vitamin D levels and then explored the correlation between vitamin D levels and BPPV after entirely eliminating the effect of sex and age on vitamin D levels by grouping.

MATERIALS AND METHODS

We identified 380 consecutive patients with first diagnosis of idiopathic BPPV from the First Affiliated Hospital of Harbin Medical University dizziness clinic between September 2015 and November 2018. These individuals included 283 females (age range = 19–85 years, mean age ± SD = 50.5 ± 13.5 years) and 97 males (age range = 21–83 years, mean age ± SD =51.3 ± 13.8 years). Diagnoses were confirmed via medical history and positive provocative maneuver (either Dix-Hallpike or Roll test). Among the 380 patients, 268 were diagnosed with posterior semicircular canal canalolithias, 69 were diagnosed with horizontal semicircular canal canalolithias and 43 were diagnosed with horizontal semicircular canalcupulolithiasis. In addition, we collected 25(OH)D records of 3,125 control subjects, including 1,919 females (age range = 18–92 years, mean age ± SD =50.6 ± 15.2 years) and 1,206 males (age range = 18–96 years, mean age ± SD =51.7 ± 15.1 years) from the Screening and Prevention of Disease health center of the First Affiliated Hospital of Harbin Medical University between January 2017 and December 2017. Fasting early morning venous blood from both BPPV patients and control subjects were measured serum 25-hydroxyvitamin D (25(OH)D) levels using the automatic chemiluminescence immunoassay analyzer (Liaison XL, Type 2210, DiaSorin S.p.A, USA) and concentrations between 30 and100 ng/ml were considered normal. The study excluded patients with comorbidities including Meniere's disease, vestibular neuritis, head trauma within three months, vestibular migraine, those with a history of total thyroidectomy, patients who took calcium or vitamin D therapy for one year before the study, or those with histories of prolonged bedrest secondary to orthopedic surgery within the past six months. The Ethics Committee of the First Affiliated Hospital of Harbin Medical University approved the study. All patients who could be personally contacted gave consent for publication. Collected information was anonymized by code numbers and solely used for this study.

This study was divided into two parts. In the first part of this study we clarified whether age and sex had an effect on vitamin D levels. First, both the BPPV and control group were each divided into two subgroups according to sex (male and female). By comparing 25(OH)D level in male subgroup with that in female subgroup, we investigated the effects of sex on vitamin D levels in the BPPV and control group, respectively. Then we investigated the effects of age on vitamin D levels, which was divided into two steps. The first step, the linear correlation between age and vitamin D was tested by linear by linear association in the control group. The second step, the control group was divided into subgroups according to age (18-29, 30-39, 40–49, 50–59, 60–69, 70-79, and >80 years). Six control subjects aged over 90 years were classified into >80 year subgroup. We investigated the effects of age on vitamin D levels by comparing 25(OH)D levels between different age-based subgroups.

In the second part of this study, both the BPPV and control groups were each divided into subgroups according to sex (male and female) and age (<40, 40–49, 50–59, 60–69, and >70 years). The BPPV patients in both 18–29 and 30–39 age segment were sparse in this study and there was no statistical difference in vitamin D levels between 18–29 and 30–39 year subgroup in control group which had been validated in the first part of the study, hence we classified the BPPV patients under 40 years old into <40 age subgroup. Likewise, we classified the BPPV patients over 70 years old into >70 age subgroup. We matched the two subgroups with the same sex and age segment from the BPPV and control group respectively. By comparing 25(OH)D levels of the two matched subgroups, we separately investigated the correlations between vitamin D and BPPV in each sex and age segment.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics 19 for Windows. The correlation between age and 25(OH)D levels was tested by linear-by-linear association, one-way ANOVA and followed multiple comparison tests. In multiple comparison tests, Tamhane's T2 is appropriate when the variances are unequal. Between-subgroup comparisons were made by using T test, ANOVA test and, if necessary, Welch's ANOVA. The Mann-Whitney test was also used when the sample size of any subgroup was <30. A value of $P < 0.05$ was considered statistically significant.

RESULTS

In the control group, the 25(OH)D level in male subgroup was higher than that in female subgroup and the sex-based difference was statistically significant. ($T = 4.086$, $P_{control} < 0.01$). In the

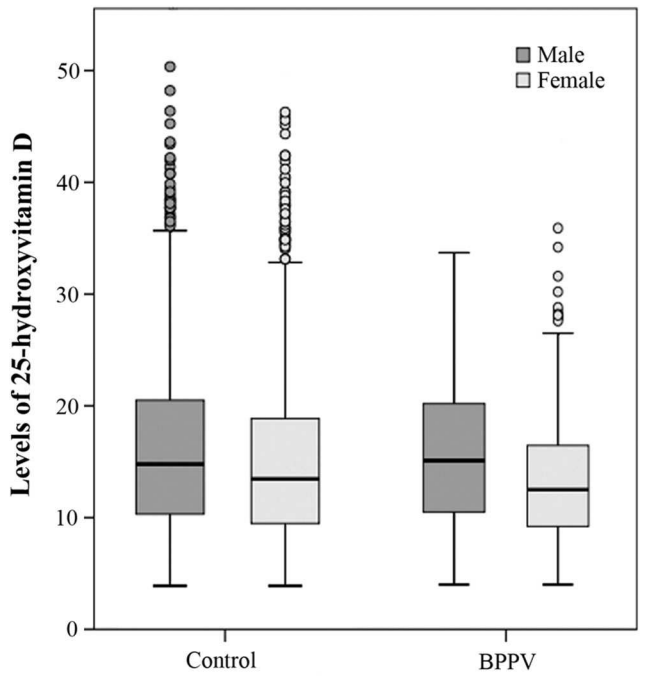

FIGURE 1 | Box blots of 25-hydroxyvitamin D levels in females and males in both the control and BPPV groups. The dark gray box blots indicate male levels of 25(OH)D and the light gray box blots indicate female levels of 25(OH)D. Each box indicates a percentile range of 25–75%, the lines through the boxes represent the medians, and the range lines indicate the upper and lower values that are not classified as statistical outliers. Circles denote 25(OH)D concentrations that are statistical outliers.

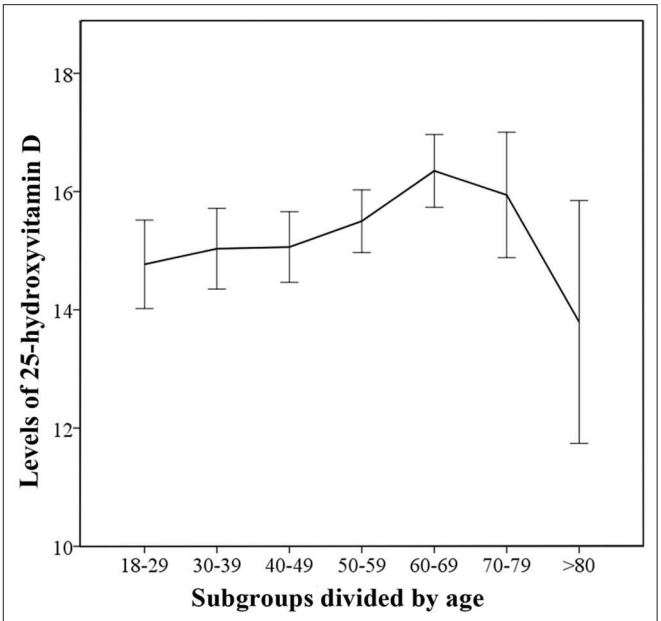

FIGURE 2 | Trends for 25-hydroxyvitamin D levels in different age-based subgroups for control group. The median 25(OH)D levels in the age-based subgroups are indicated and error bars show 95% confidence interval.

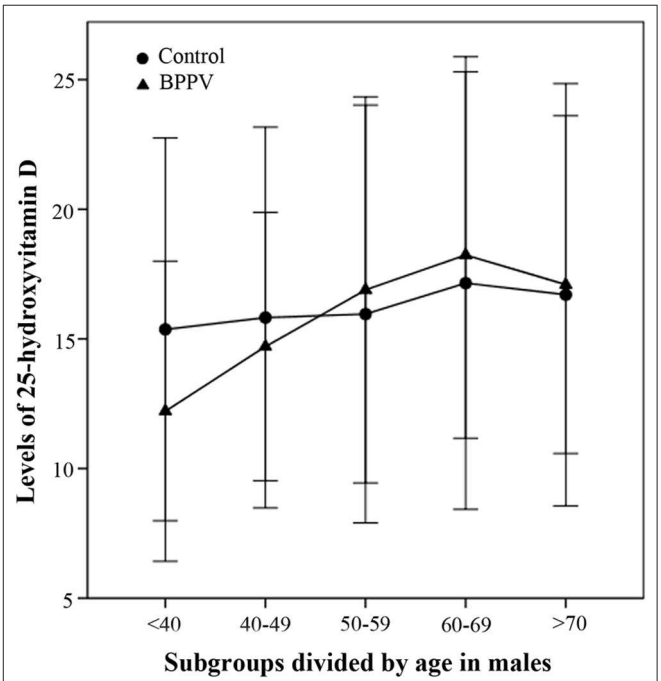

FIGURE 3 | Comparison of male 25-hydroxyvitamin D levels between the BPPV and control subgroups divided by age. The median levels of 25(OH)D levels in subgroups divided by age are indicated by black circles in the control group and by black triangles in the BPPV group. Error bars show standard deviation.

BPPV group, the male 25(OH)D level was also higher than the female 25(OH)D level (**Figure 1**). The sex-based difference was also statistically significant. ($T = 2.996$, $P_{BPPV} < 0.01$) These results confirmed that there were sex differences in vitamin D levels which were higher in males than in females.

In the control group, the 25(OH)D levels gradually increased with age, peaking for subjects in 60–69 subgroup (**Figure 2**). The linear-by-linear association showed that there was a linear trend between age and 25(OH)D levels. ($Z = 8.192$, $P < 0.01$) There were significant between-subgroup differences for age in the control group by one-way ANOVA ($F_{welch} = 2.954$ $P < 0.01$) and the followed multiple comparison tests showed statistically significant differences in vitamin D levels between 60–69 and 18–29 subgroup. ($P_{Tamhane} < 0.05$) The results confirmed that there were age differences in vitamin D levels.

In the second part of this study, the 25(OH)D levels of males in the BPPV group increased rapidly with age and peaked at age 60–69 years (**Figure 3**). The 25(OH)D levels of males aged <40 and 40–49 years in the BPPV group were, respectively, lower than those in the control group; however, the significant between-subgroup difference was observed only in the <40 year subgroup ($P_{Mann-Whitney} < 0.01$). There were no significant between-subgroup differences for the other four male age-matched subgroups (40–49, 50–59, 60–69, and >70 year subgroups).

In females, the 25(OH)D levels of females aged <40, 40–49, and 60–69 in BPPV group were respectively lower than those in the control group (**Figure 4**). Three female age-matched

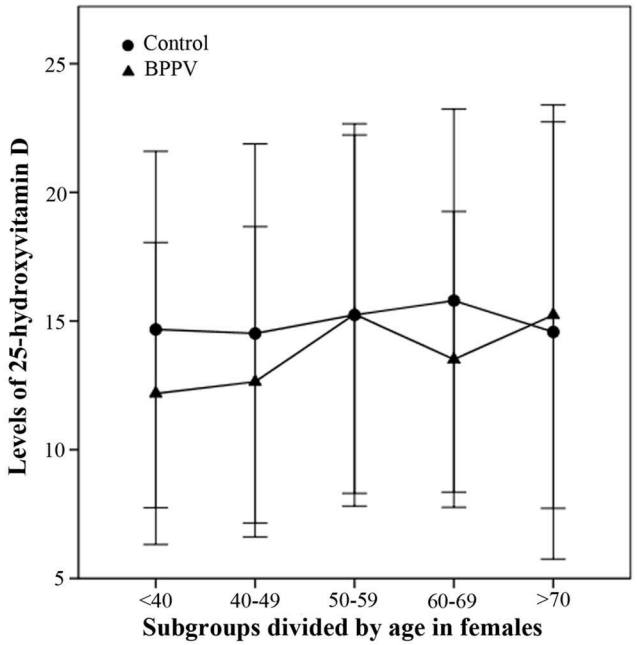

FIGURE 4 | Comparison of female 25-hydroxyvitamin D levels between BPPV and control subgroups divided by age. The median levels of female 25(OH)D in subgroups divided by age are indicated by black circles in control group and by black triangles in BPPV group. Error bars show standard deviation.

subgroups (<40, 40–49, and 60–69) showed significant between-subgroup differences (T = 2.673, $P = 0.008$ for <40; T = 2.281, $P = 0.024$ for 40–49; T = 2.524, $P = 0.014$ for 60–69). There were no significant between-subgroup differences for the other two female age-matched subgroups (50–59 and >70) (**Figure 4**). The results of the second part in this study showed that correlation between vitamin D and BPPV was diverse and varied according to sex and age segment.

DISCUSSION

In the first part of the study, the 25(OH)D levels of males were significant higher than those of females both in the BPPV and control groups. So we concluded that sex can affect vitamin D status, which was consistent with some current studies (16, 17). In addition, we found that 25(OH)D levels gradually increased with aging which showed significant age-based differences. We believed that there were age differences in vitamin D levels which was also consistent with previous research results (18, 19).

On account of sex and age differences in vitamin D levels, in the second part of the study both the BPPV and the control group were each divided into subgroups according to sex and age segment, and the possible effect originated from sex or age ratio inconsistency can be entirely eliminated when comparing the vitamin D levels between the BPPV and the control group.

We found that the 25(OH)D levels of both males and females aged <40 years in the BPPV group were significantly lower than those in the control group. The findings confirm the close correlation between BPPV and 25(OH)D in BPPV patients younger than 40 years of age. We think that the lower vitamin D level is a risk factor for BPPV in patients aged <40 years.

The etiology of BPPV is widely believed that otoconia (calcium carbonate crystals) dislodge from the macula of the utricular otolith and enter the semicircular canals and/or ampulla of the semicircular canals (canalithiasis and/or cupulolithiasis, respectively). Otoconia results from ordered deposition of inorganic calcium carbonate crystallites onto a preformed framework, consisting of an organic matrix. The ultrastructure and function of the otoconial matrix for regulating crystal growth resembles that of bone turnover. Many studies confirmed that otoconia including its frame and organic matrix were in a process of constant renewal. The morphology of the otoconia of the rat utricle and saccule changed and the calcium content of the otoconia decreased after 160-days of tail suspension (20). Vibert et al. reported ultrastructural modifications of the otoconia in terms of changes in their aspect, size and density in ovariectomized osteoporotic female adult rats; the otoconia were increased in size and decreased in their density as compared to a control group of rats (21).

As turnover in otoconia is an ongoing process, the lower vitamin D level may disturb formation of otoconia or otoconial membrane by giving rise to disequilibrium of calcium homeostasis in vestibular endolymph, which may lead to the emergence of dislodged otoconia. The dislodged and undissolved otoconia ultimately induce endolymph flow on head movement or convert structures sensitive to angular acceleration into linear acceleration, which is the fundamental pathophysiological process in BPPV. Cao et al. confirmed in patients with BPPV that the particulate matter in the semicircular canals consisted of broken-off fragments of the utricular otolithic membrane with attached or detached otoconia (22).

It is important to maintain a low Ca^{2+} concentration in the vestibule endolymph because it prevent the production of abnormal otoconia which can result in dysfunction (8, 23). Moreover, an increased Ca^{2+} concentration in the vestibular endolymph can induce reduction in its capacity to dissolve the detached otoconia (21, 24, 25). It is known to all that the epithelial Ca^{2+} channel transport system, Na^{+}/Ca^{2+} exchangers, and plasma membrane Ca^{2+} pumps expressed in the inner ear contribute to this low calcium levels in vestibular endolymph by transepithelial absorption of Ca^{2+}. Yamauchi et al. confirmed epithelial Ca^{2+} channel transport system in semicircular canal duct could maintain low Ca^{2+} concentration in vestibular endolymph; particularly, they found that epithelial Ca^{2+} channel can be upregulated by 1, 25-dihydroxyvitamin D (26). Therefore, we speculate that the lower vitamin D level is likely to affect the formation of otoconia or resorption of detached otoconia by disturbing the calcium concentration of utricular endolymph in BPPV. This can also explain the findings that low vitamin D levels appear associated with recurrent BPPV and BPPV recurrences can be relieved with vitamin D supplementation (8, 9, 11). In recurrent BPPV patients, it is likely that the detached otoconia cannot be reabsorbed normally and eventually fall back into the semicircular canal again.

TABLE 1 | 25(OH)D levels (ng/ml) and number in subgroups divided by sex and age.

	Male		Female	
	BPPV	**Control**	**BPPV**	**Control**
<40	12.21 ± 5.79 (17)	15.37 ± 7.38 (270)	12.18 ± 5.87 (60)	14.67 ± 6.92 (491)
40–49	14.70 ± 5.18 (21)	15.82 ± 7.34 (244)	12.64 ± 6.03 (70)	14.51 ± 7.37 (342)
50–59	16.89 ± 7.45 (27)	15.95 ± 8.06 (293)	15.27 ± 6.96 (79)	15.24 ± 7.43 (512)
60–69	18.24 ± 7.07 (25)	17.15 ± 8.73 (267)	13.51 ± 5.75 (49)	15.79 ± 7.44 (384)
>70	17.09 ± 6.51 (7)	16.71 ± 8.14 (132)	15.23 ± 7.51 (25)	14.58 ± 8.82 (190)

25-hydroxyvitamin D levels are shown average ± standard deviation. The number in parentheses indicates the number of samples.

In female BPPV patients, 25(OH)D levels in the 40–49 and 60–69 age subgroups were both significantly lower than those in the corresponding control subgroups. Therefore, we think that the lower vitamin D level is also a risk factor for BPPV in female patients aged 40–49 and 60–69 years.

In this study, the females BPPV patients aged 50–59 years has the highest proportion in all BPPV patients (**Table 1**), which is consistent with the findings of other scholars (2). However, it is very special that the 25(OH)D level in 50–59 year subgroup was very close to that in the corresponding control subgroup, which showed no statistical difference. This implies that the vitamin D level have nothing to do with BPPV in female patients aged 50–59 years.

Females usually start amenorrhea around age 50 when estrogen levels begin to rapidly decrease. The decline of estrogen weakens its inhibitory effect of on osteoclasts and therefore the activity of osteoclasts is increased. In addition, the rapid decline of estrogen also inhibits intestinal calcium absorption and reabsorption of urinary calcium, which in turn disturbs and causes loss of bone mass. As turnover in the otoconia is ongoing, such disturbances of calcium metabolism may generate failures in the remodeling of the internal structure and the attachment of otoconia on the otoconial membrane (25). A previous morphometric analysis revealed that the otoconia in ovariectomized rats shown larger volume and less dense than those in the control group (21). Yang et al. also revealed that estradiol deficiency was an essential risk factor for idiopathic BPPV in postmenopausal females (27).

It seems that estrogen deficiency, not the lower vitamin D level, is related to BPPV and lead to the highest BPPV incidence in female BPPV patients aged 50–59 years. Is it true? If estrogen deficiency is a risk factor for BPPV, females aged 60–69 years in this study should have a higher proportion than those aged 50–59 years because of lower estrogen levels along with aging. But the fact was that females aged 50–59 years had the highest proportion in all BPPV patients. In addition, it is particularly in this study that the female BPPV patients aged 60–69 years with the lower estrogen than those aged 50–59 years, showed statistically significant decrease in the 25(OH)D level compared with the corresponding control subgroup, which affirm the lower 25(OH)D level is a risk factor for female BPPV patients aged 60–69 years.

Estrone, a weak estrogen, is gradually become the primary ingredient of estrogen after amenorrhea in females. The estrone conversion rate in postmenopausal females is twice as fast as that in females of childbearing age and blood estrone concentrations range from 90 to 150 pmol/L. In postmenopausal women, although the estrogen levels are greatly reduced, the estrone which replaced estradiol can maintain basically normal physiological functions such as metabolic equilibrium of calcium. Thus, we conjecture that the lower vitamin D level and the rapid decline in estrogen are both risk factors for BPPV in female patients, and the correlation between vitamin D and BPPV in female BPPV patients aged 50–59 years is covered up by the rapid decline in estrogen caused by amenorrhea. Without the impact of sudden estrogen decline in females aged 60–69 years, we can detect it again that the lower 25(OH)D level is a risk factor for BPPV. It is the rapid decline in estrogen, not estrogen deficiency that led to the highest incidence of BPPV in females aged 50–59 years (28). It is well known that estrogen replacement therapy is beneficial to rehabilitate disordered calcium metabolism and prevent osteoporosis for females in perimenopausal period. We think that such strategies should be considered by doctors and involved in the treatment and prevention of BPPV in females undergoing perimenopause, which is consistent with the view of other scholars (29).

There were no significant between-subgroup differences in 25(OH)D levels for three male age-matched subgroups (40–49, 50–59, and 60–69 year subgroups). We think that vitamin D has nothing to do with BPPV in males aged 40–69 years.

For both male and female BPPV patients aged >70 years, the 25(OH)D levels were not lower but slightly higher than those in the control subgroup, which showed no statistical significance. We think that vitamin D levels has nothing to do with BPPV patients over 70 years old. Senile osteoporosis, formerly known as primary osteoporosis type II, has a particular pathophysiology. It appears very late in life, typically after 70 years old, and involves thinning of both the trabecular and cortical bones. On account of otoconia form in a manner similar to bone and primary osteoporosis type II also generally occur over 70 years old, we speculate that the occurrence of BPPV in adults older than 70 years is related to senile osteoporosis, which requires further research.

One limitation of this study is that in the BPPV group, the sample size in each male age-based subgroup was relatively small, which might compromise the generality of the results. The ratio of female to male for BPPV patients in this study was close to 3:1 and therefore the incidence of BPPV in males was obviously lower than that in females. Besides, the BPPV group was further divided into subgroups according to sex and age segment, which eventually led to small sample size in male age-based subgroups. Future research would expand the sample size, especially the male BPPV patients to consolidate the generality of the results. This study found the degree of correlation between the lower vitamin D level and BPPV in males was much lower than that

in females. It was due to relatively small sample size in male subgroups or other reasons, which need further clarification in future research.

CONCLUSION

We affirm that there are sex and age differences in vitamin D levels. For both male and female patients with BPPV aged <40 years and female patients with BPPV aged 40–49 and 60–69 years, the lower vitamin D level is a risk factor for BPPV. In female patients with BPPV aged 50–59 and >70 years, and male patients with BPPV aged >40 years, the correlation between vitamin D and BPPV is non-existent.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of the First Affiliated Hospital of Harbin Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PS and XZ: design or conceptualization of the study, analysis or interpretation of the data, and drafting or revising the manuscript for intellectual content. YX: analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. ZZ and YL: drafting or revising the manuscript for intellectual content. LW: revising the manuscript for intellectual content. QG: interpretation of the data, revising the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Risk Factors for the Occurrence of Benign Paroxysmal Positional Vertigo: A Systematic Review and Meta-Analysis

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Background and Purpose: The lifetime prevalence of benign paroxysmal positional vertigo (BPPV) is high, especially in the elderly. Patients with BPPV are more susceptible to ischemic stroke, dementia, and fractures, severely reducing quality of life of patients. Many studies have analyzed risk factors for the occurrence of BPPV. However, the results of these studies are not identical. We performed this meta-analysis to determine potential risk factors associated with the occurrence of BPPV.

Methods: PubMed, EMBASE, and the Cochrane Library (January 2000 through March 2020) were systematically searched for eligible studies analyzing risk factors for the occurrence of BPPV. Reference lists of eligible studies were also reviewed. We selected observational studies in English with a control group and sufficient data. Pooled odds ratios (ORs) or the mean differences (MDs) and 95% confidence intervals (CIs) were calculated to measure the impacts of all potential risk factors. Heterogeneity among studies was evaluated using the *Q*-test and I^2 statistics. We used the random-effect model or the fixed-effect model according to the heterogeneity among the included studies.

Results: We eventually included 19 studies published between 2006 and 2019, including 2,618 patients with BPPV and 11,668 participants without BPPV in total. In this meta-analysis, the occurrence of BPPV was significantly associated with female gender (OR = 1.18; 95% CI, 1.05–1.32; $P = 0.004$), serum vitamin D level (MD = −2.12; 95% CI, −3.85 to −0.38; $P = 0.02$), osteoporosis (OR = 2.49; 95% CI, 1.39–4.46; $P = 0.002$), migraine (OR = 4.40; 95% CI, 2.67–7.25; $P < 0.00001$), head trauma (OR = 3.42; 95% CI, 1.21–9.70; $P = 0.02$), and total cholesterol level (MD = 0.32; 95% CI, 0.02–0.62; $P = 0.03$).

Conclusion: Female gender, vitamin D deficiency, osteoporosis, migraine, head trauma, and high TC level were risk factors for the occurrence of BPPV. However, the effects of other risk factors on BPPV occurrence need further investigations.

Keywords: benign paroxysmal positional vertigo, risk factors, occurrence, systematic review, meta-analysis

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is one of the most common types of vestibular vertigo, accounting for ∼17–42% of patients with vertigo (1, 2). Patients suffering from BPPV are characterized by transient episodes of vertigo provoked by head position changes (3). The lifetime prevalence of BPPV is estimated at 2.4%, and the 1-year prevalence of BPPV in the elderly is much higher than that in other age groups (4). In addition, some studies have suggested that patients with BPPV were more susceptible to future ischemic strokes, dementia, and fractures, which severely reduces quality of life of patients, especially in the elderly (5–7). Thus, identifying potential risk factors for the occurrence of BPPV can help prevent this disease. Furthermore, some serum indicators may also help improve the clinical misdiagnosis of some atypical BPPV.

Although canalith repositioning maneuver is an effective treatment for BPPV, nearly 50% of patients experienced at least one recurrence in 2 years after treatment (8). Many of the risk factors investigated in this meta-analysis, such as hypertension and migraine, may also be risk factors for BPPV recurrence, which may help improve the treatment and prognosis of this disease (9).

However, the underlying causes of BPPV remain unclear. In recent decades, many studies have investigated risk factors for the occurrence of BPPV, including female gender, serum vitamin D deficiency, osteoporosis, vascular risk factors, head trauma, and other potential risk factors (10–26). However, there are some controversies among these studies. The primary purposes of this meta-analysis are to identify the underlying risk factors for BPPV occurrence and summarize the evidence for screening high-risk populations to reduce the incidence of BPPV.

METHODS

Literature Search Strategy

The electronic databases PubMed, EMBASE, and the Cochrane Library (January 2000 through March 2020) were systematically searched by two researchers (JB Chen and WS Zhao) for eligible observational studies analyzing risk factors for the occurrence of BPPV. The MeSH terms "Risk Factors," "Benign Paroxysmal positional vertigo," and all related free words were combined to search relevant literature as comprehensively as possible. Reference lists of all eligible studies were also reviewed to identify other potentially relevant studies.

Selection Criteria

Articles included in this meta-analysis must meet the following criteria: (1) clearly define the experimental group (patients diagnosed with BPPV) and the control group (participants or patients without any history of vertigo); (2) all BPPV patients included in studies were diagnosed by a characteristic history of recurrent positional vertigo or a typical nystagmus during Dix-Hallpike tests or Roll test; (3) reported sufficient data on risk factors investigated in our meta-analysis; (4) the outcome was BPPV; (5) case–control studies, cohort studies, or other observational English studies analyzing relevant risk factors for occurrence of BPPV. The following studies were excluded from this meta-analysis: (1) sufficient information could not be obtained; (2) the outcome was the recurrence of BPPV, not the occurrence of BPPV.

Data Extraction and Quality Assessment

Two reviewers (JB Chen and WS Zhao) independently assessed the quality of each study included in this meta-analysis using the Newcastle Ottawa Scale (27). Studies were evaluated according to three dimensions including selection, comparability, and outcome (cohort studies) or exposure (case–control studies). Any discrepancies between the two reviewers were resolved through discussion with another author (XJ Yue). The total NOS scores of all included articles are shown in **Table 1**. Studies with NOS scores $\geq$7 were considered high quality.

A standardized pre-extraction form was used to extract available data, including study characteristics, sample demographic information, medical comorbidities, and serum indicators. For each risk factor, we performed a detailed analysis and compared their definitions in the original literature. Data extraction was independently completed by the same two reviewers according to the revised extraction form from January 2020 to February 2020. All disagreements between the two reviewers were fully discussed, and furthermore a third reviewer (XJ Yue) was consulted for unresolved discrepancies to reach a consensus. The following data were extracted for each included study: (1) Study characteristics: fist author, study region, sample size, publication year, and study design (case–control or cross-sectional study); (2) sample demographic information: gender, age (mean ± SD), body mass index (BMI), smoking, drinking, and regular exercise; (3) medical comorbidities of participants: osteoporosis, osteopenia, migraine, stroke, head trauma, hypertension (HTN), diabetes mellitus (DM), and hyperlipidemia; (4) serum indicators: total cholesterol level (TC) (mmol/L) and serum vitamin D level (ng/ml).

Statistical Analysis

The impacts of all potential risk factors on the occurrence of BPPV were measured by calculating odds ratios (ORs) or mean differences (MDs) and 95% confidence intervals (CIs). ORs were calculated for categorical variables including female gender, osteoporosis, osteopenia, migraine, stroke, head trauma, hypertension, DM, hyperlipidemia, smoking, drinking, and regular exercise. MDs were calculated for continuous variables including age, serum vitamin D level, and TC level. Heterogeneity among studies was tested and quantified using the Cochrane Q-test and I^2 statistics. A fixed-effect model was used when heterogeneity was not significant ($I^2 < 50\%$) and a random-effect model was used when heterogeneity was significant ($I^2 > 50\%$) (30). In addition, funnel plots of some risk factors were used to assess the publication bias in included studies. All statistical analyses were performed using the Review Manager 5.3 software.

TABLE 1 | Baseline characteristics of each study included in this meta-analysis.

Reference	Study region	Study design	Sample size (case/control)	Mean age (SD/IQR)	BMI (mean ± SD)	Risk factors included	NOS score
Karataş et al. (12)	Turkey	Case–control study	78/78	51.4 ± 12.2/48.9 ± 12.5	26.2 ± 3.0/26.0 ± 2.3	F1, F2, F3, F4, F9, F10, F15	7
Yuan et al. (20)	Beijing, China	Case–control study	240/72	62.4 ± 12.5/63.5 ± 11.9	24.9 ± 2.9/25.6 ± 2.8	F1, F2, F12	7
Celikbilek et al. (26)	Turkey	Case–control study	50/40	33.4 ± 6.15/32 ± 6.74	25.31 ± 2.35/24.47 ± 2.77	F1, F2, F12	6
Yang et al. (14)	Korean	Case–control study	130/130	54.9 ± 12.2/54.9 ± 12.2	NA	F1, F2, F3, F4, F5	7
Işik et al. (10)	Turkey	Case–control study	64/63	NA	NA	F1, F3	6
Cai et al. (17)	Lanzhou, China	Case–control study	154/100	Median 37/37 (IQR 31–43/30–43)	Median 25.3/24.5 (IQR 24.1–27.0/24.3–27.5)	F1, F13, F14, F15	5
Jeong et al. (15)	Korean	Case–control study	100/192	61.8 ± 11.6/60.3 ± 11.3	24.9 ± 3.4/23.3 ± 3.6	F1, F2, F3, F4, F5, F9, F10, F15	9
Ding et al. (25)	Lanzhou, China	Cross-sectional study	174/348	Median 61/61 (IQR 54–69/54–69)	Median 25.8/26.0 (IQR 24.3–27.4/24.4–27.6)	F1, F9, F10, F11, F13, F14, F15	7
von Brevern et al. (4)	Germany	Cross-sectional study	53/6136	NA	NA	F1, F6, F7, F9, F10, F11, F13	5
Jeong et al. (23)	Korean	Case–control study	209/202	59.8 ± 12.5/56.3 ± 8.6	NA	F1, F2, F4, F5, F9, F10, F11, F13, F14	8
Han et al. (22)	Ningbo, China	Case–control study	85/80	63.5 ± 9.72/63.9 ± 9.87	23.8 ± 3.02/23.6 ± 3.29	F2, F3, F4, F5, F9, F10	6
Wu et al. (24)	Ningbo, China	Case–control study	78/126	58.4 ± 11.4/58.5 ± 10.3	22.69 ± 3.34/23.48 ± 3.28	F2, F4, F5, F9, F10, F15	6
Wu et al. (11)	Ningbo, China	Case–control study	60/92	59.4 ± 13.2/62.1 ± 10.6	23.6 ± 2.8/23.9 ± 2.8	F2, F3, F4, F5, F9, F10, F13, F14	7
Zhang et al. (19)	Zhengzhou, China	Case–control study	104/88	73/71 (Range 65–88/65–84)	NA	F1, F9, F10	5
Yang et al. (18)	Shanghai, China	Case–control study	50/52	NA	22.62 ± 2.47/24.74 ± 12.7	F3, F9, F10	7
Chang et al. (13)	Taiwan, China	Case–control study	768/1,536	57 ± 15/57 ± 15	NA	F1, F2, F4, F6, F7, F8, F9, F10, F11	9
Sunami et al. (16)	Japan	Case–control study	156/155	56.27 ± 14.63/56.39 ± 15.66	NA	F1, F2, F13, F14	6
Pan et al. (28)	Beijing, China	Case–control study	120/60	61.30 ± 9.20/61.32 ± 9.54	NA	F1, F2, F9, F10, F12, F13, F14	8
Kim et al. (29)	Korean	Case–control study	23/2,196	54.09 ± 19.13/52.60 ± 18.43	NA	F1, F2, F8	7

NA, not available; SD, standard deviation; IQR, interquartile range; Risk Factors: F1, female gender; F2, age; F3, serum vitamin D level; F4, osteoporosis; F5, osteopenia; F6, migraine; F7, stroke; F8, head trauma; F9, hypertension; F10, diabetes mellitus; F11, hyperlipidemia; F12, TC level; F13, smoking; F14, drinking; F15, regular exercise.

TABLE 2 | The pooled results for each risk factor included in this meta-analysis.

Risk factors	Number of studies	Number of participants	Pooled results			Heterogeneity I^2		
			OR/MD	95% CI	*P* value		*P* value for heterogeneity	Analytical effect model
Female gender	15	13,819	1.18	1.05, 1.32	0.004	49%	0.02	Fixed-effect model
Age	13	7,056	0.56*	−0.17,1.29	0.13	20%	0.24	Fixed-effect model
Serum vitamin D level	7	1,254	−2.12*	−3.85, −0.38	0.02	75%	0.0006	Random-effect model
Osteoporosis	8	3,944	2.49	1.39, 4.46	0.002	79%	<0.0001	Random-effect model
Osteopenia	6	1,484	1.11	0.76, 1.62	0.59	63%	0.02	Random-effect model
Migraine	2	8,493	4.40	2.67, 7.25	<0.00001	0%	0.81	Fixed-effect model
Stroke	2	8,493	3.58	0.43, 29.93	0.24	93%	0.0002	Random-effect model
Head trauma	2	4,523	3.42	1.21, 9.70	0.02	67%	0.08	Random-effect model
Hypertension	12	10,869	1.26	0.97, 1.62	0.08	65%	0.001	Random-effect model
Diabetes mellitus	12	10,869	1.04	0.86, 1.25	0.71	18%	0.27	Fixed-effect model
Hyperlipidemia	4	9,426	1.50	0.88, 2.53	0.13	86%	0.0001	Random-effect model
TC level	3	582	0.32*	0.02, 0.62	0.03	66%	0.05	Random-effect model
Smoking	7	8,019	0.59	0.33, 1.04	0.07	80%	<0.0001	Random-effect model
Drinking	6	1,830	0.64	0.29, 1.43	0.28	89%	<0.00001	Random-effect model
Regular exercise	5	1,428	1.08	0.79, 1.47	0.63	0%	0.84	Fixed-effect model

*OR, odds ratio; MD, mean difference; CI, confidence intervals; TC, total cholesterol; *, MD.*

RESULTS

Study Selection and Characteristics

The literature search produced a total of 256 records. Six additional records were identified through screening the reference lists of each study included in this meta-analysis. After 49 duplicates were removed, we further excluded 158 records through screening the titles/abstracts. The remaining 55 studies were assessed by reviewing the full text in detail. Finally, 19 studies published between 2006 and 2019 were included in our meta-analysis. A flow diagram of the literature selection was present in **Supplemental Figure 1**. A total of 14,286 participants were included in this meta-analysis, including 2,618 patients with BPPV and 11,668 controls without BPPV. Most studies were conducted in Asia. Furthermore, 5 studies were prospective (17–19, 23, 26), 12 were retrospective (10–16, 20, 22, 24, 28, 29), and 2 were cross-sectional (4, 25). In addition, the NOS scores of each study ranged from 5 to 9, indicating a medium and high quality of all included studies. Baseline characteristics of each study and pooled results for each risk factor were summarized in **Tables 1**, **2**, respectively. Funnel plots of some risk factors showed that no significant publication bias was found in the included studies (**Supplemental Figures 2**–**5**). A total of 15 potential risk factors were assessed including female gender, age, osteoporosis, osteopenia, serum vitamin D level, migraine, stroke, head trauma, HTN, DM, hyperlipidemia, TC level, smoking, drinking, and regular exercise.

Female Gender

Fifteen studies involving 13,819 participants analyzed the relationship between female gender and the occurrence of BPPV. Four studies were not included in this risk factor analysis, because the participants in these studies were all male or female. The pooled results showed that female had a slightly higher risk of BPPV compared with male (OR = 1.18; 95% CI, 1.05–1.32; $P = 0.004$) (**Figure 1**). We used a fixed-effect model, because the statistical heterogeneity between these studies was not significant ($I^2 = 49\%$; $P = 0.02$).

Age

Thirteen studies including 7,056 participants reported sufficient data between age and the occurrence of BPPV. The pooled results showed that age was not associated with BPPV occurrence (MD = 0.56; 95% CI, −0.17–1.29; $P = 0.13$) (**Figure 1**). These results may be partly due to the fact that many included studies controlled the age between the experimental and control groups. We used a fixed-effect model, because the statistical heterogeneity between these studies was not significant ($I^2 = 20\%$; $P = 0.24$).

Serum Vitamin D Level

Seven studies including 1,254 participants measured serum vitamin D level to investigate the relationship between serum vitamin D level and BPPV occurrence. Significant relationship was found between serum vitamin D level and BPPV in our analysis. The vitamin D level was lower in patients with BPPV than in controls (MD = −2.12; 95% CI, −3.85 to −0.38; $P = 0.02$) (**Figure 1**). Statistical heterogeneity was significant ($I^2 = 75\%$; $P = 0.0006$). As shown in **Supplemental Figure 6**, the results of sensitivity analysis were consistent with previous analysis (MD = −3.09; 95% CI, −3.95 to −2.23; $P < 0.00001$; $I^2 = 22\%$; $P = 0.27$).

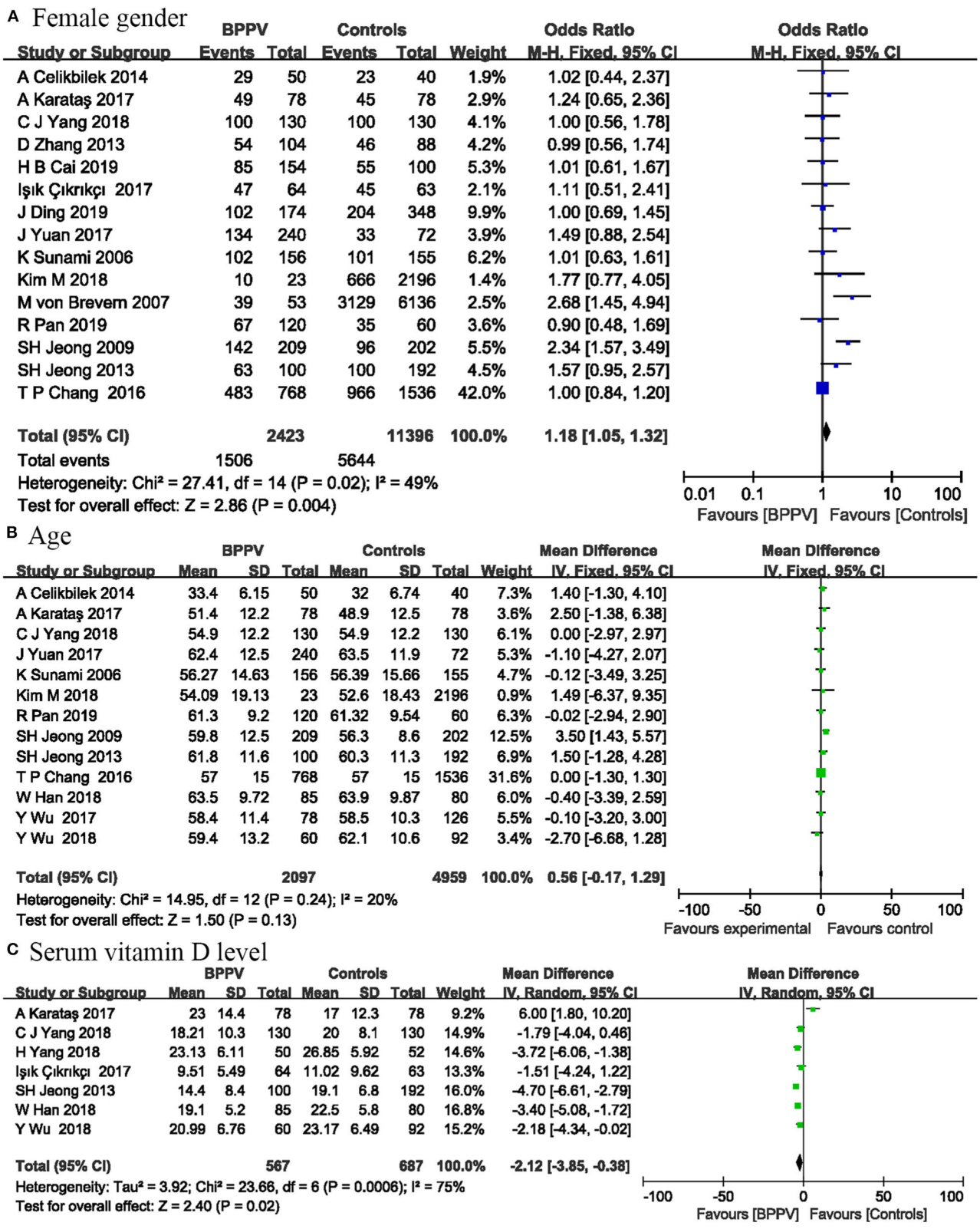

FIGURE 1 | Forest plot of female gender **(A)**, age **(B)**, and serum vitamin D level **(C)**.

Bone Mineral Density

Bone mineral density measurements were expressed as T scores and we specifically analyzed the effects of osteoporosis and osteopenia on BPPV. Osteopenia was defined as $-2.5 < T$ score $<$-1.0, and osteoporosis was defined as T score $\leq$-2.5. Eight studies including 3,944 participants investigated the effects of osteoporosis on the occurrence of BPPV. Our analysis indicated that osteoporosis was a risk factor for BPPV occurrence (OR = 2.49; 95% CI, 1.39–4.46; $P = 0.002$) (**Figure 2**). The I^2-value was 79%, suggesting significant heterogeneity among these studies. Six studies involving 1,484 participants were included in osteopenia analysis. No significant relationship was found between osteopenia and BPPV (OR = 1.11; 95% CI, 0.76–1.62; $P = 0.59$) (**Figure 2**). The I^2-value was 63%.

Migraine and Stroke

Two studies including 8,493 participants investigated the relationship between migraine and BPPV occurrence. Our analysis indicated that migraine was a risk factor for BPPV occurrence (OR = 4.40; 95% CI, 2.67–7.25; $P < 0.00001$) (**Figure 2**). No heterogeneity was detected between these studies ($I^2 = 0\%$; $P = 0.81$).

The same two studies also analyzed the correlation between stroke and the occurrence of BPPV. The pooled results showed no significant correlation between BPPV and stroke (OR = 3.58; 95% CI, 0.43–29.93; $P = 0.24$) (**Figure 2**), with significant heterogeneity between the two studies ($I^2 = 93\%$; $P = 0.0002$).

Head Trauma

Two studies including 4,523 participants investigated the relationship between head trauma and BPPV occurrence. Our analysis indicated that head trauma was a risk factor for BPPV occurrence (OR = 3.42; 95% CI, 1.21–9.70; $P = 0.02$) (**Figure 2**). The I^2-value was 67%, indicating significant heterogeneity between the two studies.

Hypertension

Twelve studies including 10,869 participants evaluated the effects of hypertension on the onset of BPPV. The pooled results suggested no significant association between BPPV and hypertension (OR = 1.26; 95% CI, 0.97–1.62; $P = 0.08$) (**Figure 3**). This risk factor was analyzed by a random-effect model ($I^2 = 65\%$; $P = 0.001$). Significant heterogeneity between studies limited the accuracy of the results.

Diabetes Mellitus

Twelve studies including 10,869 participants reported the relationship between DM and BPPV occurrence. The pooled evidence showed that DM was not associated with BPPV occurrence (OR = 1.04; 95% CI, 0.86–1.25; P = 0.71) (**Figure 3**). No significant heterogeneity was detected among these studies, and a fixed-effect model was used ($I^2 = 18\%$; $P = 0.27$).

Hyperlipidemia and TC Level

Four studies including 9,426 participants investigated the influence of hyperlipidemia on the occurrence of BPPV. Our analysis showed no significant association between hyperlipidemia and BPPV occurrence (OR = 1.50; 95% CI, 0.88–2.53; $P = 0.13$) (**Figure 3**). The I^2-value was 86%, so a random-effect model was used.

Three studies involving 582 participants measured total cholesterol level to assess their influence on BPPV occurrence. The pooled evidence showed that patients with BPPV have a higher TC level than controls (MD = 0.32; 95% CI, 0.02–0.62; $P = 0.03$) (**Figure 4**). The I^2-value was 66%, indicating significant heterogeneity between these studies.

Changeable Lifestyles

Seven studies including 8,019 participants were conducted on the relationship between smoking and BPPV. The pooled results indicated that smoking was not associated with BPPV occurrence (OR = 0.59; 95% CI, 0.33–1.04; $P = 0.07$) (**Figure 4**). Statistical heterogeneity was significant ($I^2 = 80\%$; $P < 0.0001$).

Correlations between drinking and BPPV occurrence were performed in six studies involving 1,830 participants. No significant association was found between drinking and BPPV (OR = 0.64; 95% CI, 0.29–1.43; $P = 0.28$) (**Figure 4**). The I^2-value was 89%, suggesting significant heterogeneity among included studies.

Five studies including 1,428 participants evaluated the effects of regular exercise on BPPV. Our analysis suggested that physical inactivity was not associated with BPPV occurrence (OR = 1.08; 95% CI, 0.79–1.47; $P = 0.63$) (**Figure 4**). There was no heterogeneity among these studies ($I^2 = 0\%$; $P = 0.84$).

DISCUSSION

This systematic review and meta-analysis indicated that female gender, vitamin D deficiency, osteoporosis, migraine, head trauma, and high TC level were risk factors for the occurrence of BPPV. There was no sufficient evidence to suggest that age, osteopenia, stroke, HTN, DM, hyperlipidemia, smoking, drinking, and physical inactivity were associated with BPPV occurrence. The accuracy of some of our results may be limited to significant heterogeneity or the limited number of included studies, so further research was needed to confirm some of our results.

Although many included studies controlled the sex ratio between the experimental and control groups, our analysis showed that women were more likely to develop BPPV than men. Previous studies have also suggested that women had a higher incidence of BPPV than in men, especially in the elderly women (4). This relationship may be related to estrogen deficiency in postmenopausal women, as estrogen may promote the development of osteoporosis and even BPPV (18). In addition, women BPPV patients have a higher risk of recurrence than men (9, 31). Therefore, further research between estrogen levels and BPPV may help early diagnosis and prevention of BPPV.

Our analysis of serum vitamin D level suggested that vitamin D deficiency appeared to be a risk factor for the occurrence of BPPV. This result was consistent with a previous meta-analysis (32). BPPV significantly increased the risk of fractures and osteoporosis, which may be related to vitamin D deficiency in BPPV patients (33, 34). Moreover, serum vitamin D level can be affected by estrogen deficiency (35), which may help explain

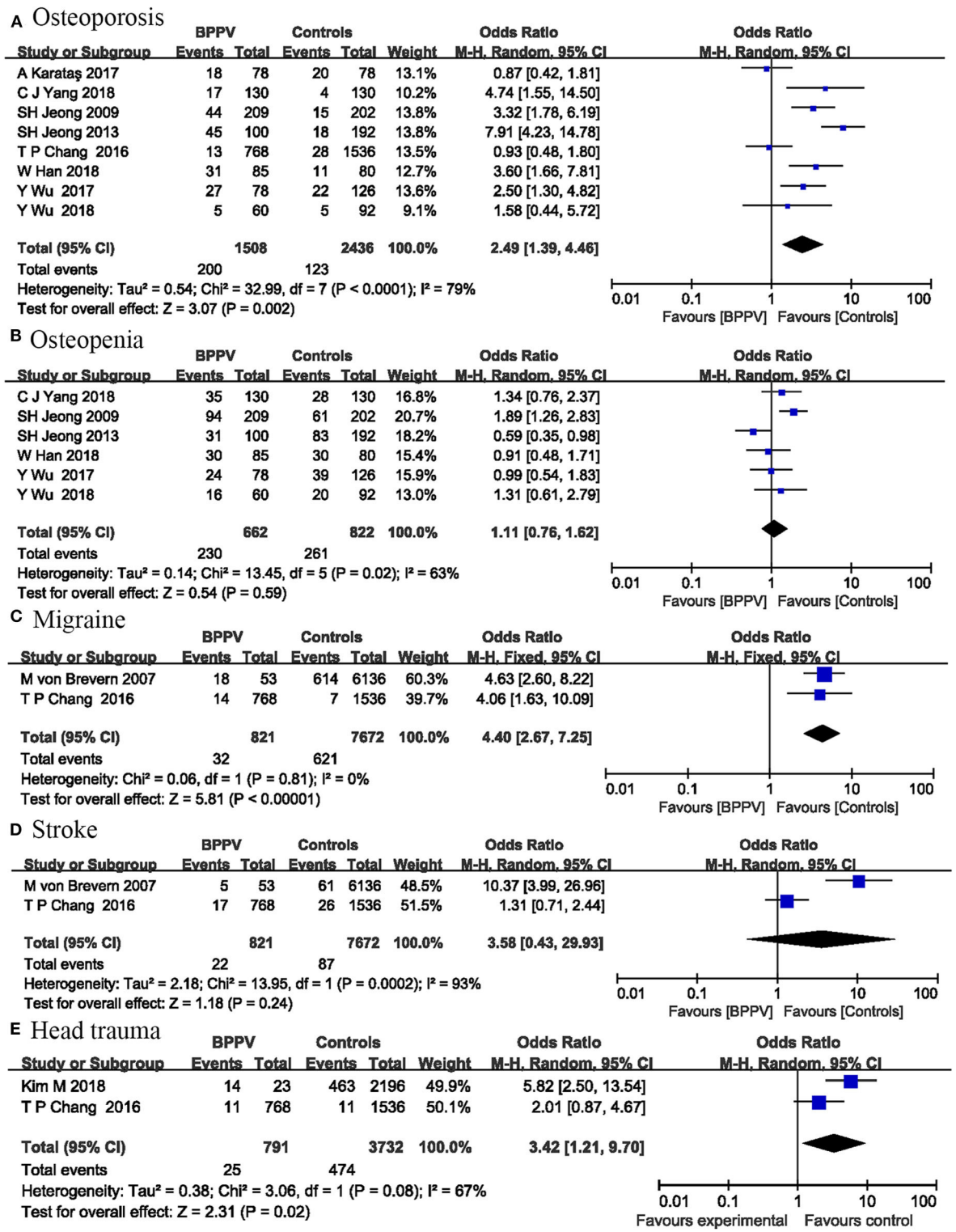

FIGURE 2 | Forest plot of osteoporosis **(A)**, osteopenia **(B)**, migraine **(C)**, stroke **(D)**, and head trauma **(E)**.

why BPPV was more common in postmenopausal women. Thus, serum vitamin D level may be used for the auxiliary diagnosis of atypical BPPV as a serum predictor. In addition, some studies showed that vitamin D supplements can effectively improve symptoms of patients with BPPV (36) and have preventive effects on BPPV recurrence (37). Hence, vitamin D supplements may

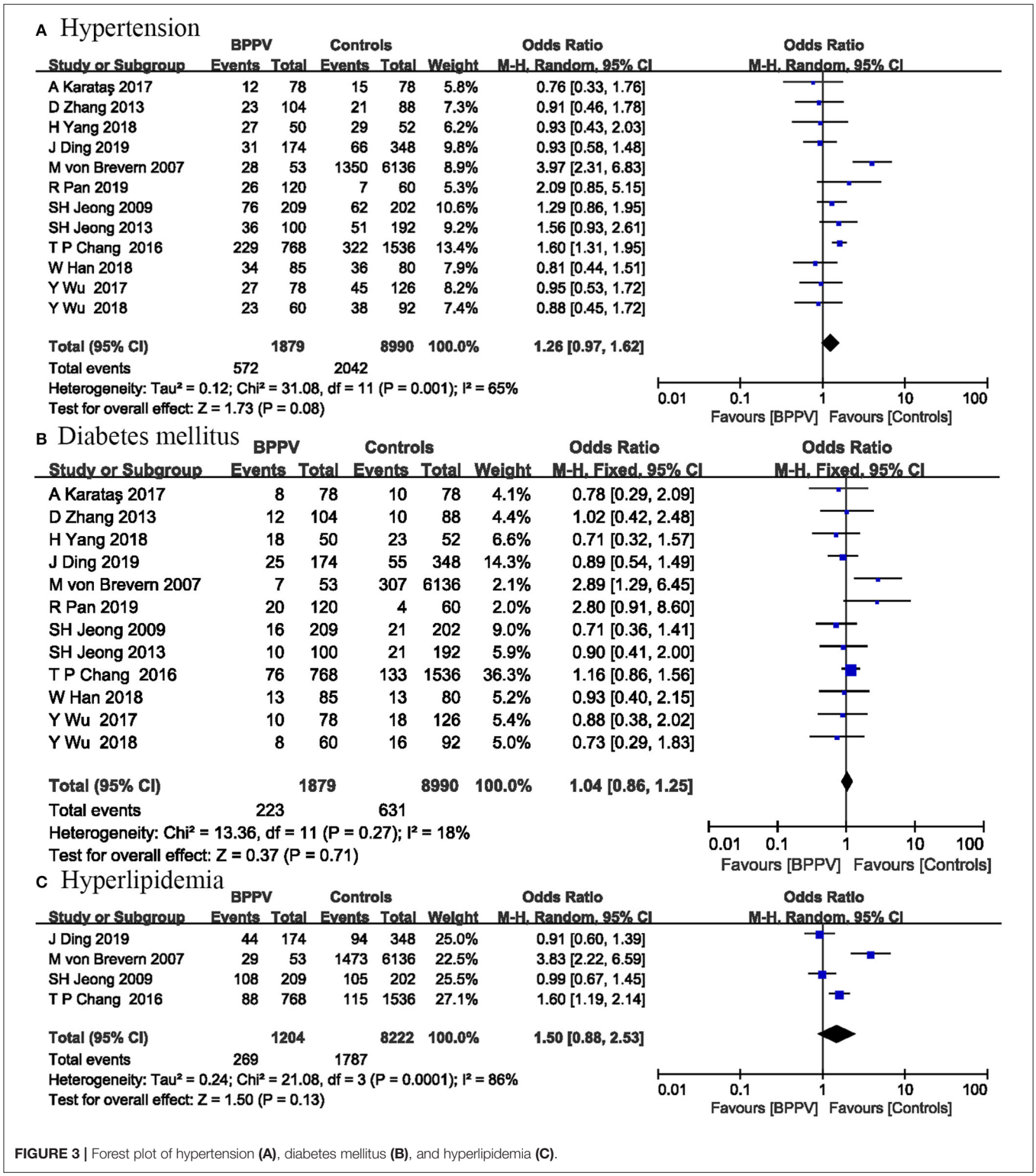

FIGURE 3 | Forest plot of hypertension **(A)**, diabetes mellitus **(B)**, and hyperlipidemia **(C)**.

have important effects on improving the diagnosis and prognosis of patients with BPPV.

Our analysis results indicated that osteoporosis was a risk factor for BPPV occurrence, but osteopenia was not. A previous systematic review also showed that BPPV may be associated with osteoporosis or osteopenia (38). Many studies suggested that bone mineral density values in BPPV patients were lower than those in controls (39). In addition,

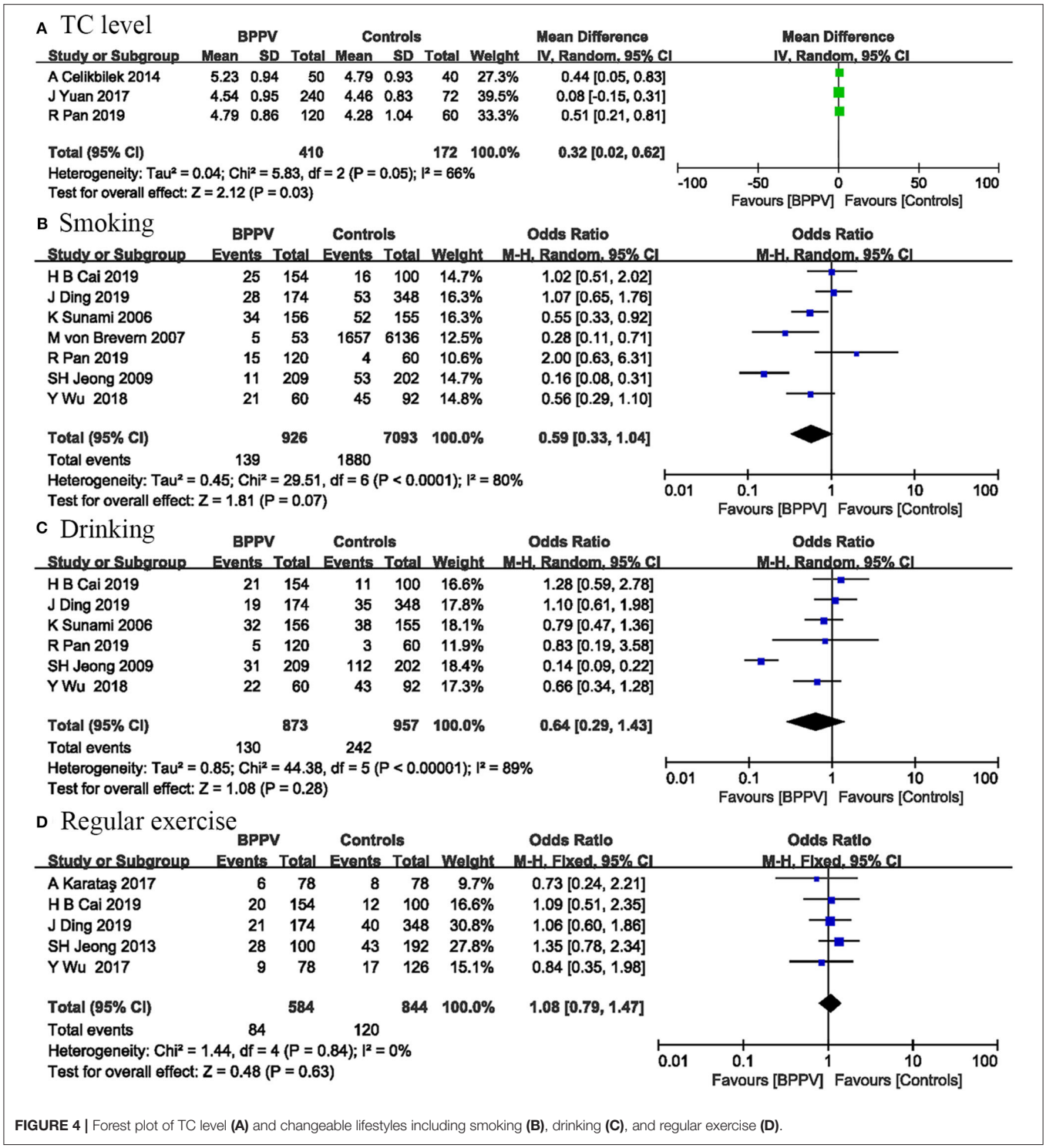

FIGURE 4 | Forest plot of TC level **(A)** and changeable lifestyles including smoking **(B)**, drinking **(C)**, and regular exercise **(D)**.

osteoporosis and osteopenia may also be associated with BPPV recurrence (40, 41). Thus, treatment of osteoporosis may help prevent the occurrence of BPPV and improve the prognosis of BPPV patients (42). Further studies were needed to determine the effects of BMD on BPPV occurrence and recurrence.

The pooled results showed that BPPV has no significant relationship with hyperlipidemia, but BPPV patients have a higher TC level. An increased TC level was a risk factor for BPPV occurrence. A higher TC level or hyperlipidemia can cause vascular damage in the inner ear, which may lead to BPPV occurrence (4). In addition, a recent study found that

the three rs2074880 genotypes in the CACNA1A (Calcium Voltage-Gated Channel Subunit Alpha1 A) gene were associated with increased levels of cholesterol in BPPV patients (28). The relationship between TC level and BPPV has not been adequately studied. Further studies were required to confirm these results.

BPPV was frequently induced by secondary factors such as head trauma, migraine, or other inner ear diseases. Recent studies showed that migraine (43) and head trauma (29) were significantly associated with an increased incidence of BPPV. Most included studies excluded patients with any history of vestibular or neurological diseases, including head trauma and migraine. Our analysis still showed that migraine and head trauma were risk factors for BPPV occurrence. However, the limited number of studies included or significant heterogeneity may limit the accuracy of these results.

Some studies have investigated associations between vascular risk factors and BPPV, such as hypertension, DM, and hyperlipidemia, but the results were controversial (4, 19). In addition, vascular comorbidities may also be risk factors for BPPV recurrence (8, 9). However, our analysis showed that migraine and high TC level were risk factors for BPPV occurrence, while HTN, DM, hyperlipidemia, and stroke were not. The limited number of eligible studies or significant heterogeneity among studies may limit the accuracy of these results. Large-scale studies of these risk factors were needed to confirm the reliability of these results.

Previous studies suggested that smoking has adverse effects on middle ear diseases and hearing loss (44) and even makes the treatment of vertigo ineffective (45). However, some studies have shown that smoking can reduce the incidence of BPPV, prevent the recurrence of BPPV, and shorten the recovery time of BPPV (16). The relationship between smoking and BPPV was quite controversial and had not been adequately investigated. We expected that smoking was a potential risk factor for BPPV occurrence, but pooled results showed no significant relationship between smoking and BPPV occurrence. Significant heterogeneity among studies may limit the accuracy of this results. Further investigations were needed to establish the effects of smoking on BPPV.

Our analysis showed no significant association between BPPV and physical inactivity. However, previous studies showed that moderate physical exercise can prevent the occurrence of BPPV and decrease the risk of falls and fractures, especially in the elderly (46). Intense physical activity may trigger posttraumatic BPPV without head trauma (47), but a study showed that BPPV caused by intense physical activity was a rare condition (48). Some included studies did not give specific definition, which may limit the accuracy of this result. The role of regular exercise and moderate exercise in BPPV needed further investigations.

LIMITATIONS

Inevitably, there were several limitations in this meta-analysis. First, searches were restricted to English literature, which means that potentially high-quality literature may not be included in our analysis. Second, some potential risk factors were not analyzed in our analysis, because too few published studies were available, such as coronary heart disease, serum uric acid level, and albumin level. Third, subgroup analysis of each risk factor was not performed due to insufficient data. Furthermore, many included studies were retrospectively conducted in Asia and BPPV had many levels of its severity, which may limit the reliability of our results. In addition, for some risk factors, the limited number of included studies, significant heterogeneity, or ambiguous definition may limit the accuracy of these results. Large-scale randomized controlled trial (RCT) studies were necessary to confirm the reliability of our results.

CONCLUSION

This meta-analysis was based on 19 studies involving a total of 14,286 participants, which provided strong evidence that female gender, vitamin D deficiency, osteoporosis, high TC level, migraine, and head trauma were risk factors for the occurrence of BPPV. However, the effects of other risk factors on BPPV occurrence needed further investigations. Further investigations should focus on exploring potential mechanisms, how to effectively intervene in high-risk populations, and preventing these risk factors as much as possible.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

JC and WZ contributed to literature search, data analysis, and drafting and revision of the manuscript. JC and XY contributed to data collection and crafting and revision of the tables and figures. PZ given constructive suggestions for the revision of this manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00506/full#supplementary-material

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Clinical Characteristics of Patients With Benign Paroxysmal Positional Vertigo Diagnosed Based on the Diagnostic Criteria of the Bárány Society

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Objectives: To analyze the clinical characteristics of patients with benign paroxysmal positional vertigo (BPPV) diagnosed based on the diagnostic criteria of Bárány Society, verify the clinical application value of the diagnostic criteria, and further explore the clinical problems associated with the diagnosis of possible BPPV.

Methods: A total of 481 patients with BPPV who were admitted from March 2016 to February 2019 were included. All patients were diagnosed by the Dix-Hallpike, straight head hanging and supine roll tests, the nystagmus was recorded using videonystagmography. For patients with possible BPPV (uncertain diagnosis), particle repositioning therapy and follow-up diagnosis were used to further clarify diagnosis.

Results: Based on Bárány Society's diagnostic criteria for BPPV, the distribution characteristics of different BPPV types were as follows: 159 (33.1%) patients had posterior canal BPPV-canalolithiasis (PC-BPPV-ca), 70 (14.6%) patients had horizontal canal BPPV-ca (HC-BPPV-ca), 55 (11.4%) patients had spontaneously resolved-probable-BPPV (Pro-BPPV), and 53 (11.0%) patients had HC-BPPV-cupulolithiasis (HC-BPPV-cu). In emerging and controversial BPPV, 51 (10.6%) patients had multiple canal BPPV (MC-BPPV), 30 (6.2%) patients had PC-BPPV-cu, and 19 (4.0%) patients had anterior canal BPPV-ca (AC-BPPV-ca), 44 (9.1%) patients had possible-BPPV (Pos-BPPV). Among the 44 patients with Pos-BPPV, 23 patients showed dizziness/vertigo without nystagmus during the initial positional test, five patients were possible MC-BPPV, four patients had persistent geotropic positional nystagmus lasting > 1 min when lying on both sides, and were considered to have Pos-HC-BPPV, four patients showed apogeotropic nystagmus when lying on one side, and were considered to have possible short-arm HC-BPPV, four patients showed geotropic nystagmus when lying on one side, and were considered to have Pos-HC-BPPV, three patients had down-beating nystagmus, lasing > 1 min, were considered to have Pos-AC-BPPV-cu. One patient showed transient apogeotropic positional nystagmus on both sides during the supine roll test, and was diagnosed with possible anterior arm HC-BPPV.

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Conclusions: PC-BPPV-ca is the most common among patients with BPPV, followed by HC-BPPV-ca. In emerging and controversial BPPV, MC-BPPV, and Pos-BPPV were more common. For the diagnosis of Pos-BPPV, a combination of the history of typical BPPV, particle repositioning therapy and follow-up outcome is helpful to clarify the diagnosis.

Keywords: benign paroxysmal positional vertigo, Bárány society, diagnostic criteria, possible BPPV, clinical characteristics, diagnostic strategies

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common paroxysmal vestibular disorder, with a lifetime prevalence of 3–10% (1). BPPV is characterized by positional vertigo and nystagmus that is triggered by changing head position, i.e., otoliths that detached from utricle are dropped into the canal and move along with gravity when head position changes (2). According to anatomical structures, BPPV can be divided into posterior canal BPPV (PC-BPPV), horizontal canal BPPV (HC-BPPV), anterior canal BPPV (AC-BPPV), and multiple canal BPPV (MC-BPPV) (3). PC-BPPV and HC-BPPV are more prevalent, and AC-BPPV is very rare (4). According to the pathophysiology of BPPV, it can be divided into canalolithiasis (ca) and cupulolithiasis (cu). In 2015, experts from various countries in the International Bárány Society discussed and formulated the consensus diagnostic criteria for BPPV, which objectively reflects the status of diagnosis and treatment of BPPV in clinical practice (5). In addition to the common types of BPPV, emerging and controversial BPPV are also included in the diagnostic criteria. The diagnostic criteria interpret these BPPV types, and provide clinicians with criteria and information for diagnosing BPPV. Further validation of the diagnostic criteria, especially the emerging and controversial BPPV among Chinese population has important clinical significance.

Given the above background, we included 481 patients with BPPV who were admitted to our hospital, aimed to analyze the clinical distribution characteristics of different BPPV types based on Bárány Society's diagnostic criteria for BPPV, and further analyzed the problems associated with the diagnosis of possible BPPV.

SUBJECTS AND METHODS

Subjects

A total of 481 patients with BPPV who were admitted to the Department of Neurology, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine from March 2016 to April 2019 were included. All patients gave written informed consent. This study has been approved by the ethics committee of our hospital. All patients underwent routine neuro-otological examinations, such as cranial nerve examination, Romberg's test, and Fukuda test, pure tone audiometry, eye movement test, bithermal caloric test and dynamic position test. Eye movement test include gaze, saccade, smooth pursuit, and optokinetic nystagmus tests. Dynamic position tests include Dix-Hallpike, supine roll, and straight head hanging (SHH) tests. A videonystagmograph (VNG, Interacoustics, Denmark) was used to record the nystagmus in BPPV patients. If necessary, MRI and other examinations were performed to exclude central paroxysmal positional vertigo.

Diagnostic Methods

The diagnosis of BPPV is mainly based on the diagnostic criteria for BPPV formulated by the Bárány Society in 2015 (5). BPPV types include PC-BPPV-ca, HC-BPPV-ca, HC-BPPV-cu, and spontaneously resolved-probable BPPV (Pro-BPPV), AC-BPPV-ca, PC-BPPV-cu, MC-BPPV, and possible-BPPV (Pos-BPPV). The latter four types are emerging and controversial types of BPPV.

The spontaneous nystagmus was recorded in a sitting position with or without visual fixation. Dix-Hallpike and supine roll and SHH tests were performed to induce nystagmus in BPPV patients, and then BPPV patients were classified and diagnosed according to the medical history and characteristics of nystagmus.

Diagnosis of the involved semicircular canal: (1) PC-BPPV was diagnosed if vertical upbeat nystagmus with or without torsional component was induced by Dix-Hallpike test, and the reversal of the nystagmus often occurred when returning to an upright position; if vertical upbeat nystagmus with torsional component was induced, the torsional component involved the beating of the upper pole of the eyes toward the affected side. (2) HC-BPPV was diagnosed if geotropic horizontal nystagmus was induced by supine roll test, and the side with stronger nystagmus was the affected side; if apogeotropic horizontal nystagmus was induced, the side with weaker nystagmus was the affected side. (3) AC-BPPV was diagnosed if vertical downbeat nystagmus with/without torsional component was induced by Dix-Hallpike test; if the vertical downbeat nystagmus with torsional component was induced, the torsion of the upper pole of the eyes was toward the affected side. (4) The diagnosis of MC-BPPV was based on the presence of the typical nystagmus of multiple canals involved on Dix-Hallpike, SHH, and supine roll tests. (5) Pro-BPPV was diagnosed if patients had a history of recurrent episodes of positional vertigo or dizziness, that can be induced when the patients changed from an upright position to a supine position or when patients were in a supine position and then rolled onto one side, and those recurrent episodes lasted less than 1 min. Nystagmus and vertigo were not observed in the

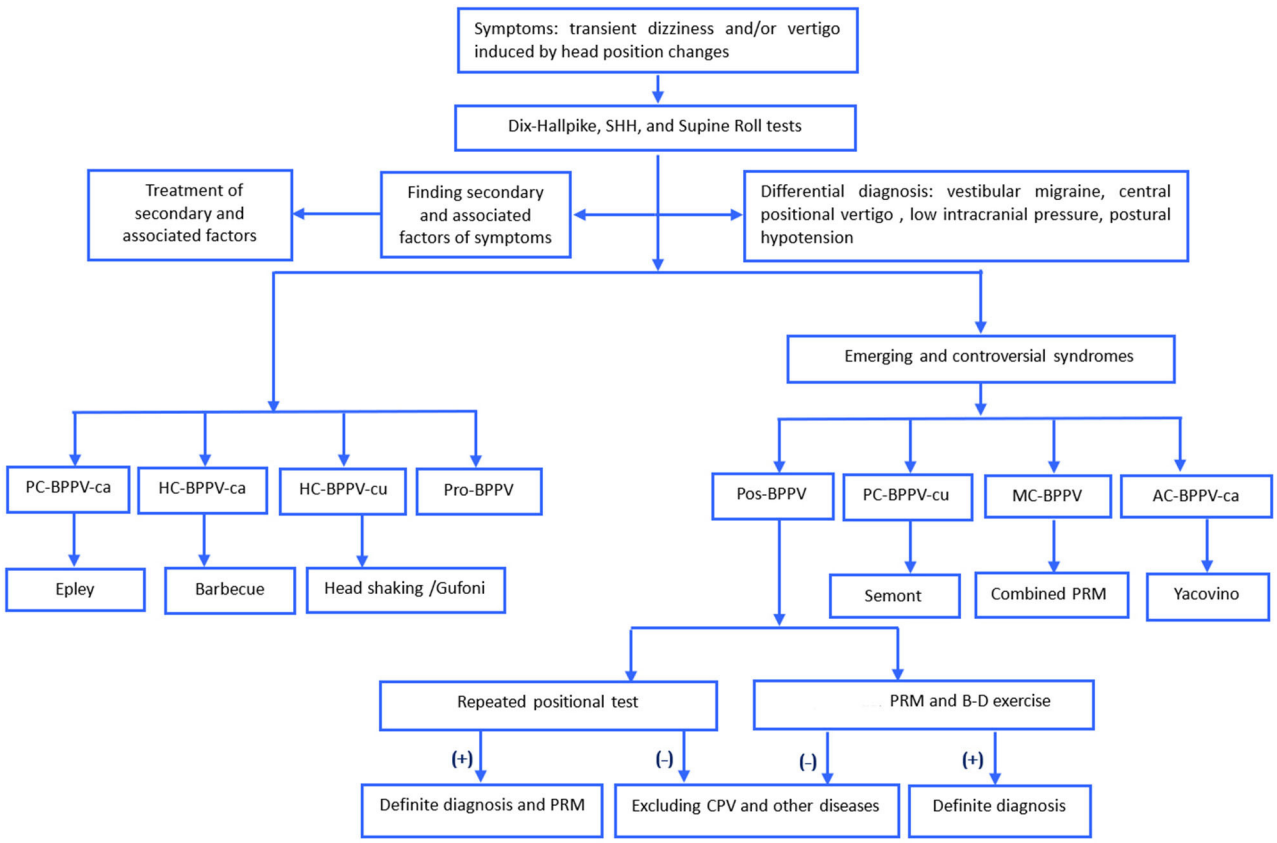

FIGURE 1 | The process for diagnosis and treatment of BPPV. AC, anterior canal, ca, canalolithiasis; cu, cupulolithiasis; B-D, Brandt-Daroff; BPPV, benign paroxysmal positional vertigo, HC, horizontal canal, MC, multiple canal, PC, posterior canal, Pos, possible, PRM, particle repositioning maneuvers; Pro, probably spontaneously resolved, SHH, straight head hanging.

position test, and the recurrent episodes were not attributable to other diseases (5).

Diagnosis of Pos-BPPV: (a) Dix-Hallpike, supine roll, and SHH tests only induced vertigo, but did not induce nystagmus, or induced atypical nystagmus disappeared after treatment with particle repositioning maneuvers; (b) multiple canal involvement were suspected, but the affected canals cannot be determined; (c) co-existence of peripheral and central positional nystagmus; (d) symptoms were not attributed to other diseases (5).

The detailed process for diagnosis and treatment of Pos-BPPV was shown in **Figure 1**. For patients with Pos-BPPV, the history of BPPV, particle repositioning therapy, and follow-up diagnosis were used to further confirm the diagnosis. (1) particle repositioning therapy was applied based on the type of vertigo and nystagmus characteristics induced by the position test and the affected side. Patients with Pos-PC-BPPV, -HC-BPPV, -AC-BPPV were treated with Epley, Barbecue, and Yacovino maneuvers, respectively. Patients who had much more complex nystagmus were treated with the combined particle repositioning therapy and/or Brandt-Daroff exercises. All patients with Pos-BPPV are followed up for one week and one month after treatment. (2) cupulolithiasis was considered if the duration of nystagmus was $\geq$1 min, and canalolithiasis was considered if the duration of nystagmus was $<$1 min.

After treatment with particle repositioning maneuvers, the Dix-Hallpike and supine roll tests were performed again at the same day or the next day. If all the nystagmus and vertigo disappeared, then a complete cure was achieved. Particle repositioning therapy was also considered effective if the nystagmus and vertigo was weaker without completely disappearing, whereas it was deemed to be non-effective if the nystagmus was unchanged or became further aggravated (6).

RESULTS

Among the 481 patients with BPPV included in this study, 157 (32.6%) patients were males, and 324 (67.4%) were females; the male to female ratio was 1:2.06. The average age of patients was 59.6 $\pm$ 14.9 years (range: 20–90 years), and the peak age of onset was 51–70 years, accounting for 52.4% of all patients with BPPV.

The distribution of different types of BPPV: (1) 159 (33.1%) patients had PC-BPPV-ca, 70 (14.6%) patients had HC-BPPV-ca, 55 (11.4%) patients had Pro-BPPV, and 53 (11.0%) patients had HC-BPPV-cu. (2) in emerging and controversial BPPV, 51

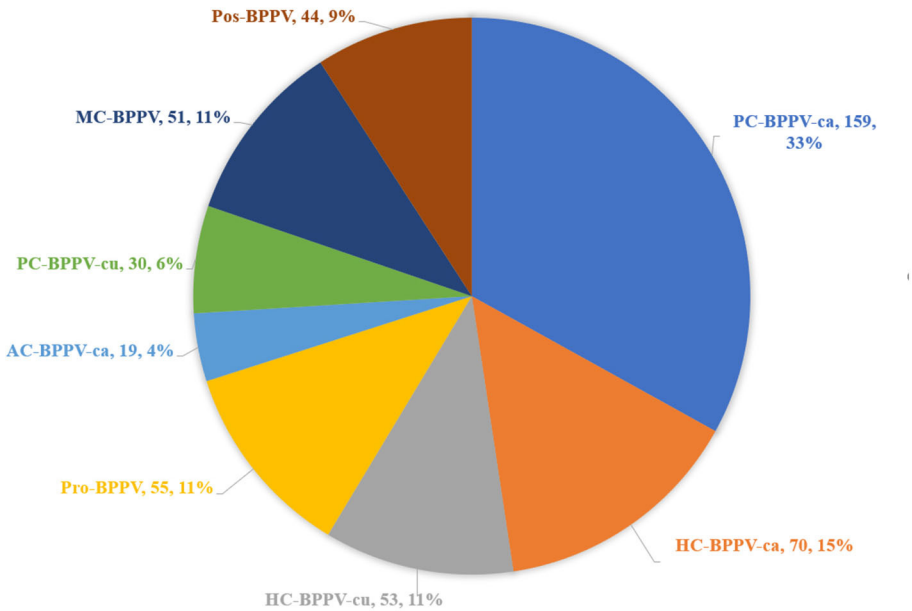

FIGURE 2 | Distribution of all types of BPPV. AC, anterior canal, ca, canalolithiasis, cu, cupulolithiasis; BPPV, benign paroxysmal positional vertigo, HC, horizontal canal, MC, multiple canal, PC, posterior canal, Pro, probably spontaneously resolved, Pos, possible.

(10.6%) patients had MC-BPPV, 44 (9.1%) patients had Pos-BPPV, 30 (6.2%) patients had PC-BPPV-cu and 19 (4.0%) patients had AC-BPPV-ca (**Figure 2**).

Among the 44 patients with Pos-BPPV, 23 (52.3%) patients showed vertigo without nystagmus induced by the position test, including 17 patients of Pos-PC-BPPV and six patients of Pos-HC-BPPV. Vertigo disappeared in 12 patients following the first particle repositioning therapy. After 1-week and 1-month of treatment, vertigo disappeared in 18 and 21 patients, respectively.

Five (11.4%) patients of the 44 patients with Pos-BPPV were suspected of having multiple canal involvement, but the affected canals were not determined. 4 Patients showed symptoms and nystagmus did not improve after the first particle repositioning therapy, and patients were instructed to perform Brandt-Daroff exercises at home. Vertigo and nystagmus disappeared in 3 patients after one week of follow-up. And after one month of follow-up, vertigo disappeared in 4 patients, recurrence was seen in one patient.

Four (9.1%) patients of the 44 patients with Pos-BPPV had bilateral geotropic positional nystagmus lasting > 1 min when lying on both sides. The slow phase velocity (SPV) of the induced nystagmus was mostly 2–6°/s. Vertigo and nystagmus disappeared in 3 patients after first particle repositioning therapy, which disappeared in all patients after one week of treatment.

4 (9.1%) patients showed apogeotropic nystagmus on the supine roll test when lying on one side, and no nystagmus was observed when lying on the contralateral side. Vertigo disappeared in all patients after first particle repositioning therapy, and vertigo was not recurrent after one week and one month of follow-up. Those patients were diagnosed with possible short-arm HC-BPPV.

Four (9.1%) patients of the 44 patients with Pos-BPPV showed geotropic nystagmus on the supine roll test when lying on one side, and nystagmus was not observed when lying on the contralateral side. Nystagmus disappeared after particle repositioning therapy, and those patients were considered to have possible HC-BPPV.

Three (6.8%) patients had down-beating nystagmus, lasing > 1 min, the direction of the nystagmus was reversed when sitting up. After treatment with Yacovino maneuver, nystagmus was significantly weakened or disappeared, and those patients were considered to have possible AC-BPPV-cu.

One (2.3%) patient of the 44 patients with Pos-BPPV showed transient apogeotropic positional nystagmus on both sides during the supine roll test. The first particle repositioning therapy was ineffective. During one week of follow up, the supine roll test induced geotropic nystagmus which was then converted into apogeotropic nystagmus when lying on the left side, and geotropic nystagmus was induced when lying on the right side. Nystagmus was significantly weakened after treatment with Barbecue maneuver on the left side, and the patient was diagnosed with possible anterior arm HC BPPV (**Table 1**).

Among the 51 patients with MC-BPPV, 29 (56.9%) had unilateral side involvement (including 23 patients of right-side involvement and six patients of left-side involvement), 13 (25.5%) patients had bilateral involvement, and the affected side was unclear in 9 (17.6 %) patients.

TABLE 1 | Clinical features of the Possible BPPV.

No	Sex	Age	Left DH	Right DH	Left Roll	Right Roll	Diagnose	Treatment	Result	One week	One month
1	F	78	CCW+U:35°/s, 15 s→ D:9°/s, 50 s	R:7°/s, > 1 min	R:5°/s + D:9°/s,45 s	–	pos–MC-BPPV	Epley+B-D	Effective	Effective	Cure
2	F	71	CCW+U:24°/s, 20 s→ D:10°/s, > 1 min	CW+U: 2°/s,20 s→ D:10°/s, >1 min	–	–	pos-MC-BPPV	Epley	Cure	Cure	Cure
3	M	27	D:8°/s, 20 s	D:8°/s, 10 s	L:13°/s, 10 s	R:49°/s, 15 s→ L:5°/s + D:11°/s, 25 s	pos-MC-BPPV	Yacovino+Barbecue +B-D	Effective	Cure	Cure
4	F	64	U:14°/s > 1 min	CW+U,10°/s, >1 min	L:9°/s, >1 min	R:51°/s, 10s→ L:11°/s >1 min	pos-MC-BPPV	Barbecue+B-D	Effective	Cure	Cure
5	M	70	L:7°/s, > 1 min	CW+U:12°/s, 5s→ R:6°/s, 38 s	L:6°/s, 35 s	R:5°/s, 30 s	pos-MC-BPPV	Epley+B-D	Effective	Effective	Recurrence
6	M	52	–	–	L:3°/s,>1 min	R:4°/s, > 1 min	Pos-RHC-BPPV	Barbecue	Cure	Cure	Cure
7	M	63	–	–	L:4°/s,>1 min	R:6°/s, > 1 min	Pos-RHC-BPPV	Barbecue	Effective	Cure	Cure
8	F	37	L:4°/s, > 1 min	–	L:3°/s,>1 min	R:2°/s, > 1 min	Pos-LHC-BPPV	Barbecue	Cure	Cure	Cure
9	M	60	L:6°/s, > 1 min	–	L:6°/s,>1 min	R:4°/s, 10s	Pos-LHC-BPPV	Barbecue	Cure	Cure	Cure
10	F	60	–	R:13°/s, 40 s	L:26°/s, 20 s	–	Pos-LHC-BPPV	Barbecue	Cure	Recurrence:RP-RH-BPPV	Cure
11	M	24	–	–	–	R: 7°/s, > 1 min	Pos-RHC-BPPV	Barbecue	Cure	Cure	Cure
12	M	36	–	–	–	R:4°/s, 40s	Pos-RHC-BPPV	Barbecue	Cure	Cure	Cure
13	F	50	–	–	–	R:6°/s, 40s	Pos-RHC-BPPV	Barbecue	Cure	Cure	Cure
14	F	56	–	–	–	L:5°/s, > 1 min	Pos-short arm RHC-BPPV	Barbecue	Cure	Cure	Cure
15	M	46	–	–	–	L:5°/s, > 1 min	Pos-short arm RHC-BPPV	Barbecue	Cure	Cure	Cure
16	M	67	–	–	–	L:6°/s,>1 min	Pos-short arm RHC-BPPV	Barbecue	Cure	Cure	Cure
17	M	46	–	–	R:6°/s, >1 min	–	Pos-short arm LHC-BPPV	Barbecue	Cure	Cure	Cure
18	M	77	–	–	R:41°/s, 30 s	L:23°/s, 28 s	Pos-RHC-BPPV	Head-shaking +Barbecue	Non-effective	Cure	Cure

(Continued)

TABLE 1 | Continued

No	Sex	Age	Left DH	Right DH	Left Roll	Right Roll	Diagnose	Treatment	Result	One week	One month
19	F	41	D:9°/s +R:11°/s,>1 min	–	D:4°/s +R:6°/s,>1 min	–	Pos-AC-BPPV-CU	Yacovino	Cure	Cure	Cure
20	F	62	CCW+D:5°/s, >1 min	CCW+D:4°/s, >1 min	–	–	Pos-AC-BPPV-CU	Yacovino	Cure	Cure	Cure
21	F	63	CW+D:10°/s, >1 min	CW+D: 4°/s, >1 min	–	–	Pos-AC-BPPV-CU	Yacovino	Effective	Cure	Cure
22	F	50	–	VWN	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
23	F	59	–	VWN	–	-	pos-PC-BPPV	Epley	Effective	Effective	Cure
24	M	28	–	VWN	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
25	F	54	–	VWN	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
26	F	36	–	VWN	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
27	F	65	–	VWN	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
28	F	45	-	VWN	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
29	F	64	–	VWN	–	–	pos-PC-BPPV	Epley	Non-effective	Effective	Effective
30	F	54	–	VWN	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
31	F	61	–	VWN	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
32	F	49	VWN	VWN	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
33	F	65	VWN	–	–	–	pos-PC-BPPV	Epley	Effective	Effective	Cure
34	F	69	VWN	–	–	–	pos-PC-BPPV	Epley	Effective	Effective	Cure
35	F	63	VWN	–	–	–	pos-PC-BPPV	Epley	Cure	Cure	Cure
36	F	39	VWN	–	–	–	pos-PC-BPPV	Epley	Effective	Cure	Cure
37	F	71	VWN	–	–	–	pos-PC-BPPV	Epley	Effective	Cure	Cure
38	F	43	VWN	–	–	–	pos-PC-BPPV	Epley	Effective	Cure	Cure
39	F	64	–	–	VWN (much severe)	VWN	pos-HC-BPPV	Barbecue	Effective	Cure	Cure
40	F	78	–	–	VWN (much severe)	VWN	pos-HC-BPPV	Barbecue	Non-effective	Effective	Effective
41	F	30	–	-	VWN	VWN (much severe)	pos-HC-BPPV	Barbecues	Cure	Cure	Cure
42	F	62	–	–	VWN	VWN (much severe)	pos-HC-BPPV	Barbecues	Cure	Cure	Cure
43	F	38	–	- -	VWN	VWN	pos-HC-BPPV	Barbecues	Non-effective	Cure	Cure
44	F	56	–	–	VWN	VWN	pos-HC-BPPV	Barbecues	Non-effective	Cure	Cure

BPPV, benign paroxysmal positional vertigo; B-D, Brandt-Daroff; CW, clockwise; CCW (from the patien's perspective), counter clockwise (from the patien's perspective); D, downbeat; DH, Dix-Hallpike; HC, horizontal canal; L, left; PC, posterior canal; pos, possible; R, right; VWN, vertigo without nystagmus.

DISCUSSION

Previous studies have shown that older people and women were more prone to develop BPPV, with peak onset at about 60 years old, and a male to female ratio of 1:2–3 (7, 8). In this study, we found that the average age of onset was 59.6 ± 14.9 years, and the peak age of onset was 51–70 years old, accounting for 52.4% of all BPPV cases. It is speculated that the likelihood of developing various chronic diseases such as hypertension, diabetes, and hyperlipidemia in older people increased with increasing age, which can cause damage to blood vessels and nerves of the inner ear, leading to disorders of the inner ear microcirculation, and utricle damage, then otoconia can easily fall off and cause the occurrence of BPPV (9–12). In this study, the male: female ratio was 1:2.1, which is basically consistent with the findings of a previous study (1). Studies have found that the high incidence of BPPV in middle-aged and older women is related to the decline in estrogen levels. The reduction in estrogen levels may lead to systemic disturbances in calcium metabolism and affect the synthesis and function of otoliths (13). Studies have found that the incidence of BPPV in women receiving hormone replacement therapy for menopausal symptoms was significantly reduced (14).

Bárány Society's diagnostic criteria for BPPV is a diagnostic guideline jointly created by vestibular specialists from many countries. The diagnostic criteria objectively reflect the clinical status of diagnosis and treatment, and provides an in-depth interpretation of different types of BPPV, which has high clinical application value. In the diagnostic criteria, in addition to the common BPPV types, some rare BPPV types are also included, nystagmus and clinical characteristics of these BPPV types are described, that is useful to clinicians in helping them diagnose BPPV. However, at present, the clinical application of diagnostic criteria for BPPV based on the Bárány Society has been rarely studied and verified. In the present study, we found that PC-BPPV-ca (33.1%) is the most common among patients with definite BPPV, followed by HC-BPPV-ca. (14.6%), Pro-BPPV (11.4%), and HC-BPPV-cu (11.0%). And among patients with emerging and controversial BPPV, MC-BPPV (10.6%) is the most common, followed by Pos-BPPV (9.1 %), PC-BPPV-cu (6.2%), and AC-BPPV-ca (4.0%). There were differences between our results and findings from a study conducted by Yao et al. (15). Yao et al. (15) found that among patients with definite BPPV, PC-BPPV-ca (41.9%) was the most common, followed by Pro-BPPV (11.8%), and HC-BPPV-ca (8.98%), and HC-BPPV-cu (1.76%), while Pos-BPPV (33.98%) is the most common among patients with emerging and controversial BPPV, followed by MC-BPPV (1.23%), AC-BPPV-ca (0.35%), and PC-BPPV-cu (0.00%). The differences in the results between our study and the study mentioned above may be related to the differences in the types of patients included.

At present, AC-BPPV is rarely reported. A study had found that the incidence of AC-BPPV is about 3% (1–17.1%) (16). It is speculated that the low prevalence of AC-BPPV may be mainly related to its spatial anatomical location, the anterior canal is located higher, it is difficult for the otoliths detached from utricle to enter into the anterior canal through crus commune. In our study, the incidence of AC-BPPV was 4%; this result is consistent with the above-mentioned study.

PC-BPPV-cu is rarely reported in previous studies. In our study, the incidence of PC-BPPV-cu was found to be 6.2%. A study showed that in patients with PC-BPPV-cu, half-Dix-Hallpike test induced upbeat nystagmus with a torsional component, the nystagmus had no latency period, did not fatigue, and lasted for more than one minute, a reversal of the direction of nystagmus occurred when sitting up (17). A study also suggested that in patients with PC-BPPV-cu, the nystagmus with torsional component can disappear when the head of patients is hanging backward by an appropriate degree during the Dix-Hallpike test. Because in this position, the cupula of the posterior canal is parallel to gravitational force lines, the cupula stops moving, and the nystagmus stops. When performing the Dix-Hallpike test on the healthy side, upbeat nystagmus with torsional component can be induced, and the upper pole of the eyes beats toward the affected ear (18).

A study had shown that the incidence of MC-BPPV was 6.8 to 20% (19), bilateral posterior canal most frequently involved (20–22). In this study, the incidence of MC-BPPV was 10.6%, a combination of ipsilateral PC-BPPV and HC-BPPV was the most common, accounting for 33.3% (17/51) of all case with MC-BPPV, while bilateral PC-BPPV accounted for only 9.8% (5/51) of the cases, our results are consistent with the results of Lopez-Escamez et al. (23) and Shim et al. (24). A previous study suggested that MC-BPPV is mostly associated with damage to both ears caused by traumatic brain injury (25). However, the incidence of traumatic brain injury in MC-BPPV patients was relatively low in our study; only two patients with bilateral PC-BPPV had traumatic brain injury. This may be the reason for the lower incidence of bilateral PC-BPPV. Besides, our research found that MC-BPPV was more likely to be unilateral (29/51, 56.9%); the right side was more commonly affected than the left side. This may be related to the fact that BPPV was more likely to involve the right side (26, 27).

In this study, the incidence of Pro-BPPV was 11.4%, which was basically consistent with the findings of Yao et al. (15), the authors reported a frequency of 11.8%. Studies had shown that the self-healing and atypical symptoms in BPPV patients are associated with their delayed hospital visit (28). The longer the time from onset of symptoms to hospital visits, the higher the incidence of Pro-BPPV. For patients whose symptoms have been completely improved during the visit, it is essential to differentiate BPPV from other paroxysmal vestibular diseases (such as vestibular paroxysmia (29), vestibular migraine (30), and TIA), to avoid misdiagnosis.

At present, a few studies have investigated Pos-BPPV. In our study, the incidence of Pos-BPPV was 9.1%. (1) Among patients with Pos-BPPV, many patients had symptoms of dizziness/vertigo but did not have prominent nystagmus during the position test, and this was called subjective BPPV. Liu et al. (31) found that the incidence of Pos-BPPV was about 13.1% (121/922), particle repositioning therapy was performed according to the symptoms of dizziness/vertigo, and the

treatment effect for patients with Pos-BPPV was the same as for patients with definite BPPV. The results of our study are consistent with the above results. The reasons for patients with Pos-BPPV who only had symptoms of dizziness/vertigo and no nystagmus may be as follows: (a) the number of detached otoliths is small, or the otoliths are dispersed in the semicircular canal, which can not cause endolymph flow when moving in the canals, and cannot reach the threshold for inducing vestibular ocular reflex; (b) patients may experience recurrent episodes of vertigo before their visit, and due to the fatigue of nystagmus, patients only showed vertigo and no nystagmus during the position test (32); (c) patients had taken vestibular suppressants (such as benzodiazepine, antihistamine, and anticholinergic drugs) before their visit, which can cause suppression of vestibular function and reduced sensitivity to the position test (33); (d) nystagmus may not be seen with the naked eye when the nystagmus is weak. Therefore, patients with an initial diagnosis of Pos-BPPV should be followed up closely. Some patients may convert to definite BPPV, but some patients may have other vestibular-related diseases. (2) Five patients (11.4%) were suspected of having multiple canal involvement, but the affected canals cannot be determined. It is speculated that the three semicircular canals are arranged orthogonally when the otoliths are present in different semicircular canals and different positions of the canals, the Dix-Hallpike or Roll tests can cause the movement of the otoliths in multiple canals, the nystagmus induced can be superimposed or cancel each other, so the types of nystagmus induced are different, resulting in difficulties in determining the affected canals. For such patients, we first adopted conventional particle repositioning therapy. After treatment, symptoms of vertigo and nystagmus were relieved in 1 patient. However, the nystagmus was slightly reduced in the remaining four patients, but nystagmus still existed, so these patients were instructed to perform the Brandt-Daroff exercises (three times per day) after returning home. After one week, vertigo and nystagmus have disappeared in 3 patients during re-examination after one week, which have disappeared in all four patients after one month, recurrence was observed in one patient. Amor-Dorado et al. (34) compared the therapeutic efficacy of Brandt-Daroff exercise and particle repositioning maneuvers in PC-BPPV patients, and found that its short-term efficacy of Brandt-Daroff exercise is not better than particle repositioning maneuvers. Therefore, particle repositioning maneuvers can be the first choice for patients whose involved semicircular canal is determined. Still, for patients whose involved semicircular canal and affected side are difficult to determine, Brandt-Daroff exercises can be used as an alternative treatment. (3) Four patients (9.8%) had geotropic paroxysmal nystagmus lasting $>$ 1 min when lying on both sides. The slow phase velocity (SPV) was 2–6°/s. It is speculated that due to the anatomical position of the horizontal canal or the small number of otolith particles in the canals, the otoconia move slowly under the influence of gravity during the supine roll test, it will take a long time to move from the position of the canal in supine position to the lowest position of the canal in a lateral position, so the intensity of the nystagmus induced was weaker and has a long duration. (4) Four (9.1%) patients with Pos-BPPV showed apogeotropic nystagmus on roll test when lying on one side, and no nystagmus was observed when lying on the other side, those patients were diagnosed with possible short arm HC-BPPV (35). One of the patients had a history of PC-BPPV-ca half a month ago. It is speculated that when the otoliths are located in the short arm of the semicircular canal, the otoliths move from the short arm to cupula if the patients lie on their affected side, cupula moves away from the ampulla, apogeotropic nystagmus was induced. When the patients lie on their healthy side, the otoliths move away from the ampulla and fall into the utricle, so no nystagmus was induced (35). (5) Four (9.1%) patients showed geotropic nystagmus on the supine roll test when lying on one side, and nystagmus was not observed when lying on the contralateral side. Nystagmus disappeared after particle repositioning therapy, and those patients were considered to have possible HC-BPPV. In 3 of these 4 patients, the geotropic nystagmus is weak, the SPV was about 4–7°/s. It is speculated that with spontaneous movement of patients, most of the otoliths may be restored themselves. At this time, there are few otolith particles in the semicircular canal, so geotropic nystagmus was only induced on one side. In the remaining one patient, left-beating geotropic nystagmus was only induced when lying on the left side during the supine roll test, and right-beating geotropic nystagmus was induced during right Dix-Hallpike test, the nystagmus disappeared after particle repositioning therapy, which may be related to the uncertainty of the movement of otoliths. (6) In the present study, three patients showed downbeat nystagmus lasting $>$ 1 min during Dix-Hallpike, the nystagmus had no latency period and did not fatigue, and the reversal of the nystagmus occurred when sitting up, those patients had a history of transient episodes of vertigo triggered by changes in body posture. Yacovino maneuver was effective in those patients; the nystagmus disappeared or was significantly weakened after treatment, therefore, those patients were diagnosed as possible AC-BPPV-cu (6). At present, there are relatively few studies investigating AC-BPPV-cu, and there is still controversy about the existence of AC-BPPV-cu. Adamec and Habek (36) reported a case of AC-BPPV-cu, this patient had a previous history of PC-BPPV, and the nystagmus completely disappeared after treatment with Yacovino maneuver. Dlugaiczy et al. (37) suggested that compared with canalolithiasis, cupulolithiasis may be a more common type of AC-BPPV caused by brain trauma. It should be noted that positional downbeat nystagmus is more commonly seen in the vestibulocerebellum, craniocerebral junction injuries or drug poisoning (38). Therefore, during the diagnosis of AC-BPPV-cu, the above diseases should be considered in the differential diagnosis to avoid misdiagnosis. (7) One (2.4%) patient showed transient apogeotropic positional nystagmus on both sides during the supine roll test. The first particle repositioning therapy was ineffective. During one week of follow up, the supine roll test induced stronger geotropic nystagmus which was then converted into apogeotropic nystagmus when lying on the left side, and the geotropic nystagmus was induced when lying on the right side. Nystagmus was significantly weakened after treatment with Barbecue maneuver on the left side, and the patient was diagnosed with possible anterior arm HC BPPV. As can be seen from above, during the diagnosis of Pos-BPPV, the history of typical BPPV, particle repositioning

therapy and dynamic follow-up outcome contribute to accurate diagnosis of Pos-BPPV.

LIMITATIONS

Our study is a single-center research, our study does not represent the general population, and the sample size is small. Further multi-center studies with a larger sample are needed to confirm the findings.

CONCLUSION

Among patients with BPPV, PC-BPPV-ca is most common, followed by HC-BPPV-ca. Among patients with emerging and controversial BPPV, MC-BPPV, and Pos-BPPV were more common. For the diagnosis of Pos-BPPV, a combination of the history of typical BPPV, particle repositioning therapy, and follow-up outcome is helpful to clarify the diagnosis.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XY contributed to the conception and design of the study. XL and D-HZ collected the clinical data. BS, L-HS, K-ZL, YH, and Z-YL analyzed the results. XL, D-HZ, and XY drafted and corrected the manuscript. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Short CRP for Anterior Canalithiasis: A New Maneuver Based on Simulation With a Biomechanical Model

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Introduction/Objective: Anterior canalithiasis is an uncommon and challenging diagnosis. This is due in part to the difficulty of defining the affected side, the extreme positioning required to carry out described therapeutic maneuvers, and the infrequent use of specific maneuvers. Our objective is to present a new treatment alternative for anterior canalithiasis which is based on the well-known canalith repositioning procedure (CRP) described by Epley and which is used routinely in the treatment of both posterior and anterior canalithiasis. Analysis of the standard CRP for anterior canalithiasis with a biomechanical model validates that this new maneuver is an enhanced treatment option for anterior canalithiasis. We call the new maneuver the "short CRP."

Methods: A previously published 3D biomechanical model of the human labyrinths for the study of BPPV was used to analyze the conventional CRP in the treatment of anterior canalithiasis. The expected position of free otoliths near the anterior ampulla of the anterior semicircular duct was followed while recreating the sequential positions of the CRP. Although the standard CRP was possibly effective, certain enhancements were evident that could increase successful repositioning. These enhancements were incorporated into the modification of the CRP presented here as the "short CRP" for anterior canalithiasis.

Results: The traditional CRP used for posterior canalithiasis can also be used for anterior canalithiasis. Although in the traditional CRP the head hangs 30° below horizontal, our simulation shows that a 40° head-hang below horizontal is an enhancement and may ensure progression of anterior otolith debris. Elimination of Position 4 of the classic CRP, in which the face is turned 45° toward the floor, was also seen as an enhancement as this position is predicted to cause retrograde movement of otoliths back into the anterior canal if the patient tucks the chin in position 4 or when sitting up.

Conclusion: A modification of the CRP called the "short CRP" can be used to treat anterior canalithiasis. Model analysis predicts possible increased efficacy over the standard CRP. Model analysis of existing BPPV treatments is a valuable exercise for examination and can lead to realistic enhancements in patient care.

Keywords: benign paroxysmal positional vertigo, anterior canalithiasis, short CRP, maneuver, biomechanical model, simulation

INTRODUCTION

Anterior canalithiasis was first described in 1994 and is the least common variant of canalithiasis (1). Canalithiasis of the anterior canal produces a nystagmus with a downbeating vertical component, and with a torsional component directed toward the affected ear. In this report, Herdman et al. reported on 12% of 77 canalithiasis patients with eye movements consistent with anterior canalithiasis. The canalith repositioning procedure (CRP) had been described by Epley 2 years earlier and was used successfully in these patients with anterior canalithiasis (2). The CRP has remained in the toolbox as a primary treatment for anterior canalithiasis ever since. Subsequent systematic literature review has established the prevalence of anterior canalithiasis at 3% of cases of BPPV (3).

Later investigators have explored many other ways to effect repositioning of debris in the distal anterior canal back into the utricle. In 1999, a reverse Epley maneuver was described in which the head is dropped into the Dix-Hallpike position with the affected ear up and the patient is then moved in 90° steps toward the unaffected side as in the CRP (4). In 2004, another variation was described which can be accomplished simply with side-lying onto the affected side with the head hanging 45° below horizontal, then rising in steps to horizontal and then to 45° above horizontal before sitting up (5). In 2004, the Prolonged Forced Position Procedure was introduced (6). Although it was an impractical, hours long inpatient treatment—making it too cumbersome for practical use—the technique proved that extreme head hanging in the midline with sequential rising to upright could be effective regardless of the side affected. Other investigators showed that rising to upright in much shorter intervals of only 1 min from the Dix-Hallpike to the unaffected side and the affected side was effective (7). Subsequently, when rising at these intervals the Dix-Hallpike position on the affected side was also found to be effective (8, 9). Finally the advantages of midline head hanging without regard to the affected side and with faster sequential rising to sitting were combined by Yacovino who showed success starting with the head hanging 30–45° and rising to 45° above horizontal for 30 s before rising to sitting (10). This Yacovino maneuver has remained, like the CRP, a part of the common treatment canon for anterior canalithiasis. Yacovino's maneuver was subsequently re-described with subtle differences: a 3 min pause in each position rather than 30 s, and rapid transitions (11).

Today, there is no consensus on the best treatment for anterior canalithiasis. The Yacovino maneuver and the CRP are perhaps the most familiar to most practitioners. Efficacy of various repositioning strategies for anterior canalithiasis is only 75% (3). This is lower than efficacy reported for posterior canalithiasis treatment (1, 8, 12). In this study, we performed analysis of the CRP as used for anterior canalithiasis using a biomechanical model and identified a simplification that may result in improved efficacy (13). This simplified maneuver is presented here and called the "short CRP."

MATERIALS AND METHODS

A 3D model developed for the study of otolith disease was used to visualize the treatment of anterior canalithiasis by studying expected otolith positions in the different phases of the CRP maneuver. Our 3D model of the human membranous labyrinth, as previously reported, was created following the same technique as reported by Teixido et al. and Wang et al. for the creation of the Download-able Virtual Model of the Temporal Bone (13, 14). The model was created from axial histological sections, which were imaged with high resolution scanning and integrated into Amira 5.2.2. The reconstructed labyrinth was cloned for the contralateral side and carefully positioned in relation to the 3D surface map of a human skull and then a skin surface was applied. Moveable markers for otoconia were created to allow known and expected positions of otoconia to be mapped while transitioning from position to position.

As the head was moved into different positions during the CRP for anterior canalithiasis, the new gravity-dependent position of the otolith mass was marked. The standard CRP maneuver sequence was followed with an otolith mass present in the right anterior canal. The classic sequence was modified to maximize forward progression, and to avoid unnecessary positions and retrograde movement of the otolith mass during repositioning. Numerous trials resulted in identification of a modified sequence which maximizes progression and reduces retrograde movement of the otolith mass. Screenshots were taken for the publication of this article.

RESULTS

Our analysis demonstrated the reported efficacy of the CRP for treatment of anterior canalithiasis with progression of otolith debris around the circumference of the anterior canal during the CRP (**Figure 1**). It also revealed potential enhancements and possible pitfalls of the traditional Epley for treating anterior canalithiasis that can influence the effectiveness of the maneuver for anterior canalithiasis that are not obvious without model

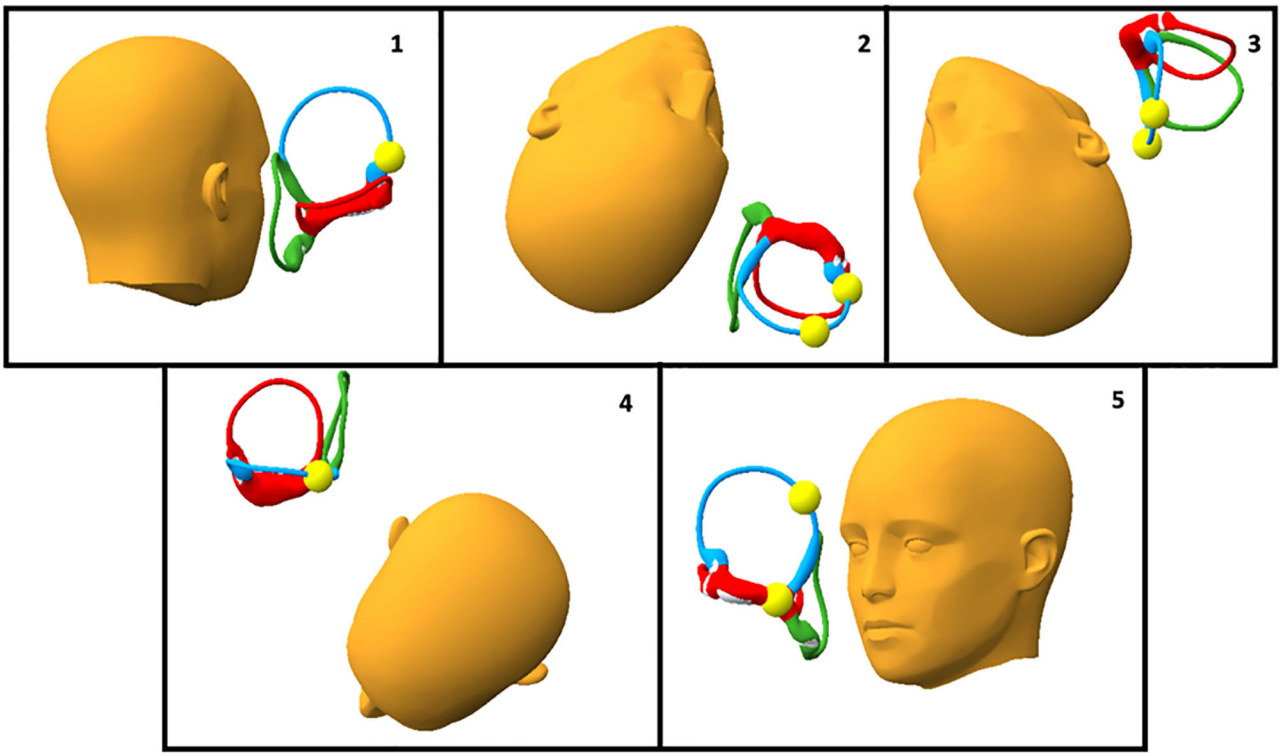

FIGURE 1 | The classic CRP has five positions shown here in a case of right anterior canalithiasis: In Position 1 the patient is seated upright with the head turned 45° to the affected side. In Position 2 the head hangs 30° below horizontal while turned 45° to the right. Position 3 is shown with the head hanging 30° and the head turned 45° to the left. Position 4 is shown with the patient rolled onto the left shoulder and with the face turned 45° toward the floor. In Position 5 the patient returns to sitting upright. Expected progression of the otolith mass is shown.

analysis. An enhancement is hanging the head to lower than 30° in position 2 to promote more definite progression of the otolith mass around the circumference of the anterior canal (**Figure 1**, Position 2). **Figures 2A,B** demonstrate the head hanging 30° and 40° below horizontal. The potential benefit of greater head hang than usual in the CRP is evident.

The most notable potential pitfall of the CRP is the position of the chin in head position 4. As seen in **Figure 1**, in Position 4 the chin is not tucked and the anterior canal is parallel to the earth so no otolith movement is expected. If the chin is tucked, however, as in **Figure 2C**, the otolith mass can progress in a retrograde fashion into the anterior canal. Sitting up with the chin tucked from this position could result in the return of otoliths to their starting position and a treatment failure.

Evident from this analysis is that Position 4 of the CRP may be omitted altogether, avoiding a potential pitfall and simplifying the maneuver. The shortened maneuver with increased head hang is presented here as the "short CRP" in **Figure 3**.

DISCUSSION

The treatment of canalithiasis has been characterized by constant modification and refinement. A review of the history of treatment of anterior canalithiasis presented above demonstrates that attempts at modification often serve only to prove another unique way to accomplish the same goal of particle repositioning. These can have their useful place if they serve the needs of selected patients with mobility and positioning problems. In our experience the maneuvers most utilized in the treatment of anterior canalithiasis are the Yacovino and the CRP. These have found their place in treatment based on their utility in the case of the Yacovino which does not require identification of the affected side, and familiarity in the case of the CRP. Both maneuvers are effective. Our analysis of the CRP in anterior canalithiasis presented in this paper is an attempt to provide a refinement that can enhance current therapy of patients with anterior canalithiasis who are currently treated with CRP.

Anterior canalithiasis treatment has been poorly studied and treatment efficacy is lower than treatment for posterior canalithiasis (12). This may be due to the difficulty in identifying rare patients for case series study, or because of the difficulties inherent in the diagnosis of anterior canal disease. These difficulties may include challenges in identifying the affected side because of an imperceptible rotary component of nystagmus. Since the position of the anterior canal axis on the globe is nearly equatorial, the rotary component is not as evident as in posterior canal disease. In some patients, downbeat nystagmus may be masked by concurrent posterior canal disease provoked in the same Dix-Hallpike position. Additionally, a patient thought to have anterior canalithiasis may actually have apogeotropic

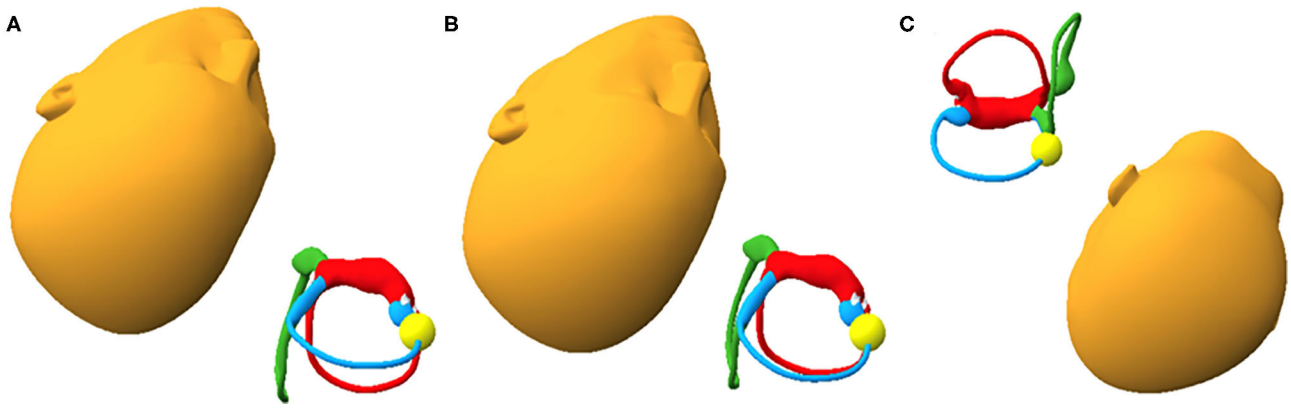

FIGURE 2 | (A) Shows anterior canalith position (yellow sphere) on the right with the head hanging 30° below horizontal and the head turned 45° to the right. **(B)** Shows anterior canaliths on the right with the head hanging 40° below horizontal and the head turned 45° to the right. Otolith movement is likely enhanced with greater head-hang. **(C)** The effect of tipping the head forward in position 4. In this circumstance otoliths may move back into the anterior semicircular duct and are in danger of resuming their starting position if the chin is tucked on rising.

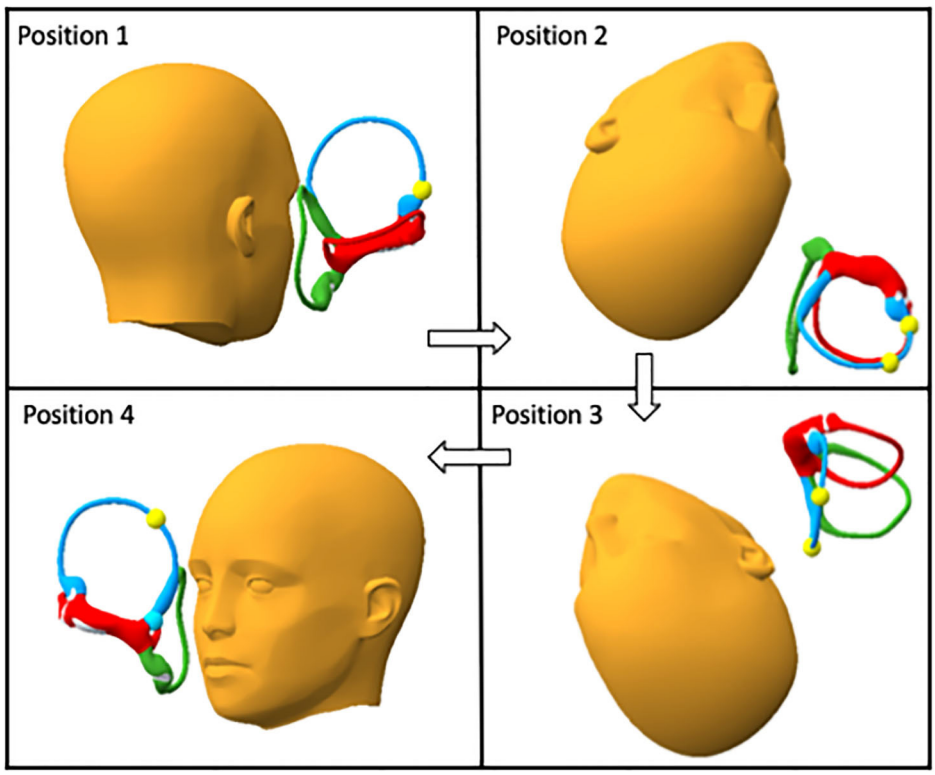

FIGURE 3 | The short Epley for anterior canalithiasis has four positions shown here: In Position 1 the patient is seated upright with the head turned 45° to the affected side. In Position 2 the head hangs 40° below horizontal while turned 45° to the right. Position 3 is shown with the head hanging 40° and the head turned 45° to the left. In Position 4 the patient returns to sitting upright. Expected gravitationally motivated progress of the otolith mass is shown as yellow spheres which mark positions before and after each position.

posterior canalithiasis or common crus lithiasis that escapes the attention of the examiner. The separation of these entities which may cause downbeating nystagmus from anterior canalithiasis is a subject of ongoing discussion (15). Other challenges to accurate diagnosis exist. Some central positional downbeat nystagmus may be incorrectly diagnosed as BPPV. Treatment deficiency may also be due to unrecognized errors in performance of maneuvers created by difficulties the practitioner may have in

visualizing the anterior canal and the membranous labyrinth in general. The ability to clearly visualize the labyrinth is possible if an accurate model is utilized. It is from this perspective that our re-analysis of existing treatments is oriented.

It is reasonable to question the utility of model analysis in BPPV treatment. The authors acknowledge that although the model is based on a human membranous labyrinth the model is based on only a single labyrinth. It resides within the bony labyrinth which itself has small but significant variations of position within the human skull (16). As such, the model may not be said to be a final predictor of all possible otolith movement phenomena related to BPPV. Other sources of variable otolith behavior such as otolith size and proximity to the duct wall have been proposed in empiric study (17). These proposed variables as well as other known phenomenon of otolith movement such as canal conversion and canalith jam may also confound model predictions. Our model comprises a freely mobile head whose positioning is not constrained by a neck and body and we have taken care to avoid positioning that is anatomically impossible. The modifications proposed are within the well-established range of movements required in the standard CRP. We feel it is reasonable to trust model analysis if the predicted otolith movements are gross movements and are reasonably similar to head position changes that produce observable eye movements in clinical practice and in maneuvers with validated efficacy as in posterior canalithiasis. A biomechanical analysis of the Dix -Hallpike maneuver was previously reported which resulted in the introduction of an expanded Dix-Hallpike maneuver which has added clinical utility by allowing separation of posterior and anterior canal responses in patients who may have simultaneous disease (18).

Our proposed maneuver has some disadvantages over the commonly used Yacovino maneuver in that it requires determination of the affected side, which can be difficult in anterior canalithiasis, and because it has more head positions than the Yacovino. Our hope is that some patients found to have anterior canalithiasis who cannot extend their necks sufficiently in the midline supine position may be effectively treated with this adaptation of the CRP.

Our current analysis has resulted in a simplification and enhancement of the CRP when used for anterior canalithiasis. The simplification eliminates the unnecessary Position 4 in the CRP treatment sequence which may compromise efficacy, and the enhancement includes head hanging below 30° to more definitely facilitate otolith progression in a direction that promotes maneuver success. We believe the "short CRP," comprised of modifications of the well-known CRP, may be an option to treat anterior canalithiasis. Successful performance on human subjects is required to prove its efficacy we believe the "short CRP," with these resulting modifications of the well-known CRP, can be used to treat anterior canalithiasis.

CONCLUSION

A modification of the CRP called the "short CRP" may be an option to treat anterior canalithiasis. Model analysis demonstrates possible increased efficacy over the standard CRP. Model analysis is a valuable exercise for examination of existing BPPV treatments and can lead to realistic enhancements in patient care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

RD'A: original concept. MT: biomechanical analysis, manuscript creation, and illustrations. RC: manuscript preparation. MM: original concept. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Functional Integrity of the Inferior Vestibular Nerve and Posterior Canal BPPV

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The functional integrity of the inferior vestibular nerve (IVN) may be evaluated by the cervical vestibular evoked myogenic potential (cVEMP) response, which requires signal transmission via the nerve. As functional integrity of the IVN innervating the posterior semicircular canal is required to produce the typical positioning vertigo and nystagmus characterizing posterior canal benign paroxysmal positional vertigo (PCBPPV), we hypothesized that normal cVEMPs would be found in most PCBPPV patients. Twenty-four PCBPPV patients participated in a prospective cohort study. All were treated by canal repositioning maneuver and had air-conduction cVEMP and videonystagmography (VNG). Follow-up evaluations including history and otoneurological bedside examination were carried out 1, 3, 6, and 12 months after the initial treatment. At the last follow-up, the patients filled the Dizziness Handicap Inventory (DHI) questionnaire. Normal cVEMPs were recorded in 19 (79%) and were absent in 5 (21%) of the subjects. The average DHI in the patients with normal cVEMP was 16.42 ± 17.99 vs. 0.4 ± 0.89 among those with pathological cVEMP ($p < 0.04$, Mann–Whitney test). Thirteen (54%) patients experienced recurrent PCBPPV (rPCBPPV). The average DHI score was significantly higher among patients having recurrence (22.15 ± 18.61) when compared to those with complete cure (2.36 ± 5.98; $p < 0.003$, Mann–Whitney test). Ten (77%) of the subjects with rPCBPPV had normal and 3 (23%) had pathological cVEMP as compared to 9 (82%) and 2 (18%) subjects in the non-recurrent (nrPCBPPV) group (Fisher's exact test—not significant). cVEMP p13 and n23 wave latencies and amplitudes, inter-aural differences in p13-n23 peak-to-peak amplitudes, and response thresholds did not differ between the groups. No differences were found between the rPCBBPV and nrPCBBPV groups in VNG caloric lateralization and directional preponderance values. We have found that in most cases, PCBPPV symptoms and signs are associated with normal cVEMP response supporting the role of IVN functional integrity. The absent cVEMPs in the minority of patients, although having similar clinical presentation, raise the possibility that the

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ipsilateral saccule is affected by the same pathology causing degeneration of the utricle macula. Alternatively, lacking inhibitory stimuli from the involved ipsilateral utricle or partial degeneration of the IVN and ganglion could explain the diminished cVEMP response.

Clinical Trial Registration: The study was registered in ClinicalTrials.gov Internet site (study ID—NCT01004913; https://clinicaltrials.gov/ct2/show/NCT01004913?cond=BPPV&cntry=IL&draw=2&rank=3).

Keywords: cervical evoked myogenic potentials, vestibular nerve, vertigo, benign paroxysmal positional, saccule and utricle, semicircular canals, surveys and questionnaires, caloric tests

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common peripheral cause of vertigo. Lifetime prevalence is estimated to be 2.4% (1), and 20–25% of patients referred to dizziness/vertigo centers are diagnosed as suffering from BPPV (2, 3).

Current understanding of posterior semicircular canal benign paroxysmal positional vertigo (PCBPPV) pathogenesis involves the dislodgement of otoconial debris detached from the utricle into the posterior semicircular canal (PSCC). The effect of the gravitational forces on these debris leads to deflection of the canal cupula, resulting in vestibular afferent firing transmitted via the inferior vestibular nerve to the vestibular nuclei (4). The dependence of PCBPPV symptoms and signs on the integrity of PSCC innervation is demonstrated by its complete resolution following singular neurectomy in reluctant cases (5).

The cervical vestibular evoked myogenic potentials (cVEMPs) are short-latency electromyographic responses that can be recorded from the ipsilateral sternocleidomastoid muscle (SCM) during its contraction phase in response to air and bone-conducted acoustic stimuli, skull tapping, and galvanic stimulation (6). The cVEMP pathway is believed to originate in the saccular macula and continues through the ipsilateral inferior vestibular nerve and ganglion, vestibular nucleus, ipsilateral vestibulospinal tracts, spinal motor nucleus, and the sternocleidomastoid muscle. This sacculo-collic reflex is characterized by biphasic waves with initial positivity (p13) followed by a negative wave (n23) (6, 7). As the cVEMP response of the sacculo-collic reflex depends on the spreading of neural signals via the inferior vestibular nerve, it has been suggested that cVEMPs would be preserved in patients having the clinical presentation of PCBPPV (8).

The aim of the study was to examine cVEMP response in patients suffering from PCBPPV. Our hypothesis was that cVEMP would be recorded in most patients suffering from PCBPPV.

PATIENTS AND METHODS

Sample and Design

Twenty-four consecutive patients suffering from PCBPPV (10 males, 14 females) aged 32–60 years (mean 51.8 ± 7.36 years; median 54.5 years) referred to a tertiary otoneurology unit were recruited to a prospective cohort study. PCBPPV was diagnosed by a Dix-Hallpike maneuver demonstrating crescendo–decrescendo geotropic rotatory nystagmus with an upbeating vertical component, which changed its direction when the patient resumed sitting position. The upper age limit of 60 years was elected in order to avoid potential bias due to the known deterioration in cVEMP response in older individuals (9). After signing an informed consent, the patients had baseline evaluation that included detailed history with emphasis on previous or existing ear disease, complete otoneurological bedside examination including microscopic otoscopy, eye-movement examination with and without Frenzel glasses, post-head shaking test, head impulse test, supine roll test, Dix-Hallpike maneuver, enhanced Romberg test, tandem walking test, and Fukuda stepping test.

Following the diagnosis of PCBPPV, treatment was completed by Epley's canalith repositioning procedure (CRP) (10). After an interval of 30 min, a second Dix-Hallpike maneuver was carried out and Epley's CRP was repeated as required. All patients in our cohort had negative findings on Dix-Hallpike maneuver following a maximum of two Epley's CRPs.

All participants had the following laboratory evaluation the days following successful CRP: pure tone, speech and impedance audiometry; videonystagmography (VNG) including tests for oculomotor system integrity (saccadic, gaze, optokinetic, and pursuit systems), tests for spontaneous, positional, and positioning nystagmus (Dix-Hallpike maneuver), and the alternate binaural bithermal caloric test (11); and cVEMPs testing including p13-n23 wave recordings and response threshold.

The study participants met the following inclusion criteria: (1) age 18–60 years; (2) negative history for concurrent or previous otological disease beside positional vertigo; (3) Dix-Hallpike maneuver positive for the presence of unilateral PCBPPV; (4) normal air-conduction pure tone, speech, and impedance audiometry; and (5) normal VNG test battery findings or compatible with peripheral vestibulopathy alone.

Follow-up evaluations including history and otoneurological bedside examination were conducted 1, 3, 6, and 12 months after the initial treatment. On the 12-months follow-up appointment, the patients filled the Dizziness Handicap Inventory (DHI) questionnaire (12).

The study protocol and procedures were approved by the committee for human experiments, Meir Medical Center, Kfar Saba, Israel, and were registered in ClinicalTrials.gov Internet site (study ID—NCT01004913; https://clinicaltrials.gov/ct2/show/NCT01004913?cond=BPPV&cntry=IL&draw=2&rank=3). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Cervical Vestibular Evoked Myogenic Potentials (cVEMP)

cVEMPs were performed bilaterally using the Navigator Pro System (Bio-Logic Systems Corp., Mundelein, IL, USA). Muscle activity was recorded in the supine position with the subject lying using Ag/AgCl electrodes. The active electrode was attached over the main bulk of the SCM muscle, approximately half the distance between the mastoid tip and the sternal notch. A reference electrode was placed over the upper sternum and the ground electrode on the forehead. Tone-burst air stimuli were presented to the ears through insert earphones at 4.3 Hz with a central frequency of 500 Hz. To achieve enough contraction of the SCM, subjects were instructed to lift their heads. Electromyographic activity was recorded simultaneously from both sides to minimize possible effects due to asymmetric muscle tone. The time window for recording was 53.3 ms; the electromyographic potential was amplified ×1,000 and filtered to the 10–1,500-Hz frequency range. Each cVEMP response was the average of the responses to 200 consequent stimuli. The eligibility criterion was correlation above 0.75 for two successive responses and p13-n23 peak-to-peak amplitude at least twice the size of the pre-stimulation baseline recording (13). Initial stimuli were provided at 90 dBHL decreasing in 5 dBHL steps. The cVEMP threshold was determined at the lowest stimulus level, still producing a response. Whenever a response could not be elicited at 90 dBHL, stimulus increase up to a maximal level of 97 dBHL was allowed. When a response could not be obtained at that level, the cVEMP was defined absent.

The following cVEMP parameters were measured: p13 and n23 wave latencies and amplitudes; p13-n23 peak-to-peak amplitude; inter-aural amplitude difference (IAD) defined as the ratio between the right and left peak-to-peak amplitude difference and the sum of both sides' peak-to-peak amplitude; and response threshold.

Statistical Analysis

cVEMP was defined as abnormal for IAD >35% or absent response (14). Caloric test results showing unilateral weakness >25% or directional preponderance >30% were considered pathological (15).

The proportions of abnormal cVEMP and caloric test results were compared between the patients who suffered PCBPPV recurrences during the 12-months follow-up period (rPCBPPV) and those having complete resolution (nrPCBBPV) employing Fisher's exact test.

cVEMP wave latencies, peak-to-peak amplitudes, IAD, and thresholds were compared between the rPCBBPV and nrPCBPPV groups by the Student unpaired two-tailed test or the

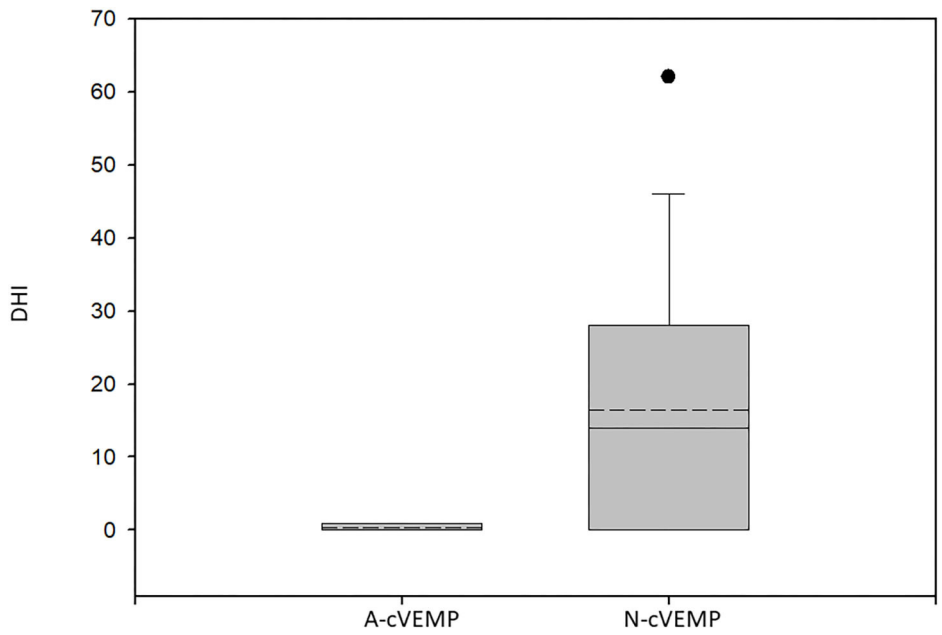

FIGURE 1 | Box plot of the Dizziness Handicap Inventory scores of patients with absent cVEMPs and those with normal responses. A-cVEMP, absent cVEMPs; N-cVEMP, normal cVEMPs; DHI, Dizziness Handicap Inventory score. The boundary of the box closest to zero indicates the 25th percentile, the solid line within the box marks the median, the dashed line marks the mean, and the boundary of the box farthest from zero indicates the 75th percentile. Whiskers above and below the box indicate the 90th and 10th percentiles. Circles above and below the 90th and 10th percentiles mark outlying data points. Significantly lower scores were found for the patients with missing cVEMPs ($p < 0.04$, Mann–Whitney test).

non-parametric Mann–Whitney test according to the Shapiro–Wilk normality test results.

DHI questionnaire results were compared using the Mann–Whitney test.

P-values <0.05 were considered statistically significant. Statistical analysis was performed using the GraphPad InStat version 3.06 software (San Diego, CA, USA).

RESULTS

Normal cVEMPs were recorded in 19 (79%) and were absent in 5 (21%) of the subjects. In all absent cVEMP cases, the missing response was ipsilateral to the PCBBPV side. None of the bilaterally elicited cVEMPs met the criteria of IAD >35%.

The mean DHI score at 12 months from diagnosis in patients with normal cVEMP was 16.42 ± 17.99 vs. 0.4 ± 0.89 among those with absent cVEMP ($p < 0.04$, Mann–Whitney test) (**Figure 1**).

VNG was performed in 19 (79%) of the patients, and pathological caloric test results were found in 6 (32%). Five had significant caloric lateralization (>25%) and 1 increased directional preponderance (>30%). Canal paresis was ipsilateral to the PCBPPV side in all cases while the directional preponderance of the caloric nystagmus slow phase velocity was to the contralateral side.

During the 1-year follow-up 13 (54%) patients experienced rPCBPPV.

Ten (77%) of the subjects with rPCBPPV had normal and 3 (23%) pathological cVEMPs as compared to 9 (82%) and 2 (18%) subjects in the nrPCBPPV group. The proportions of absent cVEMPs did not differ between the groups (Fisher's exact test).

The variance in p13 and n23 wave latencies, p13-n23 peak-to-peak amplitudes, IAD percentage, and cVEMP thresholds could not predict PCBPPV recurrences (**Table 1**).

VNG was conducted in 8 of the patients with rPCBPPV. Pathological caloric test was found in 3 (38%) of them as compared to 3 of 11 patients (27%) of the nrPCBBPV group (Fisher's exact test—not significant). No significant differences were found between the rPCBBPV and nrPCBBPV groups in VNG caloric lateralization and directional preponderance values (**Table 2**).

The average DHI in patients with pathological caloric tests was 19.33 ± 17.46 vs. 11 ± 17.16 among the patients that had normal results. This difference did not reach statistical significance (Mann–Whitney test).

The average DHI score 12 months post-presentation was significantly higher among patients having recurrences (22.15 ± 18.61) when compared to those with complete resolution (2.36 ± 5.98; $p < 0.003$, Mann–Whitney test) (**Figure 2**).

TABLE 1 | cVEMP wave latencies and amplitudes, p13-n23 peak-to-peak amplitudes, response thresholds, and inter-aural amplitude differences (IAD) (mean ± standard deviation) compared between the patients with recurrent posterior canal BPPV (rPCBPPV) and patients with no recurrences (nrPCBPPV).

	rPCBBPV	nrPCBPPV	Statistical significance
RIGHT EAR			
p13 latency (ms)	15.01 + 1.72	14.76 + 1.01	NS (unpaired *t*-test)
n23 latency (ms)	23.76 + 2.37	23.03 + 1.76	NS (unpaired *t*-test)
p13-n23 peak-to-peak amplitude (μV)	94.68 + 36.45	84.82 + 54.75	NS (unpaired *t*-test)
Threshold (dBHL)	90.83 + 5.15	88.75 + 5.17	NS (Mann–Whitney)
LEFT EAR			
p13 latency (ms)	15.19 + 3.17	15.04 + 1.24	NS (Mann–Whitney)
n23 latency (ms)	23.35 + 2.03	23.09 + 1.28	NS (unpaired *t*-test)
p13-n23 Peak-to-peak amplitude (μV)	89.49 + 35.07	74.46 + 33.96	NS (unpaired *t*-test)
Threshold (dBHL)	90.45 + 5.22	89.37 + 4.95	NS (Mann–Whitney)
IAD (%)	11.74 + 11.2	13.58 + 5.5	NS (unpaired *t*-test)

TABLE 2 | Videonystagmography caloric tests results compared between the patients with recurrent posterior canal BPPV (rPCBPPV) and patients with no recurrences (nrPCBPPV).

	rPCBBPV	nrPCBPPV	Statistical significance
Lateralization (%)	4.25 + 35.1	13.7 + 25.27	NS (Mann–Whitney)
Directional preponderance (%)	11 + 17.47	2 + 17.52	NS (unpaired *t*-test)

DISCUSSION

Although cVEMPs could be recorded in most PCBPPV patients (79%), the elicited response was missing in 5 (21%) despite the presence of characteristic clinical presentation. Functioning neural pathways transmitting the provoked signal from the PSCC ampullary crest via the inferior vestibular nerve to the medial vestibular nucleus is required for the full clinical presentation of PCBPPV to evolve. The failed cVEMP response might be explained by involvement of organs that contribute to the sacculo-collic reflex arch but with no effect on the PSCC-inferior vestibular nerve pathway. Similarly, PSCC dysfunctions have been registered with rotation test and video-head impulse testing in patients developing PCBPPV despite reduced vestibulo-ocular reflex gain for the mild and high-frequency domains, likely due to a transient canal disorder (16–18).

One possible explanation is saccular dysfunction. The utricle and saccule maculae have similar anatomic characteristics and may be affected by the same pathological process. As functional saccule is required for the cVEMP response, degeneration of this end organ or its innervation would result in pathological cVEMP.

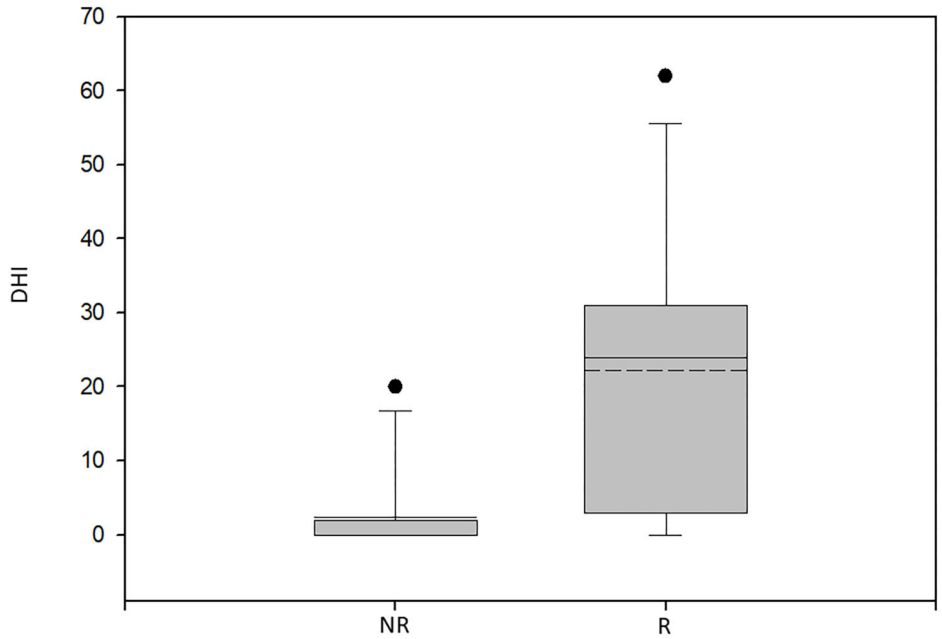

FIGURE 2 | Box plot of the Dizziness Handicap Inventory scores for the patients with recurrent BPPV and non-recurrent BPPV. NR, non-recurrent group; R, recurrent group; DHI, Dizziness Handicap Inventory score. Significantly lower scores were found for the non-recurrent group ($p < 0.003$, Mann–Whitney test).

Support for this reasoning is provided by the histopathological observation of ganglion cell loss in the saccular nerves of temporal bones from BPPV patients (19).

Another possibility is partial derangement of the inferior vestibular nerve still transmitting the canal afferent signals initiating the eye-movement and vertigo symptoms although hampering cVEMP response. Previous BPPV-related anatomical studies have reported 30–50% loss of inferior vestibular nerve neurons and degenerative changes in the inferior vestibular ganglion (19, 20). In this context, it is of interest that the mean DHI score of the patients with no cVEMP response was significantly lower than that of those with normal cVEMPs. The reduction in PCBPPV symptoms, and accompanied emotional and physical impact, which are evaluated by the DHI questionnaire, might be explained by a decrease in the transmission of the offending signals secondary to the anatomical changes described.

A limitation of the study involves the conduction of cVEMP by air conduction alone. Although the inclusion criteria precluded conductive hearing loss, it is argued that cVEMPs can be elicited by bone stimulation when air-conduction response fails albeit normal air-conduction audiometry.

Further limitation is the relatively small size of our cohort requiring a larger-scale study supporting our results.

Whereas cVEMPs test type-I vestibular hair cells located at the peri-striolar region of the saccule, subjective visual vertical (SVV) represents a test assessing regular afferents coming from more peripheral saccular regions. Testing SVV might have disclosed functional peripheral saccular regions in the face of missing cVEMP response (21).

Animal studies showed that both saccule and utricle have inhibitory projections to the ipsilateral SCM whereas the utricle has an additional excitatory projection to the contralateral SCM (22). It was estimated that the air-conducted cVEMP response is composed of 74 and 26% saccular and utricular components, respectively (23). Degeneration of the utricle macula, superior vestibular nerve, and ganglion were repeatedly described in PCBPPV (19, 20, 24, 25). Thus, reduced contribution of involved ipsilateral utricle to the cVEMP response might explain its observed absence among some PCBPPV patients.

Although the aim of our study was the examination of cVEMP in PCBPPV patients, ocular VEMP responses (oVEMPs) could have contributed to the delineation and extent of utricular involvement in our patients (26–28).

It has also been suggested that the otolithic organs exert inhibitory signals on the PSCC excitatory activity converging in the medial vestibular nucleus (19, 29). Thus, otolith dysfunction as reflected by pathological cVEMP might even contribute to the clinical presentation of PCBPPV (30–32).

While a recent study did not find differences in any of the cVEMP parameters between PCBPPV patients and matching healthy controls (27), most previous publications have reported rates of abnormal cVEMPS within the range of 23.5–39% (4, 30, 33–40). The higher occurrence of pathological cVEMP previously found might stem from the different criteria employed. While in ours and other studies (26) the normalized criterion of increased IAD and missing cVEMP responses were the parameters taken into consideration, others used in addition the less conservative criteria of prolonged wave latencies and decreased amplitudes (30, 33–40). Also, two of the studies

(33, 39) included lateral and anterior canal variants of BPPV while the reported cVEMP results did not distinguish between the groups. As p13-n23 wave latencies and amplitudes carry high intersubject and intrasubject variability (30, 41), we preferred to use the normalized parameter of IAD and qualitative approach defining cVEMP response as either present or absent.

In contradiction to ours and others' results demonstrating pathological cVEMP findings among PCBPPV patients, two previous studies with a limited number of patients found normal p13-n23 potentials in all their subjects. Murofushi et al. (8) reviewed cVEMP findings in 47 vestibular neuritis patients, 10 of which developed PCBPPV. While cVEMP response was missing in 16 (34%) of the patients implying inferior vestibular nerve involvement, it was present in all their 10 patients suffering from PCBPPV. Heide et al. (42) described three additional patients with normal cVEMPs.

Accumulating data suggest that utricular dysfunction as evaluated by oVEMPs is the main counterpart of PCBBPV while cVEMP response is more often preserved (27, 28). This supports the current understanding of PCBBPV pathogenesis involving dislodgement of otoconial debris detached from the utricle into the underlying PSCC.

The study patients were followed up for 12 months, which is the time frame in which most BPPV recurrences are anticipated (43). The rate of rPCBPPV in our cohort was 54%, higher than the 0–18% recurrence rates previously reported for the 1-year follow-up (44, 45). Although our cohort included patients suffering from isolated BPPV with no concomitant or previously diagnosed inner ear disease (primary BPPV), the presence of subclinical vestibulopathy is still a possibility. This might be reflected by the pathological caloric test results in 32% of the patients having VNG, indicating ipsilateral horizontal semicircular canal dysfunction, and absent cVEMPs in 21% implying underlying saccular or sacculo-collic pathway dysfunction. As otological comorbidities carry a higher risk for the development and recurrence of BPPV (46, 47), subclinical vestibulopathy might explain the high recurrence rate among our patients. The DHI scores of the rPCPPPV group at the end of the 12-months follow-up were significantly higher in accordance with continuous suffering due to the continuous positional vertigo.

Previous studies reported that abnormal or absent cVEMPs among PCBPPV patients were related to higher incidence of recurrence as well as to increased resistance to treatment and larger number of canalith-repositioning maneuvers required toward remission (30, 31, 39). We and others (26, 37) could not support this last notion, as the rate of absent cVEMP, wave latencies, p13-n23 amplitudes, IAD values, and response thresholds were similar in the rPCBPPV and nrPCBPPV groups and all patients in our cohort recovered following 1–2 CRPs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Committee for human experiments, Meir Medical Center, Kfar Saba, Israel. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS conceived and designed the study, analyzed and interpreted the results, and wrote the manuscript. RF collected the data, organized the database, and revised the manuscript. MK performed the tests and revised the manuscript. All authors approved the final version of the text.

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REVIEW
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Management of Lateral Semicircular Canal Benign Paroxysmal Positional Vertigo

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Benign paroxysmal positional vertigo (BPPV) is the most common cause of peripheral vestibular vertigo. It is caused by free-floating otoconia moving freely in one of the semicircular canals (canalolithiasis) or by otoliths adhered to the cupula (cupulolithiasis). The posterior canal is the most common canal affected, followed by the lateral canal. Diagnosis of the side affected is critical for successful treatment; therefore, suppressing visual fixation is essential to examination of these patients' eye movement. On the basis of our experience, we have adopted the Zuma maneuver and the modified Zuma maneuver for both apogeotropic and geotropic variants of lateral canal BPPV. Knowledge of the anatomy and pathophysiologic mechanisms of the semicircular canals is essential for correct management of these patients. Hence, using a single maneuver and its modification may facilitate daily neurotological practice.

Keywords: apogeotropic nystagmus, benign paroxysmal positional vertigo, canalolithiasis, cupulolithiasis, geotropic nystagmus, horizontal semicircular canal, lateral semicircular canal, repositioning maneuvers

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common cause of peripheral vestibular vertigo. The lifetime prevalence, the 1-year prevalence, and the 1-year incidence of BPPV were estimated at 2.4, 1.6, and 0.6%, respectively (1). The condition is characterized by brief recurrent attacks of vertigo induced by changes in head position relative to gravity, mainly when looking up, rolling over in bed, or straightening up after bending over (2). In most patients, it is caused by free-floating otoconia moving freely in one of the semicircular canals (canalolithiasis) (3–5). More rarely, otoconia are adhered to the cupula (cupulolithiasis) (6).

The cause of BPPV is mostly idiopathic. However, there are potential risk factors associated with higher incidence of BPPV, such as advancing age (7), migraine (8), genetic predisposition (9), head trauma (10, 11), vitamin D deficiency (12–14), low solar radiation exposure (15–17), and other inner ear diseases (i.e., vestibular neuritis, Menière's disease, and sudden sensorineural hearing loss) (18–20).

The posterior semicircular canal variant of BPPV (PC-BPPV) is a well-recognized condition, since it was described in 1952. It is characterized by a torsional vertical nystagmus provoked by the Dix Hallpike maneuver (21) or diagnostic Sémont maneuver (22, 23). In contrast, the first reports

of the lateral semicircular canal variant of BPPV (LC-BPPV) were published in 1985 (24, 25). This variant is characterized by linear horizontal nystagmus beating to the same side as (geotropic) or to the opposite side (apogeotropic) of the head turn in the supine roll test.

The PC is the most common canal affected, corresponding to 60 to 79% of all BPPV cases, followed by the LC, which accounts for 16 to 31% of cases (26–29). Both subtypes of BPPV can present with similar symptoms, although attacks may last longer and be more intense in LC-BPPV. Initially, the autonomic

TABLE 1 | Pros and cons of repositioning maneuvers for apogeotropic LC-BPPV.

Maneuver	Pros	Cons
Gufoni's new maneuver for apogeotropic LC-BPPV	- Transforms an apogeotropic variant into a geotropic variant - Starts by lying onto the affected side - Brisk deceleration	- Low rate of resolution with a single maneuver - Needs another maneuver after conversion to a geotropic variant - Lacks the forward head tilt before sitting up - Does not treat cupulolithiasis on the utricular side
Head-shaking in the horizontal plane	- Facilitates detachment of otoconia in cupulolithiasis - Can be combined with other maneuvers	- Low rate of resolution with a single maneuver - Needs to be repeated at least 3 times and at home - Lacks the forward head tilt before sitting up
Modified Semont maneuver	- Starts by lying onto the affected side - Brisk deceleration	- Low rate of resolution with a single maneuver - Lacks the forward head tilt before sitting up - Does not treat cupulolithiasis on the utricular side
Cupulolith repositioning maneuver (CuRM)	- Starts by lying onto the affected side - Combined with mastoid oscillation, which can help to detach the otoconia from the cupula - Treats cupulolithiasis on the utricular side	- Low rate of resolution with a single maneuver - Lacks brisk deceleration - Lacks the forward head tilt before sitting up
Zuma maneuver	- High rate of resolution with a single maneuver - Brisk deceleration - Starts by lying onto the affected side - Forward head tilt before sitting up	- -Long lasting (3 min in each step)

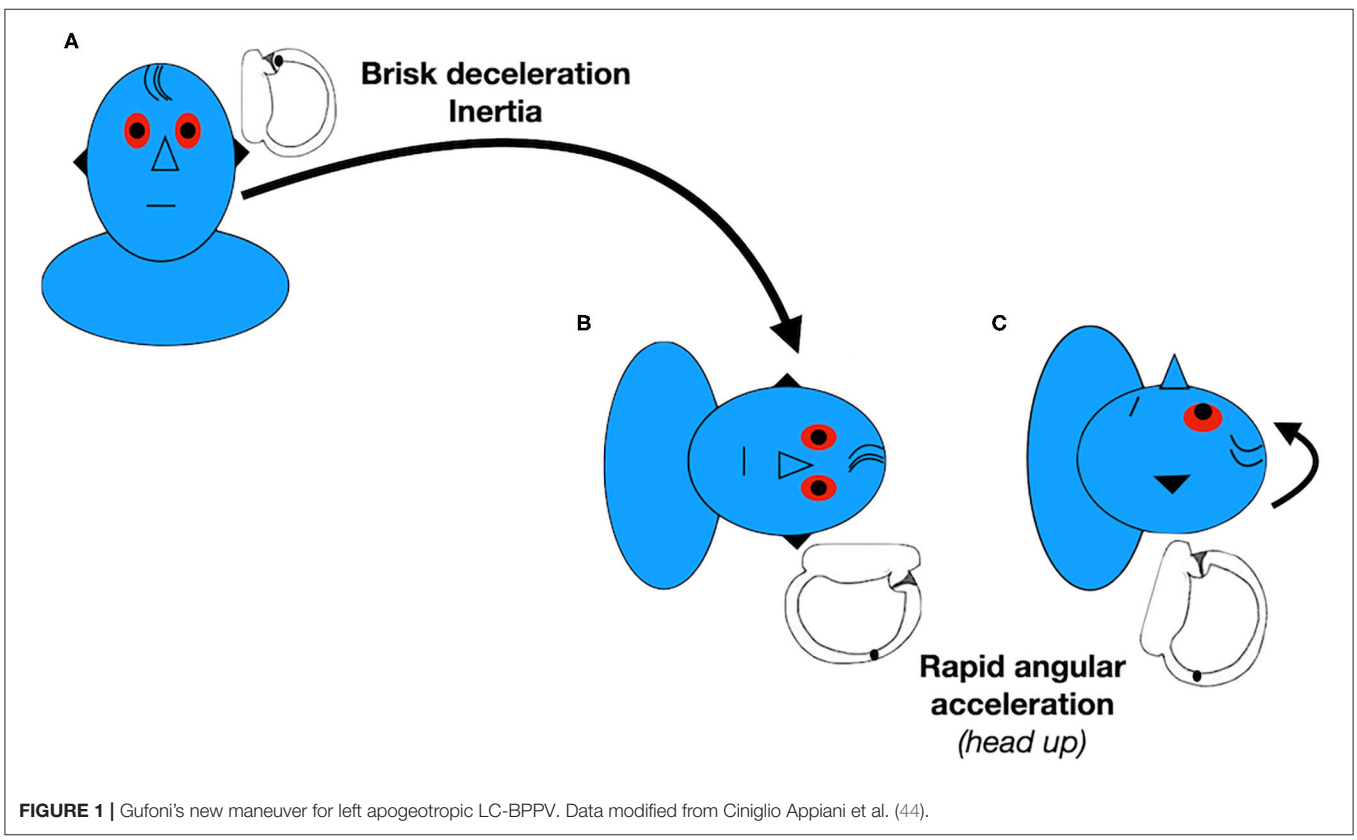

FIGURE 1 | Gufoni's new maneuver for left apogeotropic LC-BPPV. Data modified from Ciniglio Appiani et al. (44).

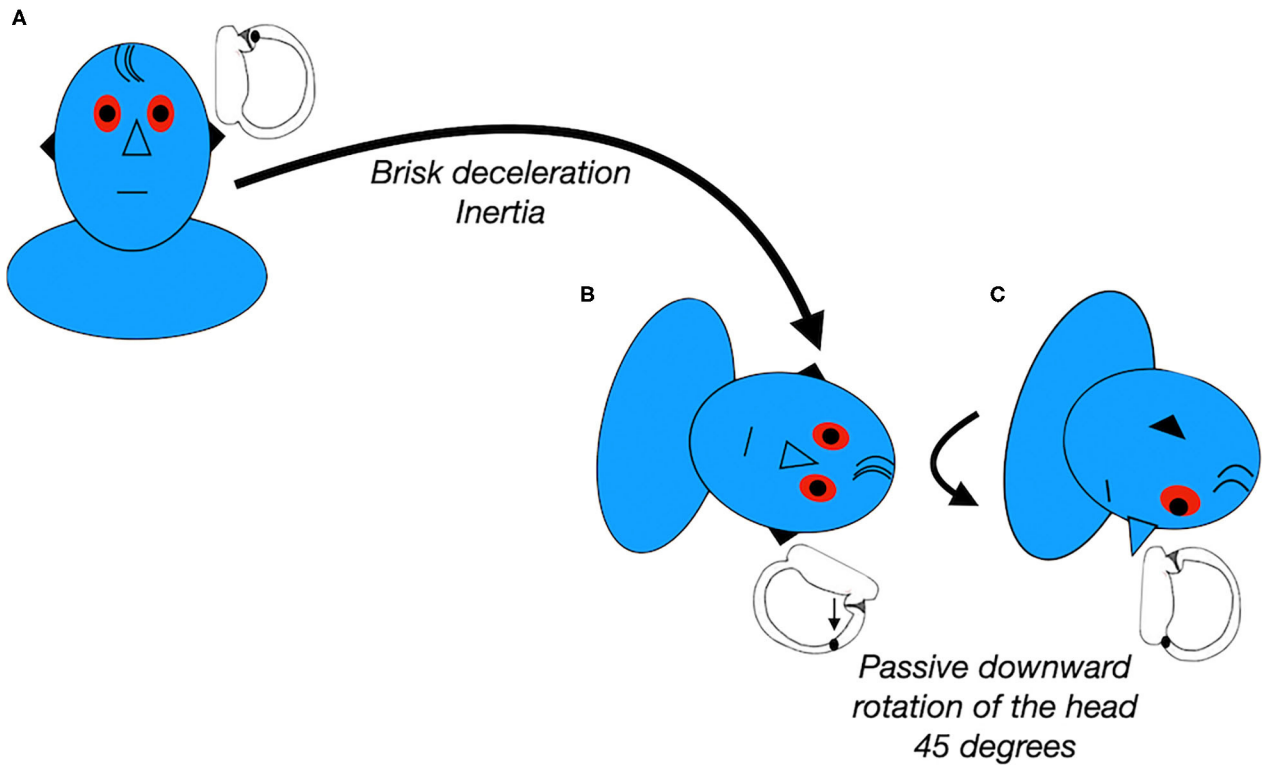

FIGURE 2 | Modified Semont maneuver for left apogeotropic LC-BPPV. Data modified from Casani et al. (48).

symptoms and the vertigo may be so severe, and provoked by any head or body movement, that patients sometimes only describe spontaneous and not positional vertigo (30). Mostly, however, the vertigo is provoked by lateral turning movements, leading patients with LC-BPPV to avoid turning their heads. Nevertheless, LC-BPPV has a higher rate of spontaneous resolution than PC-BPPV (25, 31). This can be understood if the spatial orientations of the semicircular canal are considered. The LC inclines upward and its cupular barrier is at the upper end. As a result, otoliths floating in the LC tend to move back to the utricle more easily (27).

DIAGNOSIS OF LC-BPPV

BPPV is a type of episodic recurrent vertigo provoked by head movement, but it may also present as an acute vestibular syndrome. A bedside examination should therefore be included as part of the physical examination of these patients.

Diagnosis of the side affected is critical for successful treatment (32). An important clinical sign for identifying the affected side in LC-BPPV is the intensity of the nystagmus evoked by the supine head roll test or McClure-Pagnini test. This maneuver can induce horizontal nystagmus that may beat toward the ground (geotropic variant) or toward the ceiling (apogeotropic variant). The geotropic variant is attributed to free floating particles in the posterior arm of the LC. In contrast, the apogeotropic variant of LC-BPPV is attributed to free floating particles in the anterior arm of the LC, particles attached to the cupula facing the canal, or particles attached to the cupula facing the utricle (33–36).

The McClure-Pagnini test is performed by turning the head about 90° to each side in a supine position. Since it is performed on the yaw plane, it should be more correctly called the head yaw test (HYT) while supine (30, 32, 37). The nystagmus beats with greater intensity toward the affected ear, according to Ewald's second law, which postulates that the response to an excitatory stimulus is always more intense than to an inhibitory stimulus. In geotropic LC-BPPV, the otoliths will move toward the ampulla during the HYT toward the affected ear, resulting in an ampullopetal excitatory current and causing a nystagmus beating toward the affected ear. Turning the head to the unaffected side, the particles will move away from the ampulla, resulting in an ampullofugal inhibitory endolymphatic current, causing a nystagmus beating to the unaffected ear. Conversely, in apogeotropic LC-BPPV (30, 38), the particles will move away from the ampulla during the HYT to the affected ear, resulting in an ampullofugal inhibitory endolymphatic current, causing a nystagmus beating toward the unaffected ear. Turning the head to the healthy side, the particles will move toward the ampulla, resulting in an ampullopetal excitatory endolymphatic current, causing a nystagmus beating toward the affected ear. Hence, in

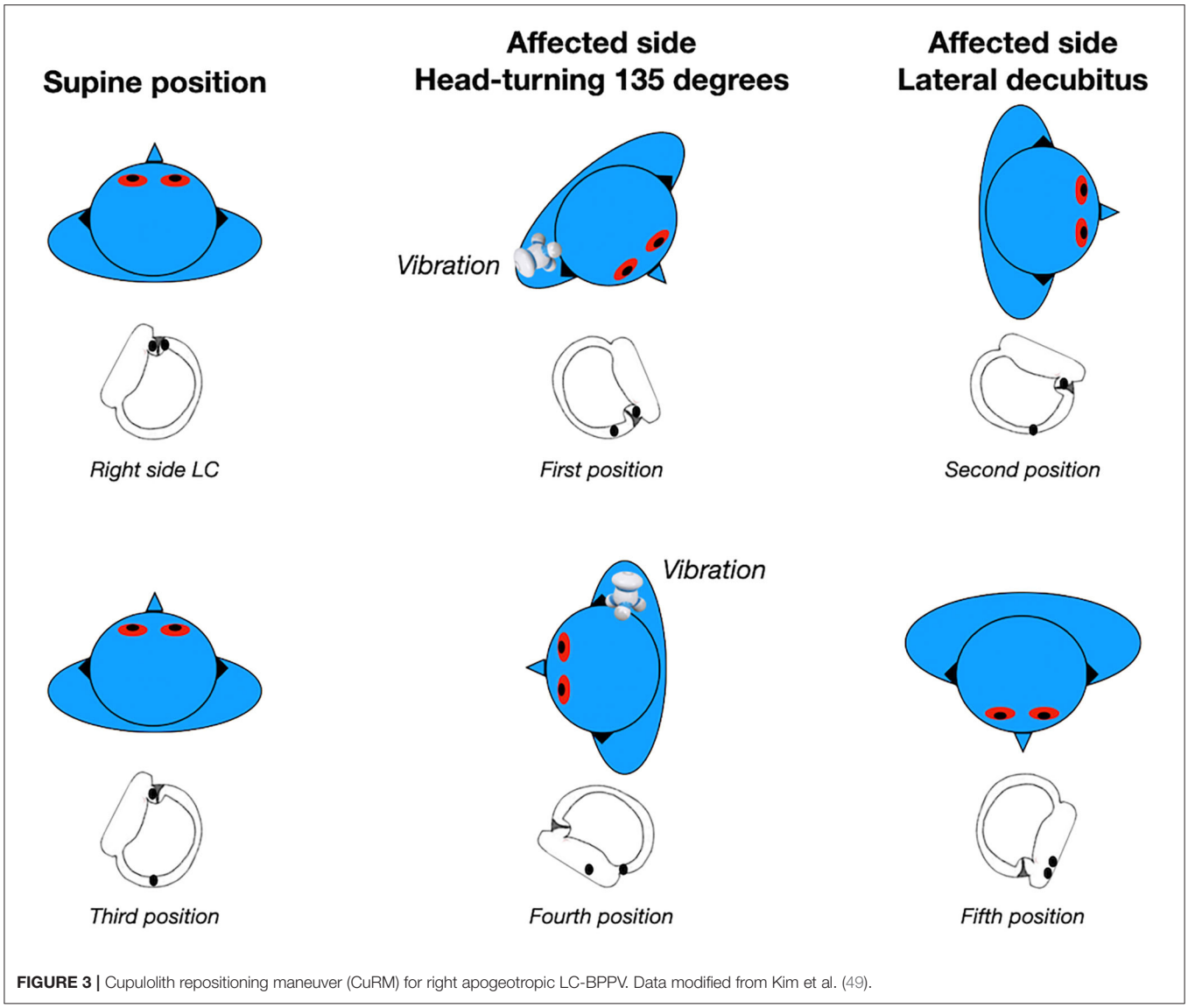

FIGURE 3 | Cupulolith repositioning maneuver (CuRM) for right apogeotropic LC-BPPV. Data modified from Kim et al. (49).

apogeotropic LC-BPPV, the affected side is the side on which the nystagmus is less intense.

However, sometimes it may be difficult to identify the differences in intensity of nystagmus in the HYT. As a result, several tests have been described for secondary signs of lateralization for identification of the affected side (39, 40).

In the Seated Supine Positioning Test (SSPT) (41, 42), the patient is briskly brought from a seated to the supine position. When the patient is brought to the supine position with the head flexed at 30°, the LC is on a vertical plane and the particles are pushed downwards. In geotropic LC-BPPV, in which the otoliths are located in the posterior arm of the LC, they move toward the utricle and away from the ampulla. This results in an ampullofugal inhibitory endolymphatic current and causes a nystagmus beating toward the unaffected ear. In apogeotropic LC-BPPV, in which the otoliths are in the anterior arm of the LC or adhered to the cupula, they move toward the ampulla. This results in an ampullopetal excitatory endolymphatic current and therefore the nystagmus beats toward the affected side.

The bow and lean test was described in 2006 (40). Since it is performed on the pitch plane, it should be more correctly called the head pitch test (HPT). First, it is necessary to confirm whether the type of LC-BPPV is a geotropic or apogeotropic variant, using the HYT. Next, the direction of nystagmus is noted when the patient bows the head over 90° and leans the head backward over 45° in the sitting position. In geotropic LC-BPPV, the otoliths move toward the ampulla in the bow test and away from the ampulla in the lean test. In contrast, in apogeotropic LC-BPPV, the otoliths move away from the ampulla in the bow test and toward the ampulla in the lean test.

Evaluation of nystagmus intensity and direction during the HPT can also be useful to distinguish between the geotropic and apogeotropic variants and to identify the affected side (39). According to a previous study, nystagmus with greater intensity

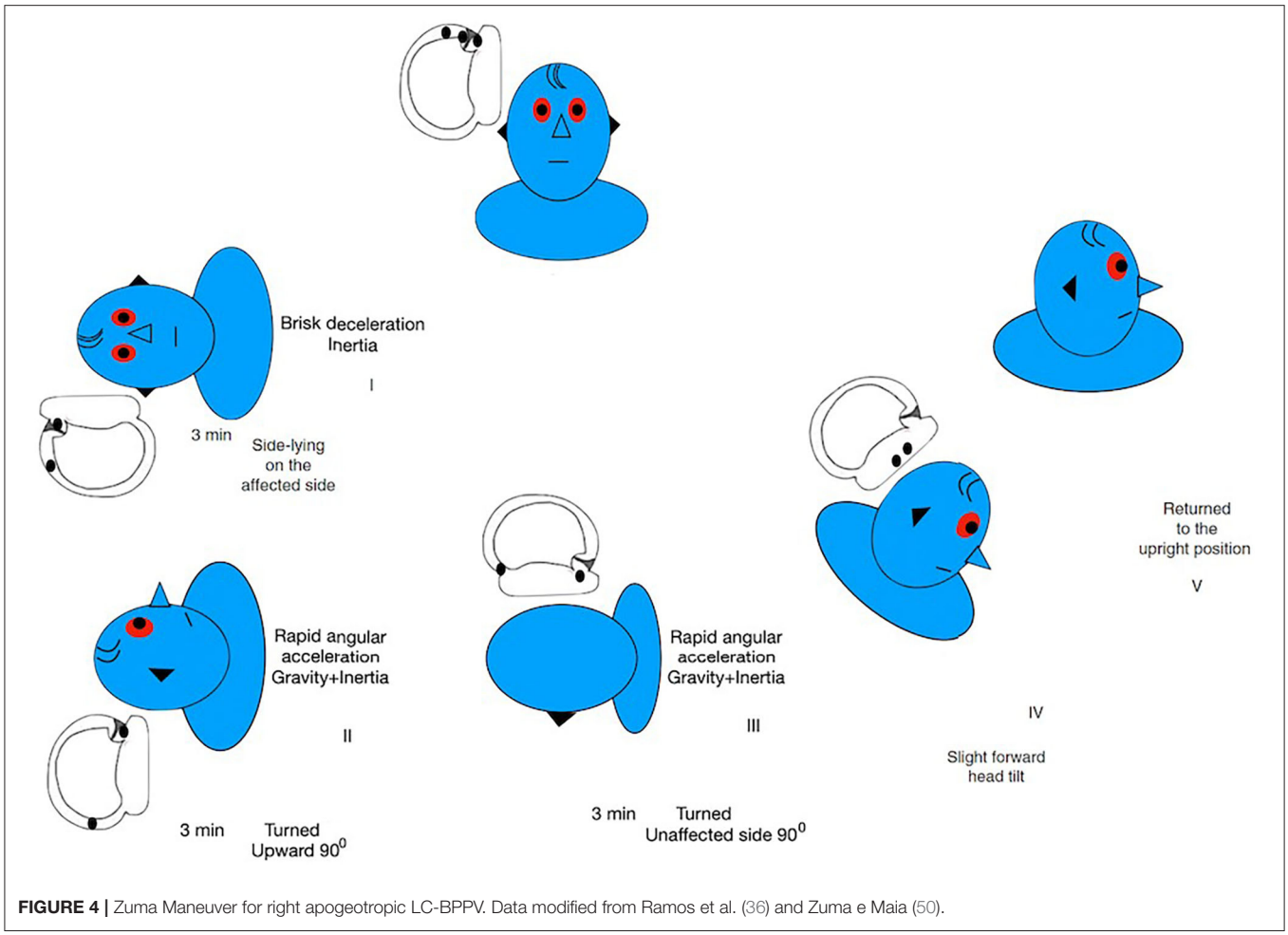

FIGURE 4 | Zuma Maneuver for right apogeotropic LC-BPPV. Data modified from Ramos et al. (36) and Zuma e Maia (50).

in the bow test than the lean test indicates an ampullopetal excitatory endolymphatic current and suggests a geotropic LC-BPPV affecting the same side as the direction of the nystagmus. Hence, if there is an intense nystagmus beating to the right in the bow test, the particles are located in the posterior arm of the right LC (geotropic LC-BPPV). Conversely, a nystagmus with greater intensity in the lean test than the bow test indicates an ampullofugal inhibitory endolymphatic current and suggests an apogeotropic LC-BPPV affecting the same side as the direction of the nystagmus.

Patients with LC-BPPV may also exhibit a pseudo-spontaneous nystagmus (PSN) and this can be differentiated from spontaneous nystagmus with the HPT in the sitting position (32). In the HPT, PSN increases its intensity with head extension over 30° and reverses direction with the head bent over 60°. The nystagmus may also stop when the head is bent to 30° (neutral position), since the LC is aligned in respect to the horizontal plane in this position. This nystagmus can be provoked by slow rotation of the patient's head horizontally, since this maneuver raises the percentage of patients who exhibit PSN to 96% (32). Inclination of the LC in respect to the horizontal plane allows the otoliths to move under the action of gravity. In geotropic LC-BPPV, the particles flow away from the ampulla and cause a nystagmus beating toward the unaffected ear. On the other hand, in apogeotropic LC-BPPV, the otoliths are pushed toward the ampulla and therefore the nystagmus beats toward the affected ear.

On the basis of our experience, we have adopted the strategy of the minimum stimulus for diagnosis of LC-BPPV (41). First, we rotate the patient's head slowly in the horizontal plane and check whether there is PSN. Then we perform the HPT, and check whether there is a horizontal nystagmus that changes direction with this test. If this nystagmus is observed, we proceed with the SSPT followed by the HYT.

MANAGEMENT OF THE APOGEOTROPIC VARIANT OF LATERAL CANAL BENIGN PAROXYSMAL POSITIONAL VERTIGO (APOGEOTROPIC LC-BPPV)

Choosing the correct repositioning procedure for the treatment of LC-BPPV is very complicated, since diagnosis of the affected side and the subtype of the BPPV is critical for successful treatment (43).

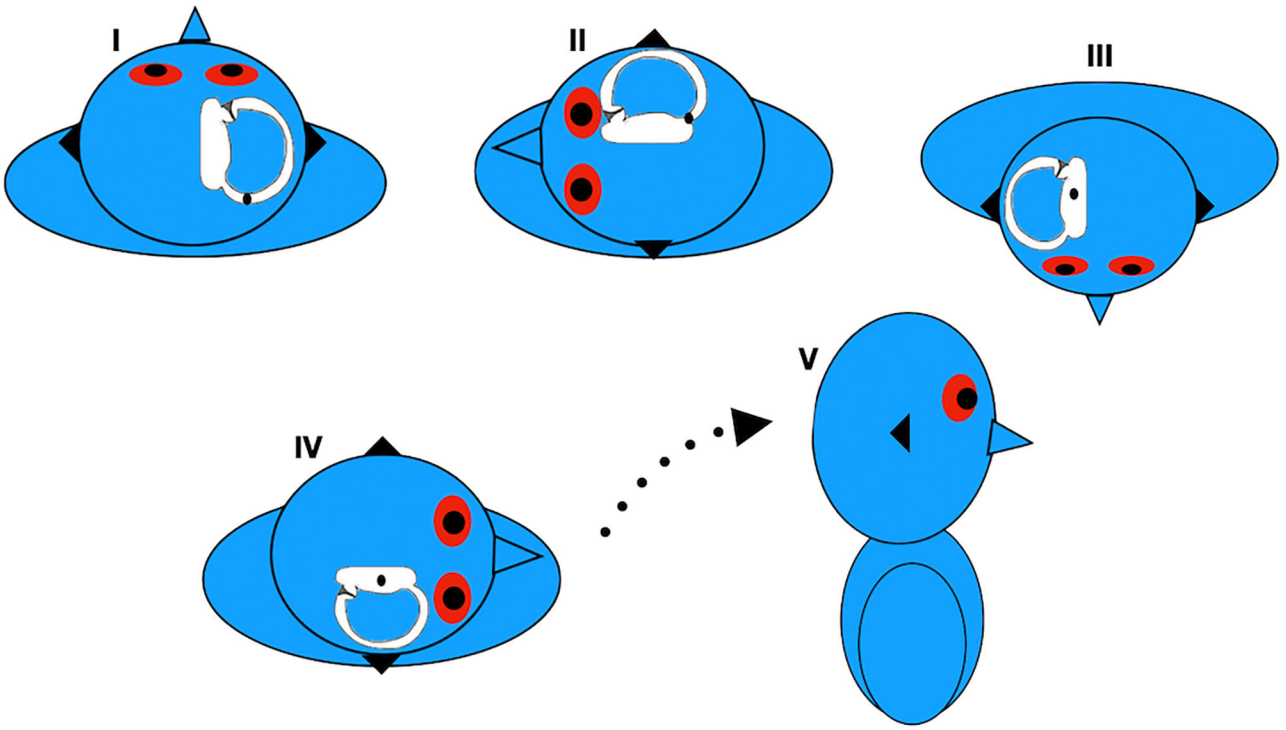

FIGURE 5 | Roll maneuver for right geotropic LC-BPPV. Data modified from Lempert and Tiel-Wilck (55).

Apogeotropic LC-BPPV is attributed to particles attached to the cupula facing the canal, particles attached to the cupula facing the utricle, or free-floating particles in the anterior arm of the LC (33–36). Consequently, the objective of the repositioning maneuver for this variant is to detach the otoliths from the cupula (in patients with cupulolithiasis facing the canal) and remove them and free particles from the anterior arm through the posterior arm toward the utricle. Otoliths that are adhered to the cupula on the utricular side can move straight to the utricle during the repositioning maneuver.

Several repositioning treatments have been proposed for apogeotropic LC-BPPV, such as the new Gufoni maneuver for the apogeotropic form of LC-BPPV (44, 45), head-shaking in the horizontal plane (46, 47), the modified Sémont maneuver (47, 48), the cupulolith repositioning maneuver (CuRM) (49) and, recently, the Zuma maneuver (50). **Table 1** lists the pros and cons linked to each of these maneuvers for apogeotropic LC-BPPV.

The new Gufoni maneuver for apogeotropic LC-BPPV consists of quickly moving the patient, starting from the sitting positioning, onto the affected side, followed by a quick 45° upward turn, before returning to the sitting position (44) (**Figure 1**). The inertia provoked by the brisk deceleration before the patient is brought to the lying down position may detach the particles from the cupula. In this position, the anterior and posterior arm of the LC are placed in the vertical plane, so otoliths may flow from the canal side of the cupula or from the anterior arm into the posterior arm. The 45° upward head turning is intended to facilitate movement of the detached particles from the utricular side of the cupula toward the utricle or movement of the otoconia from the canal side of the cupula toward the posterior arm of the LC (51). Some authors have previously reported achieving conversion from the apogeotropic into a geotropic variant of LC-BPPV in all patients (44). A randomized clinical trial (45) observed 59% of vertigo and nystagmus resolution with a single administration of the new Gufoni maneuver for apogeotropic LC-BPPV.

Previously, authors have presented head-shaking in the horizontal plane as a treatment for apogeotropic LC-BPPV. This maneuver is intended to break otoconial debris into pieces and detach the particles from the cupula through alternate accelerating and decelerating forces (46, 47, 51). There are several descriptions of this method. According to one previous study, (46) 3 series of 30 rapid right-left shakes of the head around the yaw axis were performed with the patient in supine position and then repeated at home twice a day for at least 3 days. A more recent study (47) proposed movement of the patient's head sideways in a sinusoidal fashion at an approximate rate of 3 Hz for 15 seconds in the sitting position with the head pitched at 30°. They reported response rates of 17 and 33%, respectively. A previous randomized clinical trial (45) showed better response in patients treated with the head-shaking maneuver compared with patients who underwent a sham maneuver. However, there was no difference in comparison with patients treated with the new Gufoni maneuver for apogeotropic LC-BPPV.

In the modified Sémont maneuver, the seated patient is briskly brought into a side-lying positioning onto the affected side,

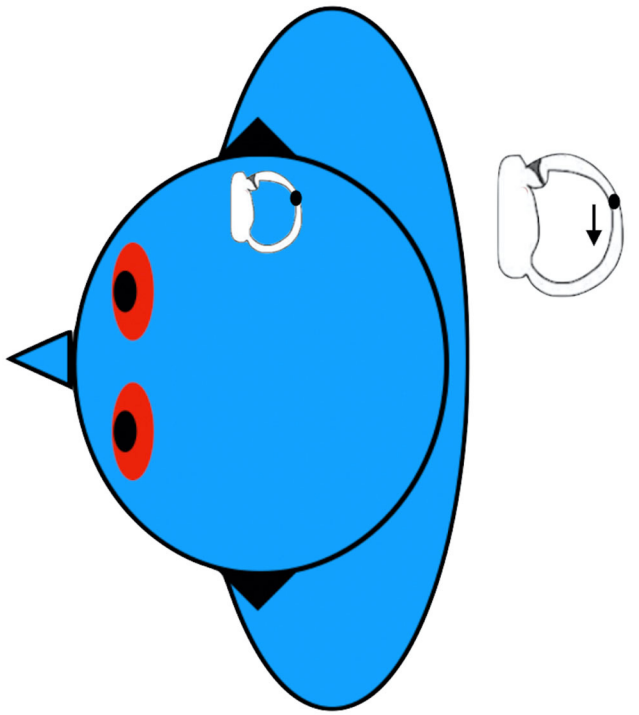

FIGURE 6 | Forced Prolonged Position for right geotropic LC-BPPV. Data modified from Vannucchi et al. (46).

followed by turning the head 45° downward, before returning to the sitting position (**Figure 2**). Theoretically, the principles of this maneuver should combine the effect of inertial and gravitational forces in order to detach the otoconia from the cupula and move it into the utricle. The efficacy of this maneuver for patients with apogeotropic LC-BPPV varies widely, ranging from 13 to 44% (47, 48).

The cupulolith repositioning maneuver (CuRM) (49) also aims to target cupulolithiasis in which the otoconia are facing the utricle. These authors proposed a modification of the roll maneuver with an additional step, in which the patient completes a 90° head turn to the healthy side while in supine position (51). First, the patient's head is rotated 135° to the affected side and mastoid oscillation is applied to the affected side for 30 s with a 60 Hz hand-held vibrator (1st position). Next, the patient's head is turned 45° to the healthy side (2nd position, lateral decubitus on the affected side). Then, the patient's head is turned 90° to the healthy side (3rd position, supine position). For the 4th position, the patient's head is turned 90° to the healthy side and oscillation is applied again (4th position, lateral decubitus on the healthy side). For the 5th position, the patient's head is rotated 90° in the same direction (5th position, prone position), and the patient is slowly brought back to the sitting position without neck extension (**Figure 3**). The mechanisms involved are a combination of mastoid oscillation for detaching the otoliths from the cupula and gravitational forces for moving them through the canal toward the utricle. A double-blind randomized prospective study did not detect statistically different therapeutic efficacy comparing the CuRM (38%) with the head shaking maneuver (12%) (52). However, the resolution rate with the head-shaking maneuver was very low in this study.

The Zuma maneuver (50) was proposed in 2016 for detaching both the otoconial debris from the anterior arm of the semicircular canal and the debris attached to the cupula. It is performed with the patient in the sitting position. First, the patient is asked to quickly lie down on the affected side (step I) and is held in this position for 3 min. Then, the patient's head is rotated 90° toward the ceiling (step II) and held in this position for another 3 min. After 3 min, the patient moves the body into dorsal decubitus and the head is turned 90° toward the unaffected side (step III) and held in this position for another 3 min. Finally, the patient's head is tilted slightly forward (step IV), followed by a slow return of the patient to the sitting position (step V) (**Figure 4**). The forward head tilt before sitting up in step IV was proposed to avoid enabling the particles to move back toward the posterior arm of the canal. This maneuver was highly effective in a study with 8 patients with administration of a single maneuver (50). It combines the inertial and gravitational forces to both detach the otoliths and move them toward the utricle. A recent retrospective study (53) compared patients treated with the Zuma maneuver or the modified Gufoni maneuver for apogeotropic LC-BPPV. It reported rates of vertigo and nystagmus resolution in patients with no previous history of BPPV of 59% and 48% for the Zuma maneuver and the modified Gufoni maneuver, respectively. This difference was not statistically significant. However, in patients with previous episodes of BPPV, resolution rates for vertigo and nystagmus were, respectively, 82 and 64% for the Zuma maneuver and 25 and 13% for the new Gufoni maneuver.

Furthermore, we have previously demonstrated the usefulness of observing the pattern of the nystagmus evoked in each step of the Zuma maneuver in patients with apogeotropic LC-BPPV (36). According to the hypothesis presented previously, we can deduce where otoliths are located. We can also elucidate the otoliths' paths toward the utricle and confirm the correct diagnosis.

MANAGEMENT OF THE GEOTROPIC VARIANT OF LATERAL CANAL BENIGN PAROXYSMAL POSITIONAL VERTIGO (GEOTROPIC LC-BPPV)

Geotropic LC-BPPV is attributed to free floating particles in the posterior arm of the LC. Consequently, the objective of the repositioning maneuver for this variant is to move the otoliths through the posterior arm into the utricle.

In 1994, the roll maneuver was reported for treatment of geotropic LC-BPPV. This maneuver is performed in the supine position and consists of a 270° head rotation toward the unaffected side in rapid steps of 90° at 30-s intervals (54, 55). In the same year, a modification of this maneuver was described that included a head rotation of 360° in quick steps of 90° with

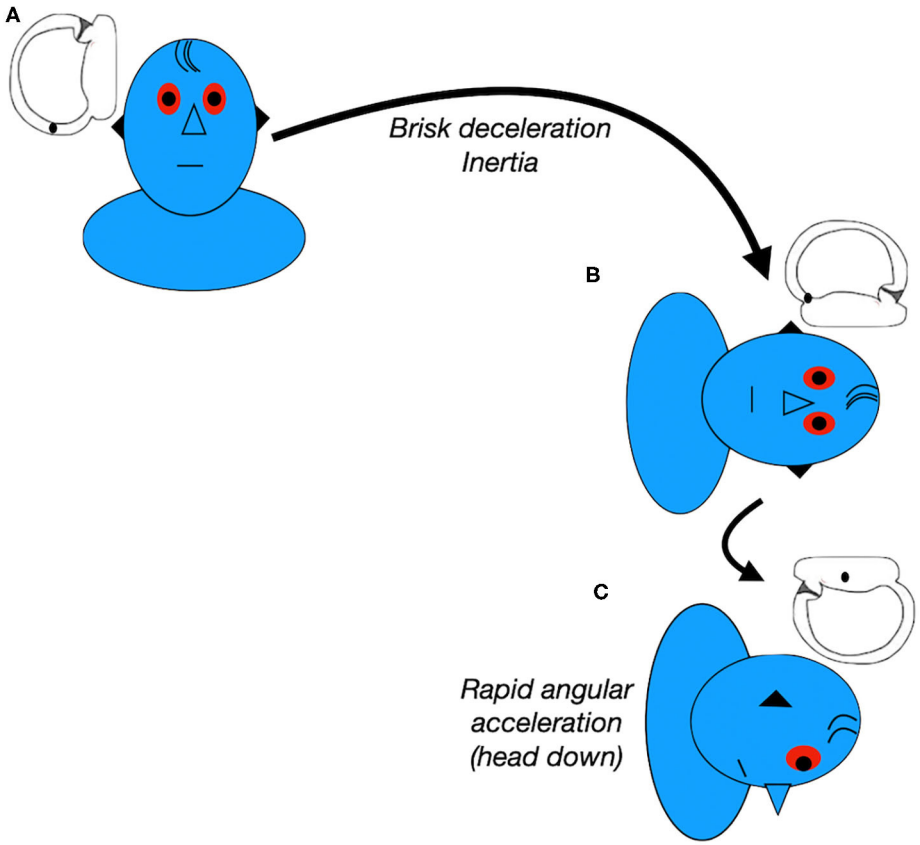

FIGURE 7 | Gufoni maneuver for right geotropic LC-BPPV. Data modified from Ciniglio Appiani et al. (65).

TABLE 2 | Pros and cons of repositioning maneuvers for geotropic LC-BPPV.

Maneuver	Pros	Cons
Roll maneuver	- High rate of resolution with a single maneuver - Goes from the affected to the unaffected side	- May be hard to perform in patients with obesity, advanced age, or restricted cervical movement - Lacks the forward head tilt before sitting up
Forced Prolonged Position	- May be associated with less intense vertigo	- Starts by lying onto the unaffected side - Needs to stay in this position for 12 h - Lacks the forward head tilt before sitting up - May not be performed properly by elderly patients and patients with musculoskeletal or cardiologic diseases
Gufoni maneuver	- High rate of resolution with a single maneuver - May be associated with less intense vertigo	- Starts by lying onto the unaffected side - Lacks the forward head tilt before sitting up
Zuma modified maneuver	- High rate of resolution with a single maneuver - Goes from the affected to the unaffected side	- Many steps compared to other maneuvers for geotropic LC-BPPV

60-second intervals (56) (**Figure 5**). Theoretically, the principles of this maneuver should combine the effects of inertial and gravitational forces, in order to move the otoconia into the utricle (51, 55, 57–59). Due to the whole-body rotation, it may be hard to perform it in patients with obesity, advanced age, or restricted cervical movement. Furthermore, these factors can affect maintenance of the head in the correct plane and the speed of the rotation (59).

The Forced Prolonged Position technique was also reported in 1994 as a treatment for the geotropic variant of LC-BPPV (46, 60). Patients were asked to lie on their beds and turn their heads or whole body from the supine position toward the unaffected side (**Figure 6**). This position should be maintained for 12 h in order to facilitate gravitational movement of the otoliths from the posterior arm of the LC toward the utricle (57, 61, 62). However, elderly patients and patients with

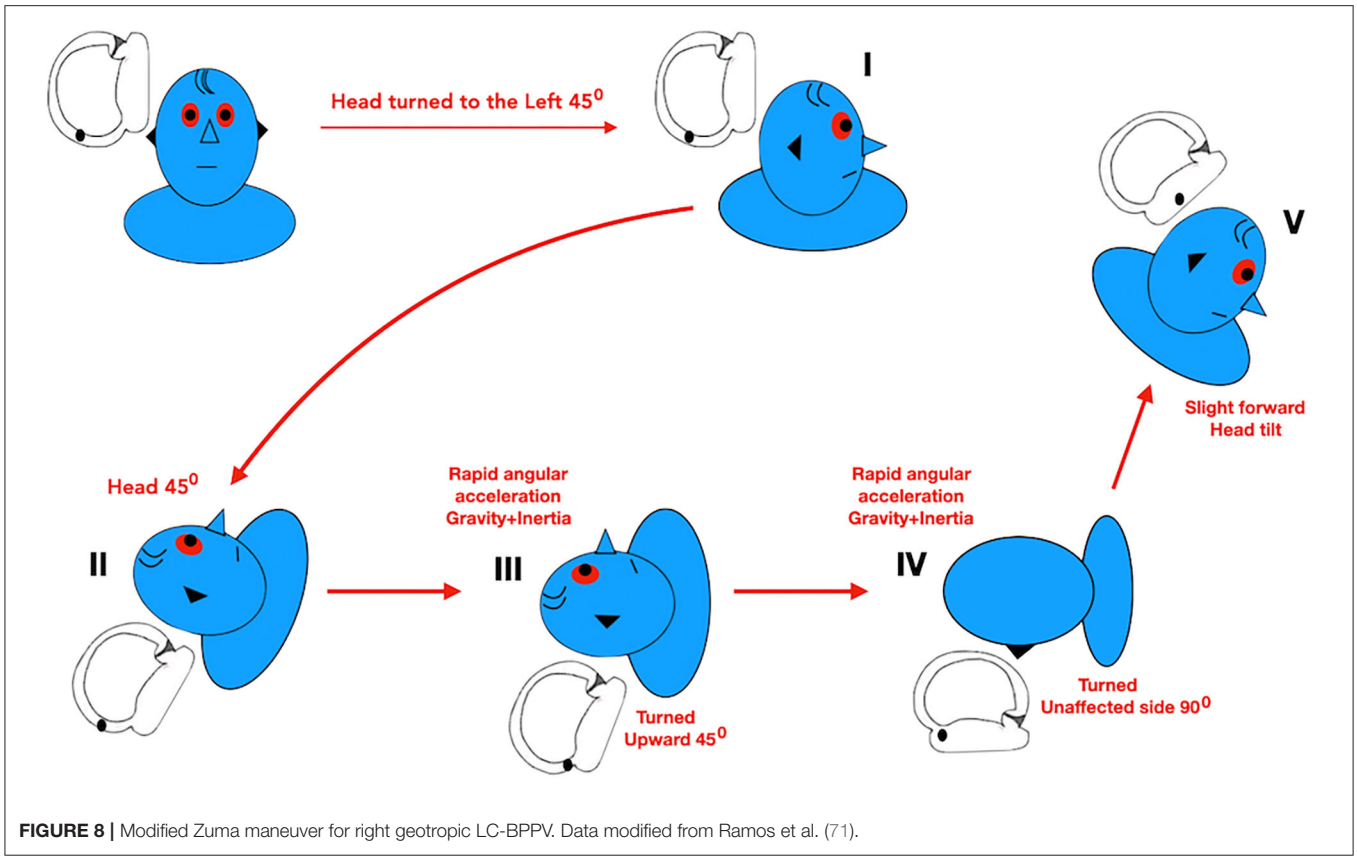

FIGURE 8 | Modified Zuma maneuver for right geotropic LC-BPPV. Data modified from Ramos et al. (71).

musculoskeletal or cardiological diseases may not manage to perform it properly (59).

The Gufoni maneuver was first presented in 1998 (original publication in English by Ciniglio Appiani et al. in 2001) (63–65). In this case, the patient in the sitting position is briskly moved into a side-lying position onto the unaffected side and remains in this position for 1 min after the end of the nystagmus. Then, the patient's head is quickly turned 45° downward and held in this position for 2 min. At the end, the patient slowly returns to the sitting position (**Figure 7**). In the side-lying position, the posterior arm of the LC is placed in the vertical plane and otoliths flow toward its nonampullated end. Since this maneuver is performed onto the unaffected side, it may be associated with less intense vertigo. The 45° downward head turning places the outlet of the posterior arm of the canal in a vertical plane and consequently facilitates movement of the particles into the utricle (58, 59).

All of these authors reported good results for treatment of geotropic LC-BPPV. The high rate of spontaneous resolution of LC-BPPV and the proximity of the posterior arm of the LC to the utricle may help with the effectiveness of repositioning maneuvers. Previous cohort studies and case series reported efficacy ranging from 67 to 100% after the Lempert maneuver (48, 55, 66, 67). Some randomized controlled studies were published recently. One of these studies found response rates of 88% after the Gufoni maneuver, compared with the sham maneuver for geotropic LC-BPPV (68). Other authors (69) showed better responses after a maximum of 2 maneuvers (Roll maneuver or Gufoni maneuver) than a sham maneuver on the initial visit day (69, 60, and 35% respectively). On the other hand, another randomized prospective clinical trial (70) compared the effectiveness of the roll maneuver plus forced prolonged positioning vs. Gufoni maneuver for geotropic LC-BPPV with response rates of 81 vs. 93%.

Table 2 demonstrates the pros and cons linked to each of these maneuvers for geotropic LC-BPPV.

Knowledge of the anatomy and pathophysiological mechanisms of the semicircular canals is essential for the correct diagnosis and treatment of any BPPV. Adhering to the concept that repositioning of otoliths should be performed from the affected side toward the healthy side, similarly to every PC-BPPV maneuver (i.e., Epley and Sémont Maneuvers), we have chosen the modified Zuma maneuver (71) for treatment of geotropic LC-BPPV. This maneuver was effective for geotropic HC-BPPV after a single application.

The modification in relation to the original maneuver (50) is a 45° head turn to the unaffected side in the sitting position (step I). The patient is then asked to lie down on the affected side (step II). Next, the patient moves into dorsal decubitus and the head is turned 45° toward the unaffected side (step III). The head is then turned 90° toward the unaffected side (step IV). Finally, the patient's head is tilted slightly forward, followed by a slow return to the sitting position (step V) (**Figure 8**) (71).

CONCLUSIONS

Precise diagnosis of the BPPV, the side affected, and the subtype are critical for successful treatment. We have adopted the minimum stimulus strategy (41) for evaluation of patients with suspected BPPV. Therefore, suppressing visual fixation [using Frenzel goggles, M-glasses (72), or video-Frenzel] is essential to examination of these patients' eye movement.

There is no single correct maneuver for each kind of BPPV, since several authors have reported good results with different types of repositioning maneuver. Personal experience is really important for defining a strategy to manage these patients. On the basis of our experience, we have adopted the Zuma maneuver and the modified Zuma maneuver for both apogeotropic and geotropic variants of LC-BPPV (50, 71). Knowledge of the anatomy and pathophysiologic mechanisms of the semicircular canals is essential for correct management of these patients. Hence, using a single maneuver and its modification may facilitate daily neurotological practice. Meanwhile, we can adhere to the concept that otolith repositioning should be performed from the affected side toward the healthy side.

Theoretically, based on a 3D biomechanical model of the semicircular canals (73, 74), the original Zuma maneuver could also be performed for patients with geotropic LC-BPPV. In step I of this maneuver, the otoliths, initially located in the posterior arm of the LC, flow in the direction of the anterior arm (moving away from the utricle and toward the ampulla) and cause an ampullopetal excitatory endolymphatic current. During the remaining steps of the maneuver, the otoliths would flow back to the posterior arm before entering the utricle. Therefore, for geotropic LC-BPPV, performing the modified Zuma maneuver instead of the original maneuver avoids an unnecessary excitatory stimulus and movement of the otoliths away from the utricle. In the modified Zuma maneuver, the particles only move toward the utricle, causing an inhibitory stimulus.

Another important consideration should be mentioned. In the last step of both the Zuma maneuver and the modified Zuma maneuver, before the patient returns to the sitting position, the head can be tilted slightly forward in order to encourage the particles to move toward the utricle, otherwise the otoliths could move back toward the lumen of the LC (50).

AUTHOR CONTRIBUTIONS

FZ, BR, RC, CB, and PM contributed to conception and design of the study. BR and FZ wrote the first draft of the manuscript. MS revised the manuscript and added suggestions about figures and tables, and the objectives of this paper. All authors contributed to manuscript revision, read, and approved the submitted version.

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Congruous Torsional Down Beating Nystagmus in the Third Position of the Semont's Maneuver in Patients Treated for Canalithiasis of Posterior Semicircular Canal Benign Paroxysmal Positional Vertigo: Its Significance and Prognostic Value

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Due to its mechanical pathogenesis, benign paroxysmal positional vertigo treatment is mainly physical: when posterior semicircular canal is involved, Semont's maneuver is reported as one of the most effective liberating procedures. In the case of a canalolithiasis, the efficacy of the maneuver is corroborated by the appearance of some nystagmus findings during its performance. Liberating nystagmus, that can occur in the second position of Semont's maneuver and whose direction is congruous with the excitation of the affected posterior semicircular canal has proven to be a favorable prognostic sign. On the other hand, in clinical experience, we've frequently verified the appearance of another nystagmus during the execution of the maneuver: upon reaching the third position, when replacing the patient seated, a torsional down beating nystagmus, with the torsional component "congruous" with the stimulation of the vertical semicircular canals of the affected side, can often be appreciated. Such a sign can occur with or without having had the previous liberating nystagmus in the second position and is almost always associated with an intense vertigo and/or body pulsion. In this study, we describe the incidence and characteristics of the congruous torsional down beating nystagmus that can arise by assuming the third position of Semont's maneuver in a cohort of patients treated for posterior semicircular canal benign paroxysmal positional vertigo due to canalolithiasis. In the best of our knowledge, such a sign has never been described and explained before. On the basis of the pathophysiology and of the possible canal receptors stimulation during the different phases of Semont's maneuver, we formulated different hypothesis on how such a nystagmus can be generated. We observed that such a sign, when

elicited, has a very good prognostic meaning for healing purposes, even better than that of liberating nystagmus. Therefore, congruous torsional down beating nystagmus should always be checked when performing Semont's maneuver because it could help in predicting success of physical treatment and in managing patients.

Keywords: benign paroxysmal positional vertigo treatment, Semont's liberatory maneuver, posterior semicircular canal, down beating nystagmus, torsional down beating nystagmus, canalolithiasis, liberating nystagmus, benign paroxysmal positional vertigo therapy outcomes

INTRODUCTION

Posterior semicircular canal (PSC) benign paroxysmal positional vertigo (BPPV) is the most frequently diagnosed peripheral vestibular pathology (1–4). Being its pathogenetic mechanisms mostly those of canalo- (5) or cupulolithiasis (6), the therapy of choice is a physical one (7). When PSC is involved, the physical techniques for which it is reported the greater success are those of repositioning and those that take advantage of the brisk deceleration imposed to the otoconial mass. The percentage of short-term resolution obtained with the two types of maneuvers is similar, and the choice of one or the other technique is formulated according to patient's characteristics and operator's preference. The prototype of maneuvers exploiting the sharp deceleration imposed to the otoconial cluster is the Semont's liberatory maneuver (SLM) (8): a series of three rapid movements is performed in order to free the PSC from the mass of heavy particles, carrying the latter into the utriculus. During the execution of the maneuver, some nystagmus signs, which are significant for the success of the therapy, can appear: they can represent the manifestation of a correct movement of the cluster toward the exit from the canal. Namely, after the first movement of SLM, performed carrying the patient onto the pathological side, a mixed "Loading Nystagmus" (LoNy) will be generated: its direction (referring to the fast phase from here on) will be upward (toward the forehead) with the upper pole of the eyes beating toward the lower ear, thus in a counterclockwise and clockwise direction, due to the involvement of the right and left PSC, respectively. After the second movement of SLM, performed carrying the patient from the pathological onto the healthy side, a "Liberating Nystagmus" (LNy) with the same direction as the LoNy can be generated; this finding has been proved to be a good prognostic sign (9–11). Based on literature, the undisputed efficacy of SLM can be affirmed, with a short-term success rate of this physical therapy reaching about 80%. Moreover, the appearance of a LNy in the second position is related to an excellent prognosis (72–87%) in terms of resolution of symptoms and signs. From the personal practical experience, we have been able to notice that during the third movement of SLM, when returning the patient seated, a different nystagmus is often generated. When evident, the latter nystagmus is torsional vertical down beating on the whole, accompanied by a strong vertigo and retropulsion. Our hypothesis was that patients who manifest this finding have overall a faster resolution than those who do not or those who only have LNy. The purpose of our work was to verify the presence of nystagmus when taking the third position of the SLM in a cohort of patients treated for PSC canal lithiasis, to describe it, to hypothesize the mechanism by which it is generated, to quantify its impact and, above all, to evaluate its prognostic value for the resolution of PSC BPPV. A secondary objective of our study was to investigate the existence of other factors that may change the outcome of SLM and to evaluate the weight of each of them, in particular that of the time elapsed between the onset of the symptoms and the execution of the maneuver.

Since its first description, the procedure of SLM has been partially modified and simplified, with respect to the original, because of clinical and pathophysiological observations that have followed over years. The goal of SLM is to displace the otoconial debris from the ampullary portion of the PSC, where it is located when the patient is in the upright or sitting position, toward the utricle, passing through the non-ampullary tract of the canal, by taking advantage of the sharp deceleration that is imposed by means of specific brisk movements on the mass of heavy particles. SLM (**Figure 1**) starts having the patient seated in the center of the examination bed; the operator turns the subject's head 45° toward the healthy side in order to position the affected canal on the same plane on which the maneuver will be carried out. The first movement of the maneuver brings the patient from the sitting position to that of the pathological side (**Figure 1**, 1st). The latter shift should be performed with a high angular velocity and by reaching a position such that the body is displaced 110° with respect to the sitting position (the head being positioned 20° under the horizontal plane); actually, an only 90° displacement could be insufficient to move the particles in the declivous part of the PSC (12). In the case of a canalolithiasis, positioning the patient onto the pathological side causes the migration of the otoconial debris, by means of gravity, from the ampullary arm toward what it becomes the most declivous part of the PSC in the new position. Conversely, in the case of a cupulolithiasis, it is assumed that the cluster of particles weighs on the cupula, causing it to deflect toward the canal. In both cases, an excitatory stimulation of the PSC ampullary receptor takes place. The resulting nystagmus beats, therefore, upward and in a counterclockwise and clockwise direction (from the examiner's point of view from now on), due to the involvement of the right and left PSC, respectively. Once such an ocular movement, which we defined LoNy, is exhausted and waited about 45 s since the position is reached (12), the operator brings the patient onto the non-pathological side (**Figure 1**, 2nd) taking care to maintain the head still turned 45° toward it. The latter shift should have a 220° amplitude and should be executed with a high velocity. Indeed, for the second movement of SLM also, it has been demonstrated that reaching a position of the head

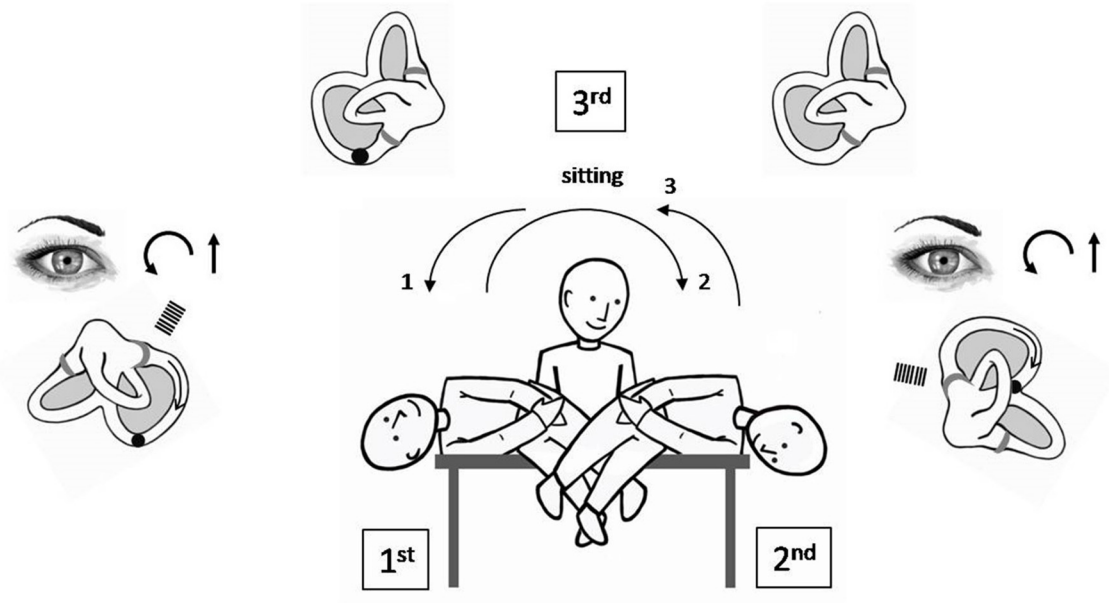

FIGURE 1 | Semont's liberatory maneuver in the case of a right PSC BPPV canalolithiasis. Procedure starts having the patient seated in the center of the examination bed. The otoconial debris is deposited into the most declivous part of the PSC. (1) patient is rapidly brought from the sitting position toward the affected side maintaining the head turned 45° contralaterally and reaching a position of the head that is 20° under the horizontal (lower than the body) (1st position). The otoconial debris moves in the ampullofugal direction causing an ampullofugal endolymphatic flow, thus an excitatory discharge of the right ampullary nerve. Paroxysmal positional nystagmus occurs, being its fast phase counterclockwise and up beating (LoNy). (2) patient is quickly moved 220° toward the healthy side, keeping the head rotated as previously, and reaching a position of the head 20° lower than the horizontal, again (2nd position). Aim of the latter movement is to make the debris to continue its ampullofugal path toward the vestibule by briskly decelerating the head in reaching the second position. In this case, a paroxysmal positional nystagmus might occur, being its fast phase counterclockwise and up beating again (LNy). (3) patient is moved back to the sitting position (3rd position).

that is lower than the horizontal is more effective in moving the cloth toward the utricle (12). With such a second movement, in the case of a canalolithiasis, the maneuver aims to move the otoconial debris still in the ampullofugal direction, toward the utricle. If such a displacement occurs, an endolymphatic flow is determined such as to give again an excitatory stimulation of the ampullary receptor; nystagmus thus generated beats upward and in a counterclockwise and clockwise direction, respectively, for the right and left PSC. The appearance of this finding, called LNy, is expressive of an effective ampullofugal movement of the heavy debris into the canal lumen, though it cannot provide any indication about the stretch covered by the otoconial mass into it, by means of the maneuver (13–15). The brisk deceleration obtained with the second movement of SLM could also lead to a backward path of the otoconial mass toward the ampulla, thus provoking an inhibitory discharge of the PSC ampullary nerve. The nystagmus so generated would have a direction opposite to that of the LoNy, being therefore down beating and with the torsional component directed clockwise and counterclockwise, respectively, for the right and left PSC. The appearance of such a nystagmus would have therefore a bad meaning with regard to the success of the maneuver (16). Even in the case of a cupulolithiasis, the sudden deceleration obtained with the second movement of SLM could theoretically give rise to two types of ocular movement; the first is a nystagmus with a direction similar to that of the LoNy, meaning that the heavy material has been detached from the cupula by flaunting it in the ampullofugal direction. The second is a nystagmus with a direction reversed with respect to that of LoNy meaning that the mass adhering to the cupula pulls it in the ampullopetal direction, thus determining an inhibitory discharge of the posterior ampullary nerve. In both a canalo or cupulolithiasis, a third possibility exists: when the patient is brought onto the second position of SLM no signs are highlighted. In this event, it is probable that there is no further movement of the particles inside of the canal because they could have already been brought out of it with the first movement or could have remained in the previous position (11, 17).

Once nystagmus in the second position is exhausted (or after about 45 s, if no findings is observed), the operator moves back the patient to the sitting position (**Figure 1**, 3rd).

Theoretically, during the latter movement, it can happen that:

(a) no further stimulation of any canal is produced because otoconial debris has already reached the utriculus; in such a case no endolymphatic flow and no nystagmus would be generated.
(b) debris moves backward into the PSC giving rise to an inhibitory stimulation of the corresponding ampullary nerve; in that case a torsional vertical down beating nystagmus would be generated with the torsional component opposite to that of the LoNy nystagmus;

(c) the otoconial cluster moves toward the vestibule, having already traveled the non-ampullary arm of the PSC; such a movement should therefore generate an endolymphatic flow into the common crus, toward the utricule. Nystagmus expected will be torsional vertical having the fast phase of both the linear and torsional components that represents the algebraic sum of the two vertical canals stimulation. Theoretically, stressing both vertical semicircular canals, should give rise to a mainly torsional nystagmus because the linear components would cancel each other while the torsional movements would sum. However, during SLM, it would be the position that each vertical canal reaches, together with the efficacy of the endolymphatic currents generated inside of them, that will origin the final ocular movement.

In literature, no author has dealt with describing the possibility of presenting and the characteristics of nystagmus findings in the third position of SLM, after having or not a LNy in the second one. Moreover, no study on the prognostic value of these signs have been published. Albera et al. only focused on the prognostic value of vertigo occurring in the last position of SLM (10). On the other hand, practice suggested us that the onset of a nystagmus in the third position of the SLM is a common occurrence and that, when present, it has a direction compatible with the simultaneous stimulation of two vertical semicircular canals of the affected side. In particular, nystagmus observed during SLM on return to central position is, in our experience, a torsional down beating nystagmus whose torsional fast phase is "congruous" with that of the LoNy (cTDBNy) and whose pathophysiological explanation will be given later. Furthermore, in everyday clinical practice, we had the feeling that patients presenting this finding, although suffering more from physical therapy, had a better and faster course than those who showed only the LNy.

MATERIALS AND METHODS

Subjects and Clinical Methods

Our work deals with a logistic regression study, conducted at the Audiology Unit of Careggi University Hospital in Florence on a series of 55 selected outpatients suffering from PSC BPPV. Cases were collected during a 1-year period, between November 2018 and December 2019.

Subjects came to visit at various distances from the onset of symptoms, which made it possible to evaluate acute patients but also those who had long-lasting dizziness.

An accurate specialist and general history was collected for all patients, aimed at identifying the peculiar characteristics of BPPV, its origin, the presence of any other neuro-otological and/or systemic pathology capable of influencing the clinical picture.

All subjects underwent an otomicroscopic examination and audiometric and impedance testings. All patients were submitted to a bedside neuro-otological examination, including studying of the visuo-oculomotor systems (saccadic and smooth pursuit) and searching for gaze-evoked, rebound, spontaneous, positional, and positioning nystagmus. Nystagmus findings were observed with and without visual fixation, under Frenzel glasses or infrared video-oculoscopy. Vestibulo-oculomotor reflex function testings were also performed for all patients at different stimulation frequencies: head impulse test, head shaking test, and binaural bithermal calorics.

Since the presence of central vestibular signs had been a reason for exclusion from the sample, subjects did not undergo neuroradiological examinations, neither at the first evaluation nor at the control visit. Instead, these investigations were performed when the patients had not resolved BPPV in the foreseeable time or showed semeiological atypia during follow-up.

Patients who had the following inclusion criteria were selected: (a) diagnosis of a primitive idiopathic PSC BPPV; (b) geotropic positional torsional up beating nystagmus evoked by the Dix-Hallpike's positionings and showing the characteristics of a canalolithiasis of the PSC (i.e., nystagmus arising with latency, with a "crescendo-decrescendo" paroxysmal trend, with a duration <60 s and a direction reversal, with a lower amplitude, when returning to the sitting position); and (c) BPPV strictly involving a single canal.

The following exclusion criteria have been envisaged: (a) positional vertigo secondary to labyrinthopathy, surgery, or trauma; (b) concomitant diseases affecting the vestibular system or the inner ear; (c) positional nystagmus suggesting PSC cupulolithiasis (i.e., without latency, without crescendo-decrescendo trend, with a long duration, over 1 min, and without a clear reversal in the sitting position); (d) orthopedic, cardiological, neurological, or other systemic contraindications to the execution of the maneuver; and (e) presence of situations that could compromise the proper execution of the release maneuver, such as obesity, physical malformations, and orthopedic disorders.

Once a diagnosis of PSC BPPV was made according to the established criteria, patients were informed about the nature of their vertigo and the possibility of performing physical therapy. A procedure of SLM was then described together with the possible dizzying events occurring during the execution, as well as the postural and general sequelae that the maneuver could determine in the following days, even in the case of a positive result. Subjects were also advised of the intention to immediately verify the outcome of the SLM by repeating the diagnostic Dix-Hallpike's positioning.

During the performance of SLM, without using devices inhibiting fixation, we checked the presence of: (a) LoNy in the first SLM position; (b) LNy in the second SLM position; and (c) any nystagmus in the third SLM position and, in that case, we detected its qualitative, direction, and plane characteristics; in particular, attention was paid to the appearance of a vertical torsional nystagmus, with a direction compatible with the excitatory stimulation of one or both vertical canals, or with PSC inhibition. After a short period of rest (2–3 min), a suitable Dix-Hallpike's diagnostic retest was performed. During the latter positioning, the absence or presence of signs of PSC canalolithiasis, as well as their typology, was assessed.

All patients treated were scheduled to undergo a neurootological examination within a short time (max 10

days) and suggested to avoid abrupt movements on the vertical plane in the following 48 h, inviting them to sleep uplifted on the two nights following the maneuver.

Subjects were discharged without prescribing any further investigation if they were asymptomatic at the check-up, being recovery verified by the absence of findings; in case of persistence of PSC BPPV nystagmus, patients were again treated with the same maneuver or with a different physical therapy. For patients with vertigo refractory to therapy or with a persistence of vestibular signs other than those typical of PSC BPPV, an in-depth diagnostic procedure was planned.

Data were collected, updated, and archived in a database that served for clinical and statistical considerations.

The following further characteristics of the sample were considered: sex, age, affected side, time from the onset of symptoms, presence of a LNy, presence/absence and typology of nystagmus in a suitable Dix-Hallpike's positioning early retest, performed few minutes after SLM, and presence/absence and typology of nystagmus signs at the control visit.

Statistical Analysis

The first exploratory model has been carried out to better understand the relationships between the nystagmus presence/absence in the second (liberating) and in the third position of SLM and the Dix-Hallpike's position retest. The Dix-Hallpike's retest has been considered as a dependent variable since it has been pointed out to be an early index of resolution of the clinical picture. Nystagmus evidence in Dix-Hallpike's retest has been codified with three possible outcomes: "*absent*," "*excitatory*," or "*inhibitory*," where "*inhibitory*" describes those situations in which nystagmus has been generated by an ampullopetal stimulus. For this purpose, we inferred the parameters of a multivariate multinomial-logit model.

Then, the relationships with healing has been explored. In particular, we took a look both at the most predictive signs of the final resolution and at the possible intervenient effects among them. For the latter purpose, two nested multivariate logit model has been used.

In all the three models, we included four control variables to avoid overestimation of the relationships due to unconsidered intervenient effects. These four variables are: sex, age, affected side, and time (in days) from the beginning of the symptoms.

Estimated coefficients together with the related standard deviations and *p*-values are reported in **Tables 1**–**3** for models 1, 2, and 3, respectively.

TABLE 1 | Model 1.

	Response variable	
	Dix-Hallpike Nystagmus (ref. cat.: "excitatory")	
	("Absent")	("Inhibitory")
Age	−0.017 (0.028)	−0.033 (0.040)
Sex ("*man*")	0.504 (0.849)	0.039 (1.207)
Affected side ("*left*")	0.684 (0.931)	1.217 (1.198)
Symptoms onset	0.004 (0.006)	−0.007 (0.013)
LNy ("*present*")	1.764 (1.086)	11.438*** (1.481)
cTVDBNy ("*present*")	−0.225 (0.823)	−1.837 (1.183)
Observations	55	
Akaike Inf. Crit.	110.391	

*Estimates of multinomial logit model for nystagmus findings on Dix-Hallpike diagnostic retest. *p < 0.1; **p < 0.05; ***p < 0.01.*

TABLE 2 | Model 2.

	Response variable
	Definitive resolution (*ref. cat.: "yes")*
Age	−0.004 (0.025)
Sex ("*man*")	−0.322 (0.666)
Affected side ("*left*")	0.197 (0.728)
Symptoms onset	−0.004 (0.004)
LNy ("*present*")	1.732* (1.022)
cTVDBNy ("*present*")	1.496** (0.674)
Observations	55
Akaike Inf. Crit.	74.650

Estimates of logit model for the definitive resolution test. In this specification, findings in Dix-Hallpike diagnostic retest are not included in the explanatory variables.
**p < 0.1; **p < 0.05; ***p < 0.01.*

RESULTS

Clinical Findings

From the analysis of the population examined, a different composition of the sample with regard to gender emerges: 35 out of 55 subjects were females (64%) and 20 males (36%). The age affected by PSC BPPV varied, in our cohort, from 39 to 93 years, average age 68.3 years.

Thirty-eight patients out of 55 (69.1%) presented a right PSC BPPV; the remaining 17 showed, instead, typical semeiological findings of a left one.

Concerning the time elapsed between the onset of symptoms and the diagnosis, the distribution of the patients examined is such that a large percentage was assessed at a relatively short distance, but the sample is composed for a conspicuous part also by subjects for whom the disease has been dated for a longer time. In particular, 24 patients were seen within the first week, 13 within 1 week to 30 days, and 18 subjects within a year from symptoms onset.

In the ipsilateral diagnostic Dix-Hallpike's position, all patients showed the typical nystagmus finding for an ampullofugal PSC stimulation with the peculiar characteristics of canalolithiasis.

Reaching the first position of the SLM, all the patients presented the LoNy, generated by the expected displacement of the otoconial cluster from the ampullary to the non-ampullary tract of the PSC; as explained, this is a vertical torsional nystagmus, with the characteristics of a finding justifiable with a canalolithiasis, the direction of which was upward (geotropic) and torsional counterclockwise and clockwise, for the right and left PSC, respectively.

TABLE 3 | Model 3.

	Response variable
	Definitive resolution (*ref. cat.: "yes"*)
Age	−0.004 (0.025)
Sex (*"man"*)	−0.316 (0.672)
Affected side (*"left"*)	0.228 (0.759)
Symptoms onset	−0.004 (0.004)
LNy (*"present"*)	1.620 (1.103)
cTVDBNy (*"present"*)	1.611** (0.697)
DHNy (*"absent"*)	−0.046 (0.863)
DHNy (*"inhibitory"*)	0.661 (1.180)
Observations	55
Akaike Inf. Crit.	78.091

Estimates of logit model for the definitive resolution test. In this specification, findings in Dix-Hallpike diagnostic retest are added to the explanatory variables.
$^{*}p < 0.1$; $^{**}p < 0.05$; $^{***}p < 0.01$.

Forty-nine/55 (89.1%) patients showed a nystagmus in the second position of SLM. In all subjects, this finding has been a LNy, which means that its direction was similar to that of LoNy, both for the vertical and the torsional component.

When reaching the second position of SLM, no findings occurred in the remaining 6/55 patients (10.9%). Absence of nystagmus is likely to be attributed to the lack of any further movement of the otoconial debris into the canal, after the declivous position is reached with the first movement. Therefore, not having any nystagmus in the second position has a neutral meaning until it is not associated with any subsequent finding.

However, none of the 55 subjects, in the second position of the SLM, showed a nystagmus indicative of an inhibitory stimulation of the PSC (apogeotropic), suggestive of a backward path of the clot in the ampullopetal direction.

On returning to a sitting position, with the third movement of the SLM, 27 out of 55 (49.1%) patients showed a vertical torsional nystagmus having the linear component directed downward (down beating, geotropic) and the torsional component "congruous" with the stimulation of the vertical canals of the affected side.

None of the latter 27 subjects witnessed the appearance of a nystagmus compatible with an inhibitory stimulation of the lonely PSC.

The appearance of signs during both diagnostic and therapeutic movements has invariably been associated with a corresponding patient's dizzying sensation.

Namely, very often the triggering of nystagmus with the assumption of the third position of the SLM was accompanied by a violent vertigo and retropulsion. In our study, however, we did not deal with examining the symptoms, but only the signs.

Among the 49 subjects who presented LNy in the second position of SLM, 34 (69.4%) had a negative Dix-Hallpike's early retest; eight out of these 49 patients (16.3%) had a torsional down beating, without latency and not paroxysmal nystagmus, compatible with a residual otoconial clot of the non-ampullary arm, which partially returned toward the ampulla by assuming such a position, thus causing an inhibitory stimulation of the PSC. The latter finding is not to be considered expressive of a negative result of the maneuver, but only of the persistence of some debris into the non-ampullary tract of PSC. These patients were dismissed without performing further early diagnostic retests or therapeutic maneuvers. Seven/49 patients (14.3%), despite having exhibited a LNy, still showed a nystagmus indicative of an excitatory stimulation of the PSC. Such a nystagmus was, therefore, suggestive of the permanence of a residual clot into the ampullary tract of the PSC.

Therefore, among the 49 patients manifesting a LNy, 69.4% ($n = 34$) had actually a negative Dix-Hallpike's retest, confirming the exit of the clot from the PSC non-ampullary arm; if we add to this population subjects who showed nystagmus of the inhibitory type at early retest ($n = 8$), the percentage of favorable verifications rose to 85.7%.

Six patients out of the total (10.9%) didn't show LNy: three subjects didn't manifest any nystagmus at the early retest, while the remaining three had a nystagmus, indicating the persistence of periampullary lithiasis. It is not superfluous to underline that, at the Dix-Hallpike's retest, none of these six subjects presented an inhibitory nystagmus.

Figure 2 (left side) shows the above results with regard to the correlation between the presence/absence of LNy in the second SLM position and findings highlighted at the Dix-Hallpike's retest.

Within the series, we subsequently examined the relationship existing between the absence in the Dix-Hallpike's early retest and the previous appearance of a nystagmus on returning to sitting position with the third movement of SLM. As reported, the latter nystagmus, when elicited (27 out of 55 patients, 49.1%) was always of the torsional down beating type, with the torsional component "congruous" with stimulation of the vertical canals of the affected side (cTDBNy).

In 20 out of 27 patients (74.1%) presenting cTDBNy in the third position of SLM, the further Dix-Hallpike's retest was negative. This percentage increases to 81.5% if considering also patients (2/27) manifesting a weak, without latency and not-paroxysmal inhibitory nystagmus, likely due to an endolymphatic flow generated by the movement of a residual clot into the non-ampullary tract of the PSC, in the ampullopetal direction (inhibitory nystagmus).

Five out of the 27 (18.5%) showing cTDBNy, at early Dix-Hallpike's retest, still had a nystagmus indicative of a periampullary lithiasis (excitatory nystagmus).

Twenty-eight subjects out of 55 (50.9%) did not present any nystagmus moving back to the sitting position: 17 (60.7%) of them were negative at the Dix-Hallpike's verification, 6 (21.4%) had an inhibitory and 5 (17.9%) an excitatory type of nystagmus. Correlations between absence/presence of cTDBNy in the third position of SLM and Dix-Hallpike's early retest findings are represented in the graph of **Figure 2** (right side).

The relationships existing between healing of the pathology, verified at the control visit, and the absence of signs at Dix-Hallpike's retest, was further investigated; in other words, we analyzed the concordance of immediate outcome of SLM with that verified at a distance. Among patients not having signs at

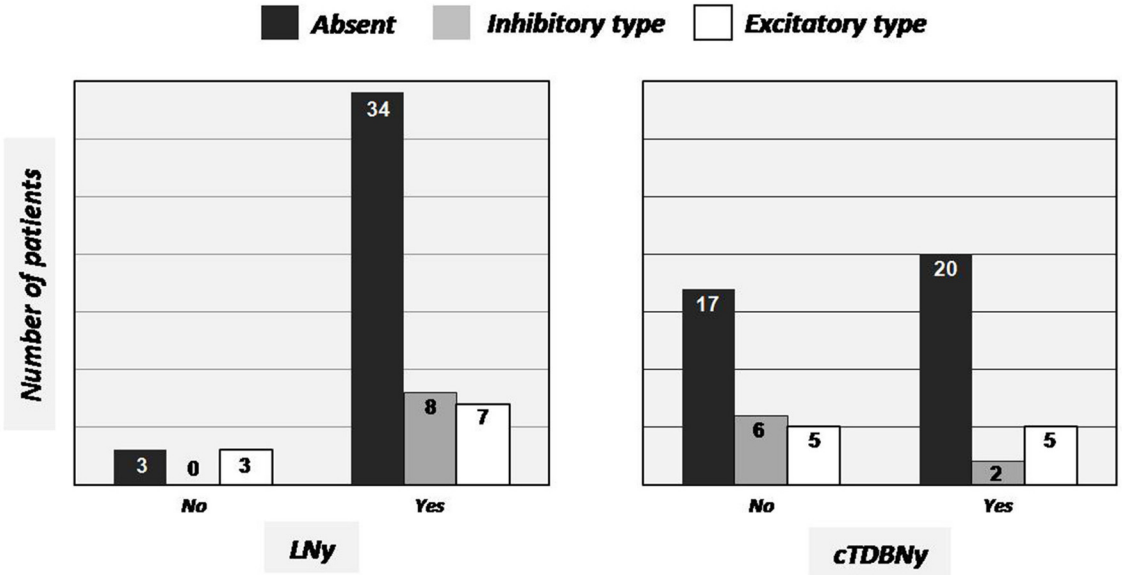

FIGURE 2 | Graphic representation of the relationships existing between the absence/presence and typology of nystagmus at Dix-Hallpike's early retest in the case of LNy (left side) and cTDBNy (right side) evidence or not.

an immediate control ($n = 37$), 64.9% ($n = 24$) were actually negative at distance. Adding to this quota also that of subjects who had nystagmus indicating PSC inhibition at the immediate verification test (6/8), it can be observed that the percentage of agreement between instantaneous and at distance positive results rose to 66.6%. However, 60% ($n = 6$) of the 10 patients having an immediate Dix-Hallpike's retest suggestive of persistence of a periampullary lithiasis, were also negative at the control visit (**Figure 3**, left side); five of these 10 patients had showed cTDBNy and, among them, three underwent resolution at the control visit.

We also took into consideration the relationships between the presence/absence of LNy and healing, regardless of the presence/absence of cTDBNy: 69.4% of patients with LNy went to recovery (34/49). Conversely, among those who did not present this finding ($n = 6$), only 33.3% ($n = 2$) were cured. These results are shown in the graph in **Figure 3** (at the center).

Similarly, and this is the fundamental node of our study, we searched the correlations between the presence/absence of cTDBNy and healing (regardless the presence/absence of LNy). Among the 27 patients who experienced cTDBNy, even the 81.5% (22/27) had solved at the follow-up visit. On the contrary, among those who did not present cTDBNy ($n = 28$), only 50% ($n = 14$) went to healing (**Figure 3**, right side).

Statistical Findings

Looking at the estimates of statistical models, whose single parameter interpretation, like the others models, has to be intended keeping fixed all the others, no meaningful changes in the odds-ratio of the immediate resolution, verified in the Dix-Hallpike retest, are produced by the presence/absence of cTDBNy (**Table 1**). On the other hand, the probability ratios between a Dix-Hallpike's retest, indicating inhibitory stimulus and that of the Dix-Hallpike's position positivity, significantly change (at a confidence level of 99%) when LNy sign is reverse. No other unitary variations in others variables seem to change the odds-ratios of the possible outcomes of Dix-Hallpike's position. In this scenario, we could hardly predict the considered immediate resolution of the disease.

However, when looking at the relationships of early retest findings with the definitive ones, we found good predictive capabilities for both LNy ($0.05 < p < 0.1$) and cTDBNy ($0.01 < p < 0.05$) (see **Table 2**). The probability ratio between positive and negative resolution is $e^{\beta 5} = e^{1.732} = 5.65$ times higher for people who showed LNy than that of people with equal characteristics that did not show it. This proportion decrease to $e^{\beta 6} = e^{1.496} = 4.46$ for people showing or not cTDBNy. The difference in the significance level has to be attributed to the higher variance of β_5 parameter, possibly due to the unbalance in the number of patients with different sign with respect to LNy.

The third model (whose estimates are resumed in **Table 3**) underlines the predictive role of cTDBNy in healing. The inclusion of Dix-Hallpike's retest nystagmus variable in the model does not affect its significance; instead, the estimated variation of the odds increases from 4.46 to 5 times higher for people who showed a cTDBNy with respect to people not manifesting it, but with equal values of the other covariates. Despite the non-significance of Dix-Hallpike's retest findings in changing the probabilities of healing may be due to an excessive fragmentation of data, it is worth to notice the loss in significance, for the (log) odds-ratio, of LNy. This result is interesting because it highlights

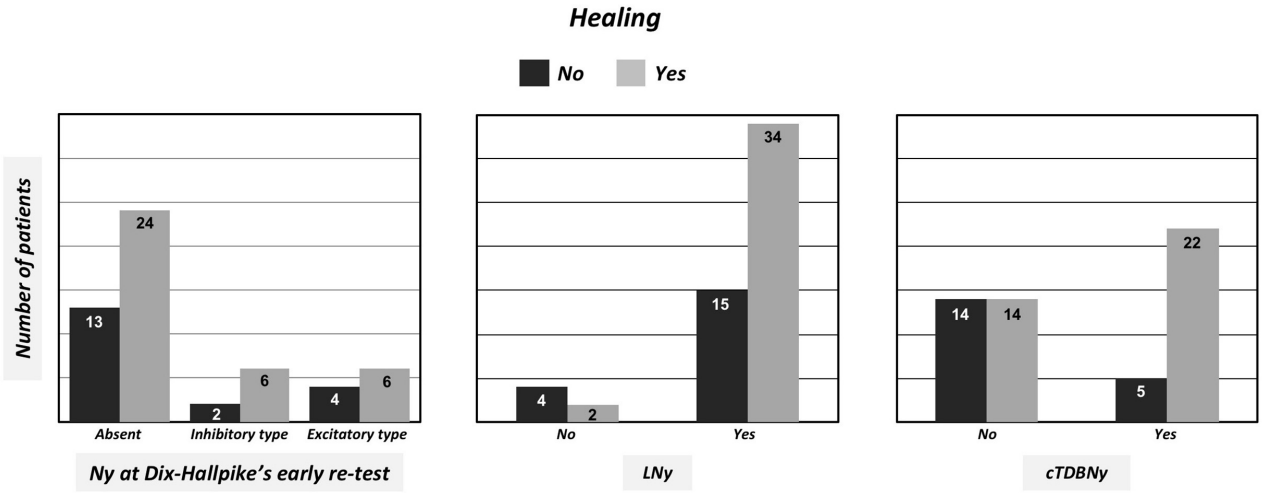

FIGURE 3 | Graphic representation of PSC BPPV healing related to the absence/presence and typology of nystagmus at Dix-Hallpike's early retest (left side), to absence/presence of LNy in the second position of SLM (center), and to absence/presence of cTDBNy in the third position of SLM (right side).

an intervenient action of the Dix-Hallpike's retest variable, which therefore can affect both the definitive healing and the LNy manifestation. This thesis is also validated by model 1 results (**Table 1**) that show the relationship between LNy and Dix-Hallpike's retest nystagmus. **Figure 4** represents the relationships highlighted by the estimates of the three models. Solid lines are for statistically significant relationships, wherever dashed lines are deduced from estimates changes between the three models, literature, and clinical experience.

Finally, regarding the four control variables included in all models, we notice how they don't seem to affect neither the Dix-Hallpike's early retest findings nor healing, meaning that the SLM outcome could not be influenced by age, sex, affected side, or interestingly, by the time elapsed between the symptoms onset and the execution of the maneuver.

The analysis of the first statistical study model shows that there is no significant relationship between cTDBNy in the third SLM position and the immediate resolution, verified by the absence of nystagmus in the Dix-Hallpike's retest (model 1). However, the prognostic role of cTDBNy in determining healing is evident. In fact, the latter sign appears to have good predictive capability for healing, with a $p < 0.05$ (model 2). Furthermore, this datum maintains significance also introducing nystagmus in Dix-Hallpike's retest among the explanatory variables under examination (**Table 3**, model 3).

LNy appearance is also significant for the resolution of the pathology, even if with a lower weight ($p < 0.1$) compared to the cTDBNy in the third position of SLM (model 2). Furthermore, by including among the explanatory variables the absence of nystagmus in Dix-Hallpike's retest, it can be observed how LNy loses significance, due to the interaction effect between the variables (model 3). Both of these aspects can be explained by the sample analysis of the statistical study: in fact, there is no homogeneity between the appearance (49 patients) and the absence (six subjects) of LNy in the second position. Consequently, the weight of the appearance of LNy is less influential than that of cTDBNy in the third position, in which there is a more homogeneous subdivision between the groups (27 patients have nystagmus, 28 patients do not).

Regarding the weight of Dix-Hallpike's retest findings in predicting healing, the absence of nystagmus was not particularly useful, at least regarding the examined patients (model 3).

In the last instance, going into the weight of the explanatory variables under examination, they are not related to the resolution of the clinical picture; especially as regarding the days between the onset of symptoms and the execution of the maneuver, statistical significance cannot be established.

DISCUSSION

The analysis of demographic data shows a substantial alignment with what reported in the literature regarding typical PSC BPPV. This feedback confirms the appropriateness of the inclusion and exclusion criteria adopted in selecting our case studies.

Moreover, in our cohort, PSC BPPV affects the right side more frequently. Therefore, in examining our patients we took care to test, in order, the left Dix-Hallpike's before the analogous positioning on the right; this behavior allowed us to carry out a complete examination always limiting patient's discomfort. Furthermore, thanks to selection criteria, we have never encountered any problem in performing all the required movements, nor have we ever been forced to suspend the examination due to patient's neurovegetative or other systemic symptoms.

Concerning the period of time elapsed between the onset of the disease and our diagnosis, it can be observed that many of the subjects in our series have been assessed in the acute or subacute phase (within 7 days). This certainly happened because our operating unit works in close collaboration with the emergency

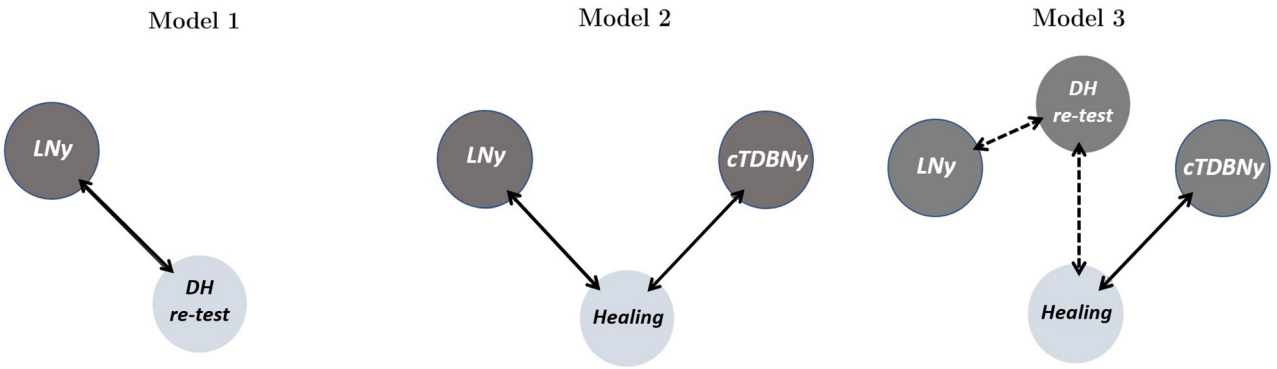

FIGURE 4 | Relationships existing among nystagmus findings at early Dix-Hallpike's retest, at short-term control visit and during SLM in different positions. Colors separate the sides of model specifications: light gray for dependent variables and dark gray for explanatory variables. Solid line arrows represent statistically significant relationships, as found by the related model, wherever dashed line arrows signal those deduced from estimates changes between the three models (see **Tables 1**–**3**), literature and clinical experience.

department, which sends us dizzying patients within a short time by means of a preferential path. It also happened that patients with recently onset vertigo came to our observation for a first evaluation, sent by the attending physician. On the other hand, there are not even a few patients who experienced long-lasting dizziness; among these there are subjects who had suffered in the past from BPPV and returned to visit because of a remote relapse or even individuals who carried out regular hearing checks.

Considering our sample, with regard to the relationship between the time of treatment and symptom's onset, we cannot definitely exclude that the resolution of the picture occurred spontaneously; in fact, the percentage of resolution of the pathology in cases seen at a shorter distance after the onset of symptoms is higher (27/37, 73%) than that found in patients for which diagnosis was made later (9/18, 50%). In any event, the probability of a spontaneous recovery rate as reported in literature is 20% for patients evaluated within 30 days, which is therefore much lower than the one we found for our patients.

From the analysis of our data, it is very clear that the lesser or the greater precocity of treatment does not significantly affect the final outcome; in fact, 27 out of 37 patients with recent vertigo (within 30 days) resolved at the first check but also nine out of 18 subjects with long-standing vertigo (30 days to 1 year) had an excellent control of the disorders with just one treatment. This result seems significant to us because it suggests that this type of vertigo does not tend to worsen over time and probably does not significantly alter labyrinthine metabolism nor the physiological mechanisms, allowing reabsorption of otoconial debris within the vestibule. From a practical point of view, this feedback indicates that, when faced with a patient who has symptoms and signs of PSC BPPV, it is possible to defer treatment for a few days because it will not compromise healing of the pathology. Treatment, if necessary, can be procrastinated to a more favorable time when subject's general conditions are better and patient, if it is useful, can come to visit pharmacologically prepared in order to control neurovegetative symptoms and even the anxiety that this disorder and its therapy can, sometimes, cause.

To confirm this, from our data it also emerges that, even in those few cases in which physical therapy has not been successful at the first session, an association with the late diagnosis/intervention can be seen.

All subjects examined and treated for BPPV had a semeiological picture suggestive of a PSC "canalolithiasis." This is a significant premise because in the presence of otoconial debris free to move within the canal lumen, by observing the eye movements, we can predict the path covered by the otoconial clot as a result of changes in head and body position performed for diagnostic or therapeutic purposes (18). On the contrary in cupulolithiasis, while the behavior of the "heavy" cupula during diagnostic movements is quite clear, it is not equally understood what happens to this receptor following therapeutic shifts. To evaluate the findings highlighting during SLM, it was therefore essential to select subjects whose nystagmus pattern indicated a canalolithiasis rather than a cupulolithiasis pathogenetic mechanism.

Although necessary in a pilot study, the exclusion of cases in which nystagmus suggested cupulolithiasis as a pathogenetic mechanism could be actually a bias in interpreting mechanisms underlying cTDBNy generation in the last step of SLM. Further studies should be needed including even cupulolithiasis cases in order to check if cTDBNy is found as frequently as in canalolithiasis. If this is does not happen, as it is most likely in our opinion, the observation will further confirm our pathophysiological hypotheses.

During the therapeutic phase, we observed nystagmus in fixation condition; visual fixation, in fact, certainly does not succeed to cancel or to significantly inhibit the large nystagmic movements that are generated during liberating maneuvers. This is all the more so in the case of nystagmus generated by vertical semicircular canals, because their torsional component is not affected by fixation, since the ocular movement takes place around the anteroposterior axis of the ocular globe and therefore does not result in the slipping of the image on the

fovea and in the consequent retinal error responsible for fixation system activation.

Canalolithiasis mechanism has been confirmed also by findings observed during SLM; actually, in the first position of SLM, all patients manifested the LoNy, which was similar to the one evidenced at the time of diagnosis. The linear and torsional components of LoNy were perfectly consistent with the excitatory stimulation of the of the pathological side on which the first movement of the SLM was performed.

The success of SLM has been ascertained by checking the disappearance or a positive modification of nystagmus in the Dix-Hallpike's early retest. It could be rightly observed that the time period that elapses between the execution of the release maneuver and the retest is short and that therefore the negativity of the maneuver is attributable to the refractory period; in reality, we believe that in the case of such short albeit intense nystagmus such as those typical of the CSP VPPB, the duration of such refractory period cannot reasonably exceed 3 min. Confirmation of the therapeutic success and therefore healing of the clinical picture was further verified by a follow-up visit carried out a few days after physical treatment.

Running SLM has never converted PSC BPPV into one interesting other semicircular canals thus confirming the lower tendency of deceleration techniques, with respect to repositioning ones, to determine a "canal switch" (19). A high percentage (65.5%) of patients met with resolution after SLM; this finding is absolutely consistent with what has been reported by other authors (9, 20–25). Moreover, 89.1% of our patients presented a LNy in the second position of the SLM; also, this figure is absolutely in line with what has been reported previously. LNy is indicated as a marker of success of the SLM and is correlated with the healing of the pathology. Soto Varela et al. (11) reported that 81% of their patients showed a LNy during the maneuver and healed. In our cases too, almost 70% (69.4%) of the patients who showed this finding were healed after the first maneuver. Therefore, LNy must be considered significant for prognostic purposes. So, as far as the success of therapeutic maneuvers is concerned, we can say that we have performed SLM in correct and effective manner. However, it should be noted that one-third of those few subjects who did not show LNy still healed at the first check-up. We therefore agree with what reported by Soto Valera et al. (11), that the absence of LNy is not necessarily linked to the failure of the therapy. The absence of such a finding is probably related to the lack of a further displacement of the otoconial cluster into the canal lumen after the initial one, achieved during the first phase SLM; therefore, it has neither a negative nor a positive meaning, with regard to the success of therapy, until it is not linked with further eventual events. The highlighting of an apogeotropic nystagmus in the second position of SLM, would have been, instead, a negative prognostic sign, because indicative of a backward path of the otoconial cluster, toward the ampulla. Such an event has never been observed in our case studies.

Conversely, LNy was linked neither to the absence nor to the finding of a torsional down beating nystagmus (apogeotropic) in the Dix- Hallpike's early retest. In other words, LNy did not clearly relate with the apparent early resolution.

From a statistical point of view, LNy seems to be correlated with the type of response at the Dix-Hallpike's retest; actually, LNy alters the probability ratios between the occurrence of an excitatory and an inhibitory nystagmus and the same it almost surely does with the probability ratios between the occurrence of an inhibitory nystagmus and a negative Dix-Hallpike's retest. On the contrary, LNy does not seem to alter the probability ratios between the occurrence of an excitatory nystagmus and a negative Dix-Hallpike's retest.

In addition, 35% of the patients who showed a favorable Dix-Hallpike's retest were still symptomatic and presented findings at a later check. This means that neither early negativity binds to the actual resolution of the picture nor the LNy is linked to a favorable early retest.

Rather, from the statistical analysis, it emerges that Dix-Hallpike's retest findings are not correlated with healing, while LNy is correlated both with Dix-Hallpike's retest results and with healing.

To the question of why sometimes the appearance of the LNy does not ensure the negativity of the early Dix Hallpike's retest it could be asked that maybe the second movement of the SLM effectively moves the debris in the ampullofugal direction but not enough to travel the whole canal; the retest positioning therefore could move the residual debris again in the ampullofugal direction.

With the third movement of SLM, which brings the patient back to the sitting position, in about 50% of our cases, we have witnessed a nystagmus whose appearance has been reported previously only in a very few patients (8/113). However, nystagmus reported by others was not described in detail, not being the subject of deepening in that study (10).

Nystagmus that we evidenced is a torsional vertical nystagmus, mandatorily indicating its origin from the vertical semicircular canals. This nystagmus, in our case study, had the linear component directed downward and the torsional fast phase effectively "congruous" with the stimulation the vertical canals of the pathological side. Referring to the torsional component, we've therefore called it "congruous torsional down beating nystagmus" (cTDBNy). This finding appeared almost without latency with respect to the assumption of the sitting position, it was often of remarkable amplitude, it had a relatively short duration, and almost always a clear paroxysmal trend. Once again, these characteristics are typical of the movement of free debris inside of the canal lumen. In fact, Squires et al. (26) have shown that heavy particles moving within the semicircular canal, without touching the walls and without passing through dilatations, produce this type of ocular movement. Symptoms accompanying cTDBNy were noteworthy and often associated with a clear retropulsion; it was our concern, in fact, to accompany, support, and contain the patient in returning to the sitting position precisely to avoid that the postural reaction could be harmful to the subject. With the third movement of SLM, a position is reached in which the posterior arm of the ASC is located in a maximum vertical position and therefore parallel to the gravitational vector. An otoconial cluster moving in the ampullofugal direction from the non-ampullary arm of the PSC would enter the common crus, thus provoking the aspiration of

its endolymphatic column. Due to the extremely vertical position reached by the ASC posterior arm when sitting with respect to that taken by PSC non-ampullary tract, the aspiration of the endolymphatic column is likely to be much more effective in determining the excitation of the ASC with respect to that of PSC. ASC excitatory stimulus gives rise to a nystagmus beating with the torsional fast phase counterclockwise and clockwise, respectively, for the right and left CSA and, with the linear fast phase, downward. Although to a lesser extent, the same endolymphatic flow due to the passage of the cluster into the common crus may also be ampullofugal into the PSC, thus generating a nystagmus with the torsional component of the fast phase similar to that of ASC but with the linear fast phase directed upward. Due to the above anatomical considerations about the position of PSC non-ampullary arm, when seated, the contribution of the latter canal to the final ocular movement is likely to be weaker. Assuming these endolymphatic dynamics, the nystagmus observed on returning to the sitting position must be characterized by the algebraic sum of the torsional components (equal for the two vertical canals) and that of the two linear components (down beating for ASC and up beating for PSC). For what is previously explained, it will be generated a predominantly torsional nystagmus, congruous, with this component, to the excitation of the vertical canals of the affected side and down beating for the prevailing linear component due to ASC excitation (**Figure 5**, 3rd, a). Indeed, it could be even hypothesized that, due to the spatial orientation of PSC non-ampullary arm in the third position of SLM, the otoconial debris descending into the common crus may also create an ampullopetal reflux of endolymph from the ASC into the PSC, thus causing a weak inhibitory stimulus of the posterior ampullary receptor. The latter endolymphatic flow into the PSC would give rise to a nystagmus having the torsional component opposite to that caused by ASC excitation, but the linear one consensually directed. In this hypothesis, despite the reciprocal cancellation of the torsional components, the resulting nystagmus would be evenly torsional, because of the prevalence of the contribution of the excitation of the ASC (Ewald's second law). Moreover, nystagmus would be maximally vertical down beating because of the addition of the two linear components due to the opposite stimulations of the vertical canals (**Figure 5**, 3rd, b).

A third hypothesis can be formulated to explain the occurrence of a cTDBNy in the third position of SLM: it could happen that, in assuming such a position, the only stimulated canal could be the anterior one. That would happen because the PSC ampullary receptor would find in the refractory period after having discharged because of the ampullofugal endolymphatic current generated with the second movement of the maneuver (and originating LNy) (**Figure 5**, 3rd, c). Against this assumption is the occasional occurrence of cTDBNy also without having observed a LNy.

In all the three hypotheses, neither of which excludes the other, cTDBNy, that we have observed in half of our patients at the end of SLM, should be considered with a "liberating meaning" being the manifestation of the migration of the otoconial cluster correctly out of the canals.

We, therefore, wanted to verify the association of cTDBNy with the positive outcome of the maneuver, at distance and in the immediate. Indeed, 22 (81.5%) out of 27 patients who had cTDBNy were healed at the control visit while only 14 (50%) of the 28 who did not manifest it went to recovery. Such a clear-cut result, statistically supported ($0.01 < p < 0.05$), can only mean that the manifestation of a cTDBNy is related to an escape of the otoconial cluster from the canal and the common crus; this finding is effectively explained with the models described above, in which, according to the mechanism of canalolithiasis, the progressive movement of the cluster in this direction is envisaged. The abrupt retropulsion, so often observed as a reaction to the appearance of cTDBNy, could be the compensatory postural reaction to the down beating ocular movement, which occurs just when the body falls forward. Our results significantly differ from those reported by Albera et al. (10) in the only previous survey that deals with this problem; this discrepancy could be attributed to the small number of patients for which this finding has been described in that series.

On the contrary, the appearance of cTDBNy was not statistically related to the subsequent absence of findings with the early Dix-Hallpike's retest. However, if we evaluate numerical absolute values, we realize that among patients showing a cTDBNy, 81.5% have manifested, at the retest, findings indicative of total or partial release of the canal.

By concluding, in the clinical practice of a second/third-level neuro-otological center, diagnosis of PSC BPPV and its therapy are a consistent part of everyday activity. The evaluation and treatment of such a large number of patients, in various stages of acute illness, involves the observation of peculiar characteristics both of the specific clinical picture and of the events that may occur during physical therapies.

By performing SLM for PSC BPPV likely due canalolithiasis we have often found that, in addition to the LNy described in the second position, a further nystagmus can occur with the third movement of the maneuver, reaching the sitting position. The latter nystagmus is vertical and torsional, the linear fast phase being directed downward and the torsional component "congruous" with the stimulation of the two vertical canals, or at most just one (cTDBNy). As far as we know, this nystagmus has never been described and explained in the literature.

We wondered how this finding could be generated from a pathophysiological point of view, whether it corresponded to a more effective movement of the otoconial cluster toward the utriculus and therefore if this manifestation was synonymous of a better prognosis.

The working hypotheses were confirmed by the clinical data and the results of the statistical analysis. The cTDBNy is statistically correlated with a good prognosis as for short-term resolution of PSC BPPV, at least that supported by a canalolithiasis. Although indicative of good results, LNy appears to have a lower prognostic value than that of the cTDBNy.

The better therapeutic outcomes are neither linked to the early retest results, immediately verified after SLM, nor with the time of the onset of the disease.

From a practical point of view, therefore, in the case of a patient suffering from PSC BPPV, the correct therapeutic

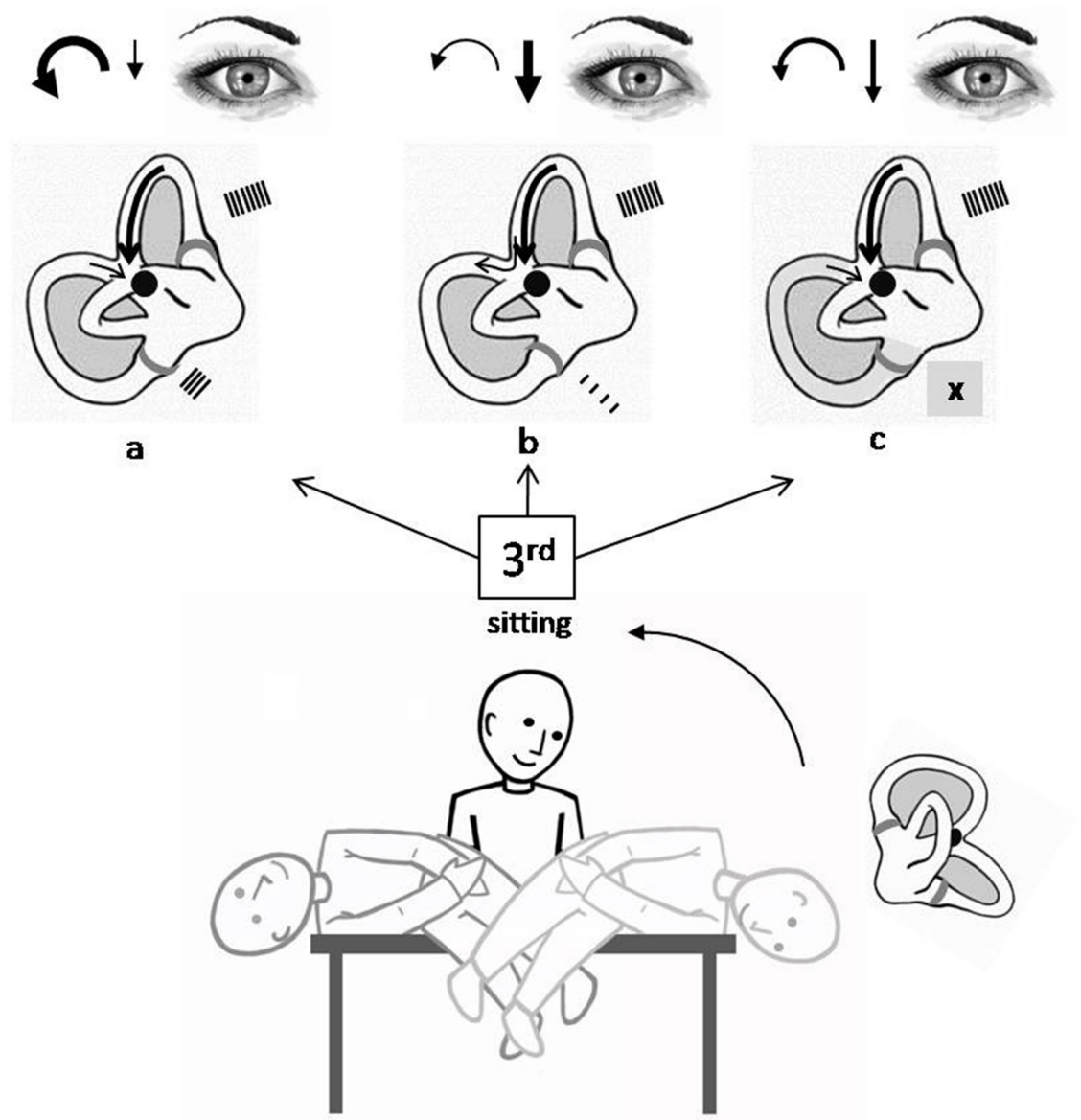

FIGURE 5 | Possible mechanisms of cTDBNy generation in the third position of SLM performed for right PSC BPPV canalolithiasis. **(a)** The descent of the otoconial clot along the common crus provokes an ampullofugal endolymphatic flow, thus an excitatory stimulus, both into the ASC and PSC. Due to the final position reached by the posterior arm of ASC, more vertical than that of the non-ampullary arm of PSC, the outcoming ampullofugal endolymphatic flow is thought to be stronger in ASC than in PSC. Congruous TDBNy has a large counterclockwise and small down beating fast phase (algebraic sum of the consensual torsional and opposite vertical components deriving from the excitation of the two vertical canals). **(b)** The descent of the otoconial clot along the common crus provokes a strong ampullofugal endolymphatic flow into the ASC and a weak ampullopetal reflux into the PSC. Congruous TDBNy has a small counterclockwise and a large down beating fast phase (algebraic sum of the opposite torsional and consensual vertical components deriving from the excitation of ASC and inhibition of PSC). ASC contribution to cTDBNy is greater because of Ewald's second law and of its vertical orientation into the final position. **(c)** The descent of the otoconial clot along the common crus provokes an ampullofugal endolymphatic flow into both the vertical semicircular canals. However, PSC does not contribute to cTDBNy generation because its receptor is still in a refractory period, after being strongly excited in reaching the second position of SLM (and having generated LNy).

behavior can be performing SLM at the time of diagnosis and checking the appearance of the cTDBNy in the third position; if this finding occurs, it is very likely that patients will be free from the disease and that they probably should not undergo other treatments.

It is not necessary to immediately verify the outcome of SLM, thus avoiding the patient's fear of recurrence of symptoms and the possible mobilization of otoconial storage, which, in turn, may result in a return of the canaliths into the canal lumen and to the nullification of the result obtained. If SLM ends with cTDBNy and vertigo, patients can be reassured about the probable resolution of the disease and scheduled for a follow-up visit within some days. Patients can even decide themselves on returning to control basing on subjective symptoms. This

also streamlines outpatient logistics by creating assessment possibilities for more urgent patients.

For what emerged from our results, it will therefore be possible to limit the post-maneuver restrictions favoring the resumption of natural movements as soon as possible, also in order to prevent the patients from continuing avoidance strategies, which instead would "paralyze" and predispose them to failure of readaptation.

It therefore seems significant to us to have identified a clinical sign, never systematically described previously, frequently highlighted during correctly performed SLM, which is simple to evaluate, even without particular technological aids, and which has a great prognostic value, even higher than that possessed from other signs equally frequently found.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BG conceived the study, provided for patient's recruitment, wrote the paper, and collaborated in hypothesis formulation. VM collaborated in study design, in hypothesis formulation, in writing, and commenting in the paper. IV collaborated in patients' recruiting and filling in the database. CC provided for statistical methods and evaluation of data. FP provided for filling in the database, collaborated in patients' recruiting, paper writing, and commenting. RP collaborated in conceiving and planning the study, in patients' recruiting, in writing the paper, and in hypothesis formulation. All authors contributed to the article and approved the submitted version.

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Feasibility of Using the Video-Head Impulse Test to Detect the Involved Canal in Benign Paroxysmal Positional Vertigo Presenting With Positional Downbeat Nystagmus

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Positional downbeat nystagmus (pDBN) represents a relatively frequent finding. Its possible peripheral origin has been widely ascertained. Nevertheless, distinguishing features of peripheral positional nystagmus, including latency, paroxysm and torsional components, may be missing, resulting in challenging differential diagnosis with central pDBN. Moreover, in case of benign paroxysmal positional vertigo (BPPV), detection of the affected canal may be challenging as involvement of the non-ampullary arm of posterior semicircular canal (PSC) results in the same oculomotor responses generated by contralateral anterior canal (ASC)-canalolithiasis. Recent acquisitions suggest that patients with persistent pDBN due to vertical canal-BPPV may exhibit impaired vestibulo-ocular reflex (VOR) for the involved canal on video-head impulse test (vHIT). Since canal hypofunction normalizes following proper canalith repositioning procedures (CRP), an incomplete canalith jam acting as a "low-pass filter" for the affected ampullary receptor has been hypothesized. This study aims to determine the sensitivity of vHIT in detecting canal involvement in patients presenting with pDBN due to vertical canal-BPPV. We retrospectively reviewed the clinical records of 59 consecutive subjects presenting with peripheral pDBN. All patients were tested with video-Frenzel examination and vHIT at presentation and after resolution of symptoms or transformation in typical BPPV-variant. BPPV involving non-ampullary tract of PSC was diagnosed in 78%, ASC-BPPV in 11.9% whereas in 6 cases the involved canal remained unidentified. Presenting VOR-gain values for the affected canal were greatly impaired in cases with persistent pDBN compared to subjects with paroxysmal/transitory nystagmus ($p < 0.001$). Each patient received CRP for BPPV involving the hypoactive canal or, in case of normal VOR-gain, the assumed affected canal. Each subject exhibiting VOR-gain reduction for the involved

canal developed normalization of vHIT data after proper repositioning ($p < 0.001$), proving a close relationship with otoliths altering high-frequency cupular responses. According to our results, overall vHIT sensitivity in detecting the affected SC was 72.9%, increasing up to 88.6% when considering only cases with persistent pDBN where an incomplete canal plug is more likely to occur. vHIT should be routinely used in patients with pDBN as it may enable to localize otoconia within the labyrinth, providing further insights to the pathophysiology of peripheral pDBN.

Keywords: benign paroxysmal positional vertigo (BPPV), downbeat nystagmus, positional nystagmus, video head impulse test (vHIT), vestibulo-ocular reflex (VOR), poserior semicircular canal BPPV, anterior semicircular canal BPPV, apogeotropic BPPV

INTRODUCTION

Positional downbeat nystagmus (pDBN) represents one of the most common findings related to central nervous system (CNS) disorders involving brainstem and cerebellum. As the main function of central vestibular system is to estimate the angular velocity, gravity orientation, and inertia processing peripheral vestibular afferents within the velocity-storage circuit, any lesions disrupting this network can generate pDBN (1, 2). Though central pDBN may also present with paroxysmal course, purely vertical direction, long duration, lack of latency, fatigability and no suppression with visual fixation represent the most prominent features of pDBN of central origin (3–7). Nevertheless, it has been widely demonstrated how pDBN may not rarely occur also in peripheral pathologies (1–3, 8). It can be elicited when the patient is brought into the straight head hanging (SHH) position and/or by Dix Hallpike (DH) maneuvers and it has been mainly related to benign paroxysmal positional vertigo (BPPV) involving the anterior semicircular canal (ASC) (3, 9–15). Despite detached otoconia, moving inside unusual sites of the labyrinth, represent the assumed underlying mechanism, peripheral pDBN patterns show features classically known as central such as lack of torsional components and long time constant (9, 11, 15). More recently, it has been hypothesized that even otoliths settling in the distal portion of the non-ampullary tract of the posterior semicircular canal (PSC) may result in pDBN (16–27). This type of PSC-BPPV has been named "apogeotropic variant" (18, 20) as nystagmus evoked in provoking positions beats away from the ground and in the opposite direction to positional paroxysmal upbeat nystagmus (beating toward the ground in DH positioning, therefore geotropic) due to classical BPPV involving PSC ampullary arm. Demi-Semont (DS) maneuver, 45°-forced prolonged position (FPP) and quick liberatory rotation represent physical treatments proposed for this PSC-BPPV variant, with the aim of moving back displaced particles to the vestibule (19, 20). Nevertheless, it is not rarely hard to identify the affected semicircular canal (SC) due to the possible missing torsional components in pDBN (9, 11, 15, 19, 20). Additionally, ASC-BPPV is generally hardly distinguishable from contralateral apogeotropic variant of PSC-BPPV as in both cases resulting pDBN is generated by the contraction of the same ocular muscles (18, 28). Thanks to the introduction of video-head impulse test (vHIT) in clinical practice, high-frequency VOR measurements for semicircular canals can be easily assessed (29, 30). This new clinical device has been widely used to measure SC function, in both peripheral and central vestibular disorders (31–36). Recently, it has been assumed that vestibulo-ocular reflex (VOR) for the affected SC may be impaired in BPPV resulting in pDBN, providing possible key data for differential diagnosis (37). To further investigate this claim, we submitted a homogeneous cohort of patients with pDBN due to vertical SC-BPPV to statistical analysis and assessed the diagnostic sensitivity of vHIT in detecting the SC involved by BPPV among cases presenting with pDBN. Reviewing our results, we also aimed to offer possible explanations for VOR-gain abnormalities for the affected SC in such cases, providing better insights to the pathophysiology of peripheral pDBN.

Abbreviations: ASC, anterior semicircular canal; BPPV, benign paroxysmal positional vertigo; CRP, canalith repositioning procedure; CNS, central nervous system; DH, Dix Hallpike; DS, Demi Semont; FPP, forced prolonged position; HSC, horizontal semicircular canal; pDBN, positional downbeat nystagmus; PSC, posterior semicircular canal; SC, semicircular canal; SHH, straight head hanging; VEMPs, vestibular-evoked myogenic potentials; vHIT, video-head impulse test; VOG, video-oculography; VOR, vestibulo-ocular reflex.

MATERIALS AND METHODS

Patients

This study was approved by our Institutional Review Boards (approval number for the promoter center: 236/2020/OSS/AUSLRE) and was conducted according to the tenets of the Declaration of Helsinki. We performed a retrospective review of clinical-instrumental data of a cohort of 93 patients presenting with pDBN who were evaluated at our centers between June 2019 and May 2020. Overall subjects were admitted either to the outpatient units or to the emergency units. In order to select only patients with peripheral pDBN due to vertical SC-BPPV, subjects exhibiting oculomotor central signs (gaze-evoked nystagmus, rebound nystagmus, pDBN not reduced or enhanced by visual fixation) or abnormal findings on gadolinium-enhanced magnetic resonance imaging (MRI) were excluded from the analysis. Likewise, patients with past history of vestibular pathologies potentially resulting in pDBN or possible VOR-gain abnormalities for vertical SCs [i.e., Meniere's disease (38), vestibular migraine (39), inferior vestibular neuritis (40), sudden sensorineural hearing loss

with vertigo (33, 41), canal dehiscences (42)], were excluded. Therefore, only patients with pDBN receding or converting into a typical BPPV positional nystagmus following proper canalith repositioning procedures (CRP) were considered. Among Authors, AC, PM, SM, SQ, ER, and EA (all neurotologists) were directly involved in the analysis of pDBN features and data collection. Patients without complete clinical data including at least pre- and post-treatment measurements for all six SC VOR-gains on vHIT were not included in the study. Finally, a residual homogeneous population of 54 patients was recruited for statistical analysis. All patients underwent the same detailed work-up including history taking and bedside examination with the aid of video-Frenzel goggles or video-oculography (VOG). Each patient underwent a comprehensive assessment for all SCs VOR-gains on vHIT before and after physical treatment and only few of them were submitted to VEMPs in different stages of BPPV. Gadolinium-enhanced MRI and/or temporal bones high-resolution CT (HRCT) scan were performed if needed. Besides personal details, patients were asked whether recent head trauma occurred. They were also investigated for history of BPPV with paroxysmal positional nystagmus documented by Video-Frenzel goggles within 30 days prior to examination. Additionally, patients were divided into subgroups according both to the time elapsed between symptoms onset and clinical assessment (<7 and >7 days) and to days needed for pDBN either to recede or to convert in typical positional nystagmus due to typical ipsilateral canalolithiasis (<7 and >7 days).

Detection of the Vertical Canal Affected by BPPV

Any of the following strategies were used for the identification of the SC involved by BPPV:

- Detection of the SC with impaired VOR-gain values on vHIT with either covert or overt saccades.
- In case of pDBN with torsional components, recent history of BPPV with paroxysmal positional nystagmus documented with Video-Frenzel goggles addressed the diagnosis toward a specific SC (i.e., recent left PSC-BPPV addressed the diagnosis toward ipsilateral ASC-BPPV in a patient presenting with pDBN with leftbeating torsional nystagmus, whereas rightbeating components would reasonably indicate ipsilateral apogeotropic PSC-BPPV).

In cases lacking of the above-mentioned findings, detection of the affected canal could only be provided after physical treatment, basing on the following findings:

- Resolution of pDBN after proper CRP designed to release a specific SC from debris, as therapeutic maneuvers, though effective in moving debris, would not result in restoring BPPV affecting other SCs.
- Conversion of pDBN in classical paroxysmal positional nystagmus involving either ipsilateral PSC (upbeating/torsional nystagmus on ipsilateral DH positioning) or horizontal SC (HSC) (either geotropic or apogeotropic horizontal direction-changing nystagmus at the supine head roll test) after any CRP performed, consistently with otoconial switch from the affected canal either to other ipsilateral SCs or to another tract of the same affected SC (i.e., conversion of pDBN with leftbeating torsional components into paroxysmal upbeating nystagmus with rightbeating torsional components elicited in right positioning consistently with debris shift into right PSC ampullary arm addressed the original diagnosis toward ipsilateral BPPV involving PSC non-ampullary arm rather than contralateral ASC-BPPV).

Physical Treatment

All patients underwent specific physical therapy aimed to move debris back to the utricle from the assumed affected vertical SC. In cases with BPPV involving the non-ampullary tract of PSC, DS maneuver was mainly used, followed by the 45°-FPP in case of persistence of symptoms following DS (20). Whereas DS maneuver mainly exploits inertial force to free the affected SC from otoconia, as it basically represents the second part of the well-known Semont's liberatory maneuver (43), 45°-FPP technique uses gravity to move particles toward the utricle, as the affected PSC is located in the uppermost part of the labyrinth in this position (20). Standard Epley's CRP (44) or Semont's maneuver were rarely used as first therapeutic choice, mainly depending on examiner's preferences or patient's compliance.

In cases with ASC involvement, patients were mostly treated with Yacovino's technique (45), followed by prolonged forced position procedure (PFPP) (46) in subjects not exhibiting immediate recovery.

In cases where affected SC could not be ascertained due to the lack of the aforementioned findings, several CRP were pursued according to examiner's experience to obtain a canal switch, to move otoconia toward another tract of the involved SC or to directly free the affected canal.

Each subject was checked within 3–4 days. In case of persistence of pDBN, additional CRP were pursued with following check within further 3–4 days, and so on until a complete recovery or a canal switch was achieved. Physical therapy outcome was considered as successful either if patients were free from symptom and signs or if they exhibited a conversion into a typical form of BPPV. In case debris moved to the ampullary tract of PSC, Epley's or Semont's maneuvers were performed according to examiner's preference or patient's compliance, whereas proper CRP for geotropic and apogeotropic variants of HSC-BPPV were used (47, 48) in case debris moved either to non-ampullary or to ampullary arm of HSC, respectively. All patients were finally checked within further 3–4 days for ensuring a complete recovery.

Eye Movements Recording

Eye movements were analyzed with video-Frenzel goggles or video-oculography (VOG). Horizontal, vertical and torsional nystagmus were qualitatively assessed. Horizontal (right/leftbeating), vertical (up/downbeating) directions of nystagmus and torsional components (right/leftbeating, i.e., with the upper pole of the eye rotating toward the right/left ear, respectively) were described from the patient's point of view. Bedside-examination included assessment of spontaneous and positional nystagmus evoked by both DH and SHH

positionings. Once evaluated any spontaneous DBN (purely vertical, with or without torsional components), positional nystagmus was checked for latency (with/without), direction (purely vertical or with torsional components), inhibition with visual fixation (yes/no), duration and temporal trend (either transitory/paroxysmal accompanied by a crescendo-decrescendo pattern if <2 min, or persistent with nearly stationary course if >2 min) and reversal when returning upright following positionings (with/without).

vHIT

Vestibulo-ocular reflex (VOR) gains for all three SCs were tested on both sides in response to high-frequency head stimuli on vHIT, an ICS video-oculographic system (GN Otometrics, Denmark). At least 15 impulses were delivered for stimulating each SC and averaged to get corresponding mean VOR-gains. Vertical SC were considered hypoactive if VOR-gains were <0.7 with at least either covert or overt saccades (29, 30). All patients underwent vHIT testing at the presentation and following CRP, whether they succeed in SC releasing or resulted in a conversion into a typical BPPV variant (i.e., as soon as pDBN either receded or converted in positional paroxysmal nystagmus).

VEMPs Testing

Cervical and ocular vestibular-evoked myogenic potentials (cVEMPs and oVEMPs, respectively) for air-conducted sounds were recorded using 2-channel evoked potential acquisition systems (either Neuro-Audio, Neurosoft, Russia or Viking, Nicolet EDX, CareFusion, Germany depending on different centers) with surface electrodes placed according to standardized criteria (49). Potentials were recorded delivering tone bursts (frequency: 500 Hz, duration: 8 ms, stimulation rate: 5 Hz) via headphones either before or following CRP. Recording system used an EMG-based biofeedback monitoring method to minimize variations in muscles contractions and VEMPs amplitudes. A re-test was performed for each stimulus to assess reproducibility. The first biphasic responses on the ipsilateral sternocleidomastoid muscle (p13-n23) for cVEMPs (ipsilateral response) and under the patient's contralateral eye (n10-p15) for oVEMPs (crossed response) were analyzed by calculating the peak-to-peak amplitude. Inter-aural amplitude difference between ear affected (Aa) and unaffected (Au) by BPPV were calculated with the asymmetry-ratio (AR): $[(Au - Aa)/(Au + Aa)] \times 100$. Otolith sensors on the pathologic side were considered damaged if potentials resulted in AR >35%, according to our normative data and to literature references (49).

Statistical Analysis

Quantitative variables were checked for normal distribution using both Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were described by mean ± 1 standard deviation for normally distributed variables or by median, interquartile range and range for non-normally distributed variables. Diagnostic sensitivity of vHIT in detecting the involved SC in BPPV with pDBN was calculated as the ratio of cases with hypoactive SC to overall patients. Conversely, diagnostic sensitivity of vHIT for persistent pDBN was calculated as the ratio of cases with persistent pDBN exhibiting a deficient SC to overall cases with persistent pDBN, whereas vHIT sensitivity for transitory/paroxysmal pDBN was derived dividing the number of cases with transitory/paroxysmal pDBN presenting with a hypoactive SC for overall cases exhibiting transitory/paroxysmal pDBN. Fisher's exact test was used for categorical comparisons. Spearman's rank correlation was used to correlate patient's age with SCs VOR-gains. Wilcoxon signed-rank test was used to compare pre- and post-treatment vHIT data for all six SCs. Mann-Whitney *U*-test was employed for pairwise comparisons between subgroups. Results were considered statistically significant if $p < 0.05$. Statistical analyses were performed using IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Fifty-four patients (20 males, 34 females, mean age 55.9 ± 13.8) with pDBN due to vertical SC-BPPV were included in the study. Recurrence of pDBN due to BPPV involving the same SC was recorded in a case and it was considered twice in the analysis. Similarly, four patients (1 male and 3 females) were considered twice as they exhibited either simultaneous or newly sequential BPPV involving other vertical SCs with pDBN. Therefore, clinical and instrumental data concerning 59 cases with pDBN due to vertical SC-BPPV were finally analyzed. Detailed information about overall 59 cases included in the study can be found in **Supplementary Tables 1, 2**.

Apogeotropic PSC-BPPV was diagnosed in 78% of cases (46/59, 26 on right and 20 on left side), ASC-BPPV in 11.9% of cases (7/59, all left-sided) whereas in 6 cases (10.1%) neither the involved SC nor the pathologic side could be ascertained (**Table 1**). Recent BPPV were reported in 46 cases (77.9%) and in 10 cases (16.9%) previous head trauma could be recorded (**Table 1**). Most subjects (35/59, 59.3%) presented at our attention more than a week from symptoms onset, without statistically significant difference between apogeotropic PSC-BPPV and ASC-BPPV cases or between subjects with identified SC and unknown affected site (**Figure 1A**). In patients with BPPV involving PSC non-ampullary arm, spontaneous purely vertical DBN was identified in 2 subjects and spontaneous torsional/vertical DBN was identified in 4 cases, consistently with a canalith jam. Spontaneous nystagmus did not exhibit direction changings either in forward or backward head bending along the pitch plane, was inhibited by visual fixation in its vertical component and increased in recumbent positionings in all 6 subjects. It likely resulted from previously performed CRP only in half of cases, whereas the remaining 3 patients presented with a spontaneous canalith jam converting into an ipsilateral SC-BPPV after DS maneuvers with the aid of mastoid vibrations. While 83.1% of overall cases and the whole population either with ASC-BPPV or BPPV involving undefined SC presented with pDBN detectable in both SHH and bilateral DH positions, both maneuvers resulted in positional nystagmus only in 78.3% of cases with apogeotropic PSC-BPPV, without statistically significant difference among subgroups

TABLE 1 | Information about personal details, history, and VOR-gain abnormalities for overall 59 cases with pDBN and different subgroups divided according to the vertical semicircular canal involved by BPPV.

Affected semicircular canal (% of overall)	Sex		Age (y)	Previous BPPV		Previous head trauma (%)	VOR-gain abnormalities (%)
	M (%)	F (%)		Defined (%)	Undefined (%)		
Overall, *n*. 59 (100)	21 (35.6)	38 (64.4)	57 ± 13.9	33 (55.9)	13 (22)	10 (16.9)	43 (72.9)
PSC, *n*. 46 (78)	16 (34.8)	30 (65.2)	57.9 ± 14.4	26 (56.5)	10 (21.7)	6 (13)	37 (80.4)
ASC, *n*. 7 (11.9)	2 (28.6)	5 (71.4)	59.7 ± 11.8	6 (85.7)	0 (0)	2 (28.6)	6 (85.7)
Unidentified, *n*. 6 (10.1)	3 (50)	3 (50)	47.3 ± 8.2	1 (16.7)	3 (50%)	2 (33.3)	0 (0)

ASC, anterior semicircular canal; BPPV, benign paroxysmal positional vertigo; F, female; M, male; pDBN, positional downbeat nystagmus; PSC, posterior semicircular canal; VOR, vestibulo-ocular reflex; y, years.

(**Figure 1B**). Overall rate of pDBN presenting with latency was 67.8% (40/59) with similar ratios in different BPPV-subtypes (65.2% in apogeotropic PSC-BPPV, 85.7% in ASC-BPPV and 67.8% in cases with unidentified SC) (**Figure 2A**). Thirty-four patients (57.6%) exhibited positional nystagmus with torsional components, whereas pDBN direction was purely vertical in 25 cases (42.4%) without significant differences among subgroups. Nevertheless, the majority of patients with BPPV involving either ASC (57.1%) or undefined SC (66.7%) presented pDBN lacking of torsional components (**Figure 2B**). In most cases (44/59, 74.6%) pDBN was persistent in provoking positions showing significant higher prevalence among subjects with debris settling the non-ampullary tract of PSC ($p = 0.039$) compared to ASC involvement. Conversely, it exhibited transitory and typical paroxysmal crescendo-decrescendo course in most cases with ASC-BPPV (4/7, 57.1%) and in half of patients where the affected SC was not identified (**Figure 2C**). The vast majority of cases (52/59, 88.1%), irrespective to the involved SC, lacked in reversal of positional nystagmus once returning in upright position, being totally absent in cases with no detectable pathologic site (**Figure 2D**). No significant difference in terms of outcome with physical therapy could be found among underlying diagnosis, being resolution of pDBN predominant over conversion into typical paroxysmal nystagmus due to either canal switch or progression toward the ampullary tract of PSC in all different BPPV-subtypes (**Figure 1C**). Despite two types of CRP (usually an impulsive maneuver followed by prolonged positioning) were enough either to release the involved canal from dislodged particles or to convert pDBN into paroxysmal nystagmus in most cases (35/59, 59.3%), all subjects with unidentified affected SC received more than 2 types of CRP to recover ($p = 0.003$; **Figure 1D**). Conversely, no substantial difference in terms of time needed to recover or convert into typical BPPV could be found among different subgroups, prevailing a time-period greater than a week across all different BPPV forms (**Figure 1E**).

Preliminary correlation analysis between patient's age and VOR-gain values for each SC (both pre- and post-treatment) in subjects with defined affected SC (*n*. 53) was performed prior to investigating VOR-gain behavior among different subgroups, to ensure lack of consistent age-related bias involving canal activity (50). Only a negative correlation between patients' age and presenting VOR-gains for the other vertical SC ipsilaterally to the affected canal (rho $= -0.279$, $p = 0.043$) and for the contralateral SC other than the canal coupled with the affected SC (rho $= -0.302$, $p = 0.028$) was found (**Figure 3**).

In 43/59 cases (72.9%) an isolated vertical SC hypofunction could be identified without statistically significant difference between apogeotropic PSC (37/46, 80.4%) and ASC-BPPV (6/7, 85.7%) (**Figure 4A** and **Table 1**). In all these patients, torsional components of pDBN, when detected, were in agreement with the excitatory (in ASC-BPPV) or inhibitory (in apogeotropic PSC-BPPV) discharge of the hypoactive SC, as expected from resulting endolymphatic flows elicited by otoconial shift in DH and SHH positionings. Moreover, proper CRP for treating the hypoactive SC succeeded either in resolution of symptoms and signs or in conversion into a typical ipsilateral BPPV with paroxysmal nystagmus involving the ampullary tract of PSC or HSC in all cases. All these patients exhibited normalization of VOR-gain abnormalities after either pDBN resolution or conversion into paroxysmal positional nystagmus, confirming a close linkage between transient high-frequency VOR impairment and BPPV-related pDBN (**Figure 5**). In none of our cases, deficient VOR-gain values could be detected for a SC unrelated to BPPV, except for a case who presented with impaired PSC VOR-gain ipsilaterally to the affected ASC (with normal VOR-gain) normalizing after successful physical therapy for ASC-BPPV. All patients presenting with spontaneous DBN exhibited hypoactive VOR-gain for the affected canal (**Figure 4B**).

When dividing overall cohort of patients according to pDBN duration, subgroup of patients presenting with persistent positional nystagmus (44/59) exhibited a significantly higher rate of cases with VOR-gain impairment (88.6%) compared to patients in which positionings elicited a transient/paroxysmal pDBN (26.7%) ($p < 0.001$; **Figure 6A**). Nevertheless, rates of cases showing pDBN reversal in upright position, different time from symptoms onset and for recovery or conversion of pDBN, different outcomes and number of CRP required did not differ between subgroups exhibiting these two different pDBN patterns (**Figures 6B–F**).

When exploring variations between presenting and post-treatment VOR-gain values for each SC among overall population with pDBN due to BPPV involving detectable SC (53 cases), a significant functional improvement could be found for the affected SC ($p < 0.001$), for its coupled contralateral canal ($p < 0.001$) and for the other contralateral vertical SC ($p = 0.002$; **Figure 5A**). Similar results could be achieved for

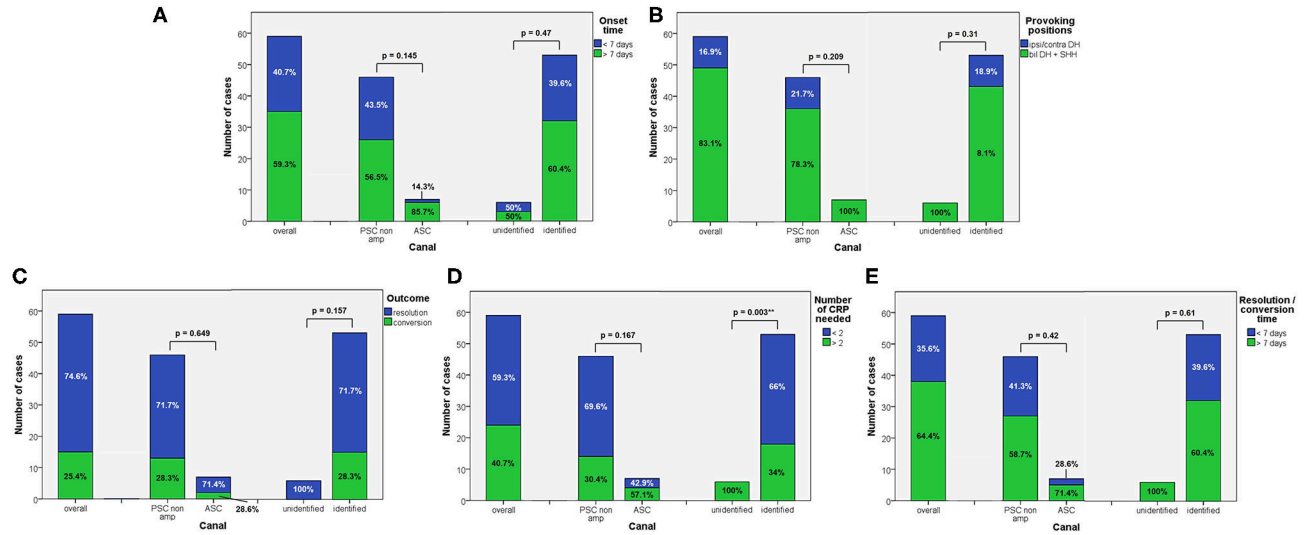

FIGURE 1 | Bar plots showing the amount of subjects among overall population of 59 cases, divided in paired subgroups based on diagnosis, exhibiting different clinical features. **(A)** Time of symptoms onset. **(B)** Provoking positions. **(C)** Outcome. **(D)** Number of CRP needed. **(E)** Resolution or conversion time. Relative percentages among subgroups are reported in each column. Statistically significant differences at the Fisher's exact test are reported and highlighted with $^{**}p < 0.01$, respectively. ASC, anterior semicircular canal; CRP, canalith repositioning maneuvers; PSC non-amp, posterior semicircular canal non-ampullary arm.

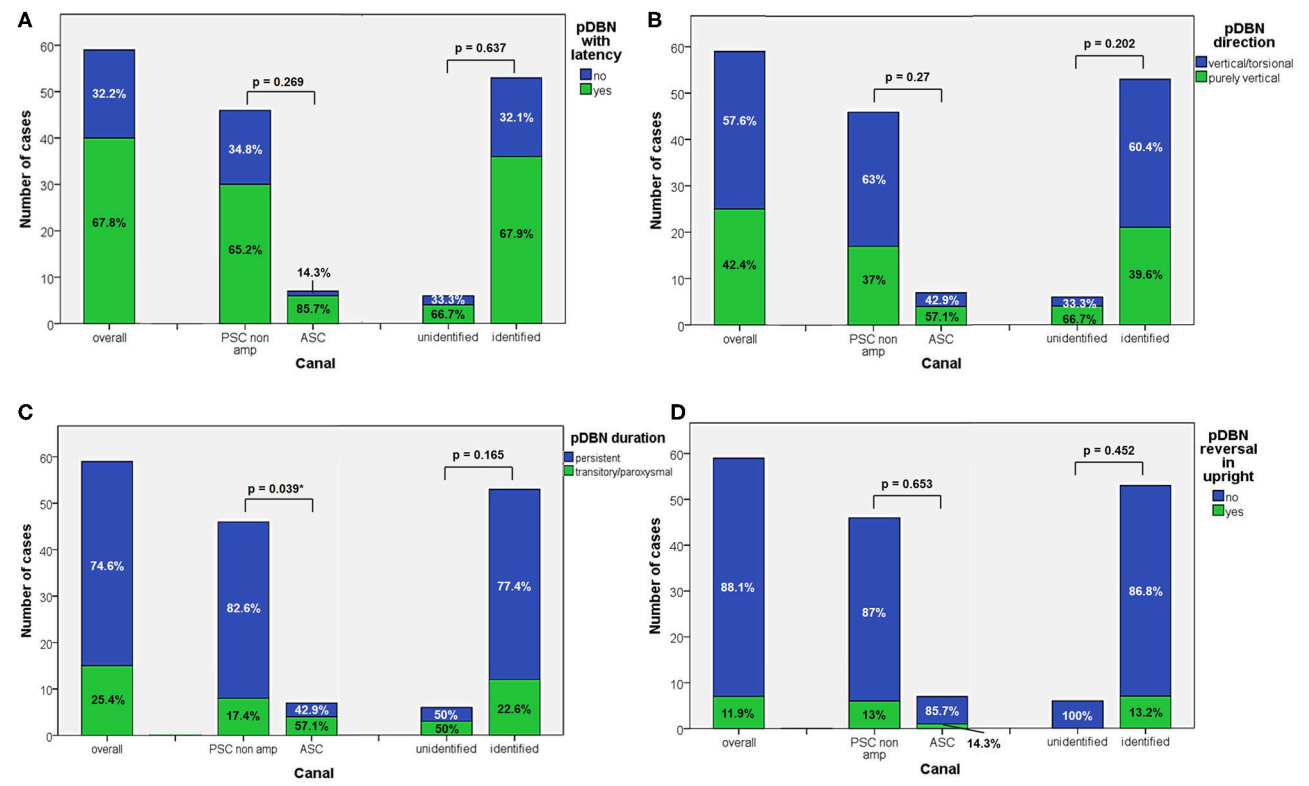

FIGURE 2 | Bar plots showing the amount of subjects among overall population of 59 cases, divided in paired subgroups based on diagnosis, presenting with different VOG features. **(A)** pDBN with latency. **(B)** pDBN direction. **(C)** pDBN duration. **(D)** pDBN reversal in upright. Relative percentages among subgroups are reported in each column. Statistically significant differences at the Fisher's exact test are reported and highlighted with $^{*}p < 0.05$, respectively. ASC, anterior semicircular canal; pDBN, positional downbeat nystagmus; PSC non-amp, posterior semicircular canal non-ampullary arm; VOG, video-oculography.

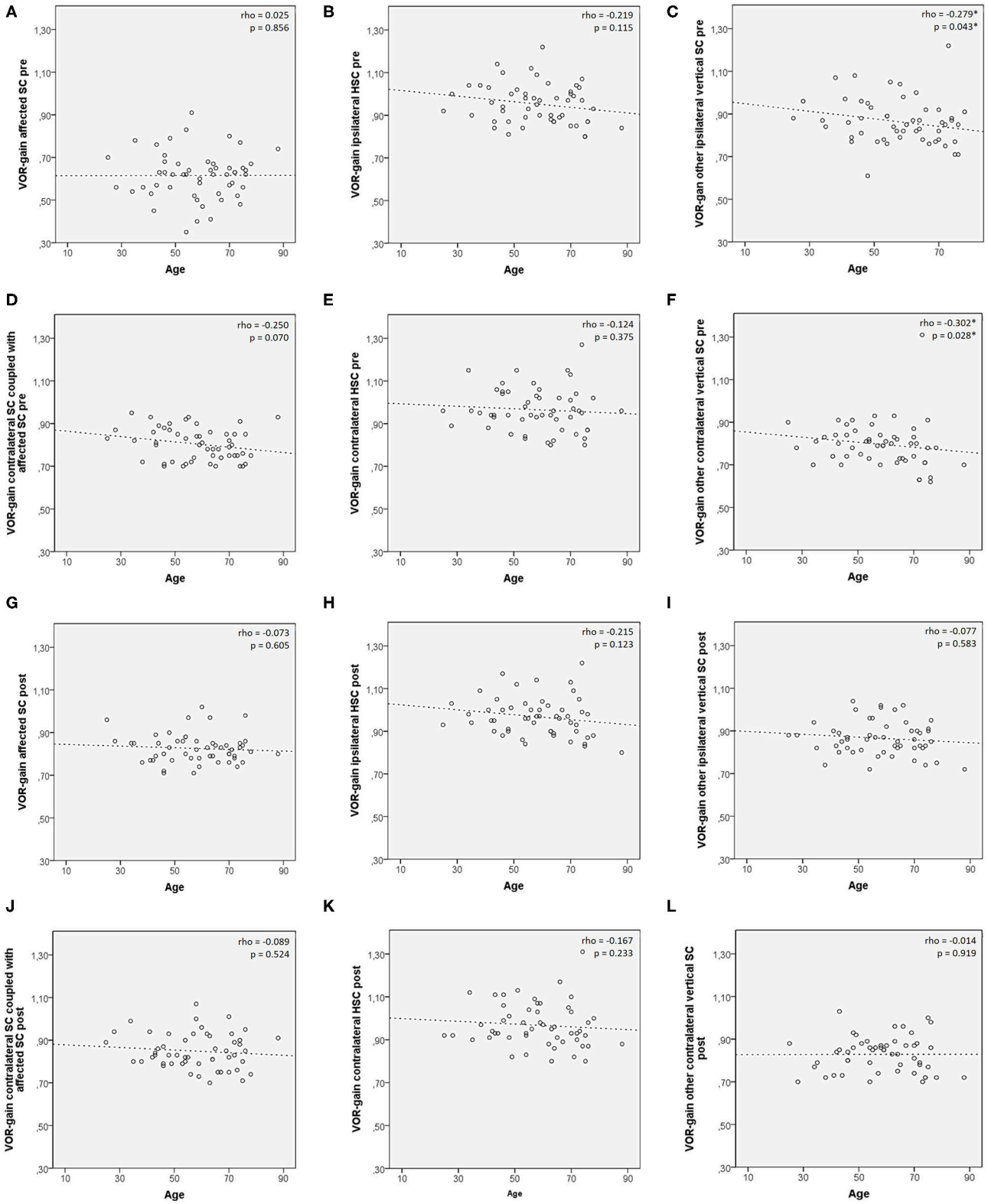

FIGURE 3 | Scatter plots correlating patients' age among 53 patients with identified affected SC with presenting VOR-gain **(A–F)** and post-treatment VOR-gain **(G–L)** for each semicircular canal. Each plot shows the linear regression line with corresponding Spearman's correlation coefficient (ρ). $p < 0.05$ are reported and marked with *. HSC, horizontal semicircular canal; post, post-treatment; pre, at presentation; SC, semicircular canal; VOR, vestibule-ocular reflex.

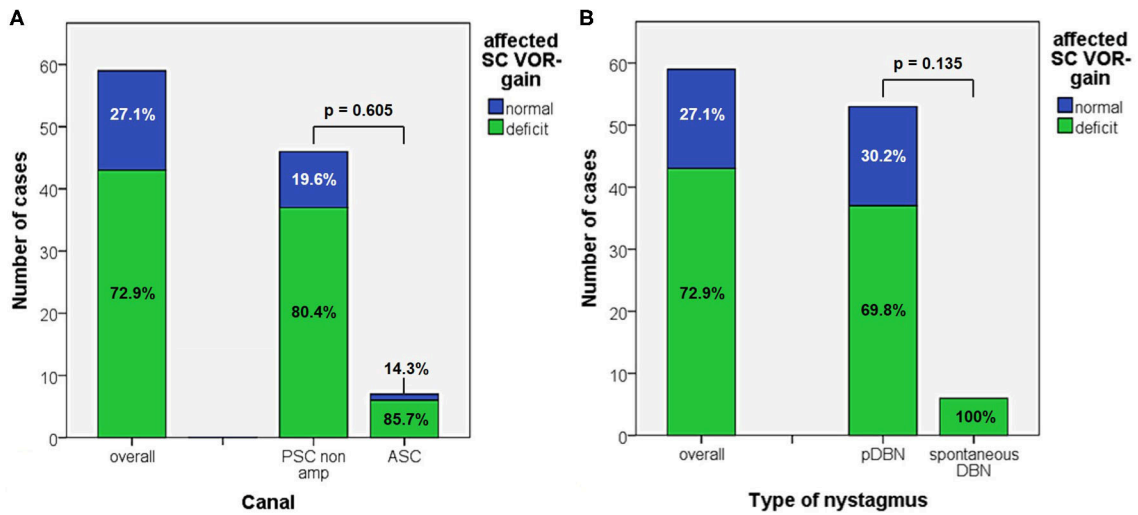

FIGURE 4 | Bar plots showing the amount of patients, divided in paired subgroups based on diagnosis **(A)** or on type of positional nystagmus **(B)**, exhibiting normal or hypoactive VOR-gain for the affected semicircular canal at presentation. Relative percentages among subgroups are reported in each column. Statistically significant differences at the Fisher's exact test are reported. ASC, anterior semicircular canal; pDBN, positional downbeat nystagmus; PSC non-amp, posterior semicircular canal non-ampullary arm; SC, semicircular canal; VOR, vestibulo-ocular reflex.

cases with apogeotropic PSC-BPPV (**Figure 5B**) and ASC-BPPV (**Figure 5C**). Increasing of VOR-gain for the affected SC following CRP was more pronounced for cases presenting with persistent pDBN than paroxysmal, irrespective to the type of canal involved (**Figure 7A**), whereas it was statistically significant only for affected SC presenting with hypoactive canal function (**Figure 7B**). No significant differences in terms of both presenting and post-treatment values of VOR-gain for the affected SC could be found considering either the type of SC involved (ASC vs. non-ampullary tract of PSC), possible pathologic sides (right vs. left) or different genders (male vs. female). Similar results were achieved dividing overall patients according to previous history of BPPV and head trauma and comparing high-frequency function for the affected SC between subgroups (**Figure 8**). Conversely, once separated overall population of 53 cases with identified involved canal according to possible pDBN features, presenting VOR-gain values for the affected SC were more severely impaired in cases with persistent positional nystagmus ($p < 0.001$) and with spontaneous DBN ($p = 0.002$) than subjects exhibiting transient/paroxysmal pDBN and lacking of spontaneous nystagmus, respectively (**Figures 9A–E**). Unlike, no significant disparities in post-treatment VOR-gain values could be found between subgroups with different pDBN characteristics (**Figures 9F–J**). Functional SC impairment at presentation was also slightly greater in patients successfully treated with one or two CRP than cases requiring more than 2 types of maneuvers either to recover or to convert pDBN into a typical BPPV variant ($p = 0.025$; **Figure 10C**). On the contrary, presenting VOR-gain for involved canal did not significantly differ considering possible onset times (<7 vs. >7 days), outcomes (resolution vs. conversion) and days needed to treat pDBN (<7 vs. >7 days) (**Figures 10A–D**), and the same was found comparing VOR-gain values following therapeutic maneuvers among subgroups (**Figures 10E–H**).

Both cVEMPs and oVEMPs to air-conducted sounds were performed only in 26/59 patients (44%) to test saccular and utricular function, respectively. Whereas, no significant difference in utricular function could be found among subgroups (**Figure 11**), cases with left-sided BPPV and exhibiting pDBN conversion in paroxysmal nystagmus showed greater cVEMPs AR than cases with BPPV involving the right ears ($p = 0.029$) and with pDBN resolution after CRP ($p = 0.035$), respectively (**Figure 12**).

DISCUSSION

BPPV is considered the most frequent disorder among peripheral vestibular pathologies with a high prevalence in adult population. Otoliths detachment from utricular macula is the underlying physiopathological mechanism currently accepted (1). Perturbations in SC dynamics due to dislodges particles gravitating within membranous labyrinth mostly result in rotatory vertigo spells triggered by head position changes. Despite positional short-lasting vertigo represent the distinguishing symptom, BPPV-related signs and symptoms may differ among individuals, mainly depending on the portion of the labyrinth involved and on how dislodged otoconia are disposed, resulting in sometimes challenging clinical scenario. In fact, despite PSC represents the most frequently involved site due to its anatomically inferior location in both supine and upright positions, HSC-BPPV accounts for a considerable rate of patents ranging from 10 to 20% of overall cases (1, 51). Conversely, due to its anti-gravity position, ASC ampullary receptor has been found to be rarely activated by endolymphatic perturbations due to detached otoconia, mainly accounting for

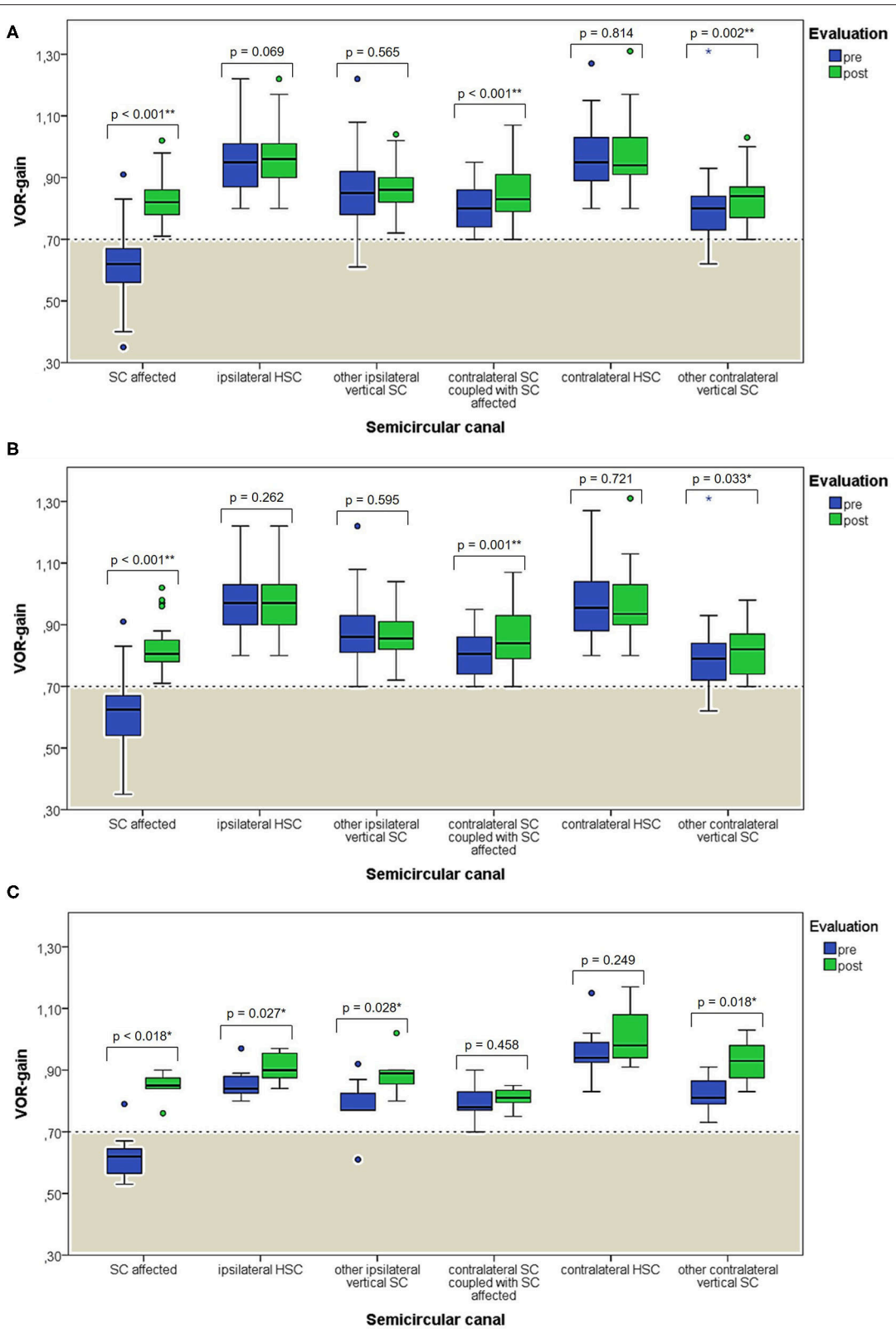

FIGURE 5 | Box plots correlating medians of VOR-gain values at presentation and following physical therapy for each semicircular canal among overall 53 subjects with identified affected SC **(A)**. The same correlation is shown considering either only cases with apogeotropic PSC-BPPV **(B)** or ASC-BPPV **(C)**. Horizontal dashed

(Continued)

FIGURE 5 | lines represent the border between normal and pathologic VOR-gain values for vertical canals (0.7) and values within gray areas represent abnormal measurements. Statistically significant differences at the Wilcoxon signed-rank test are shown. $p < 0.05$ and < 0.01 are marked with * and **, respectively. ASC, anterior semicircular canal; BPPV, benign paroxysmal positional vertigo; HSC, horizontal semicircular canal; post, post-treatment; pre, at presentation; PSC, posterior semicircular canal; SC, semicircular canal; VOR, vestibulo-ocular reflex. Values at a greater distance from the median than 1.5 times and 3 times the IQR are plotted individually as dots (weak outliers) and asterisks (strong outliers), respectively.

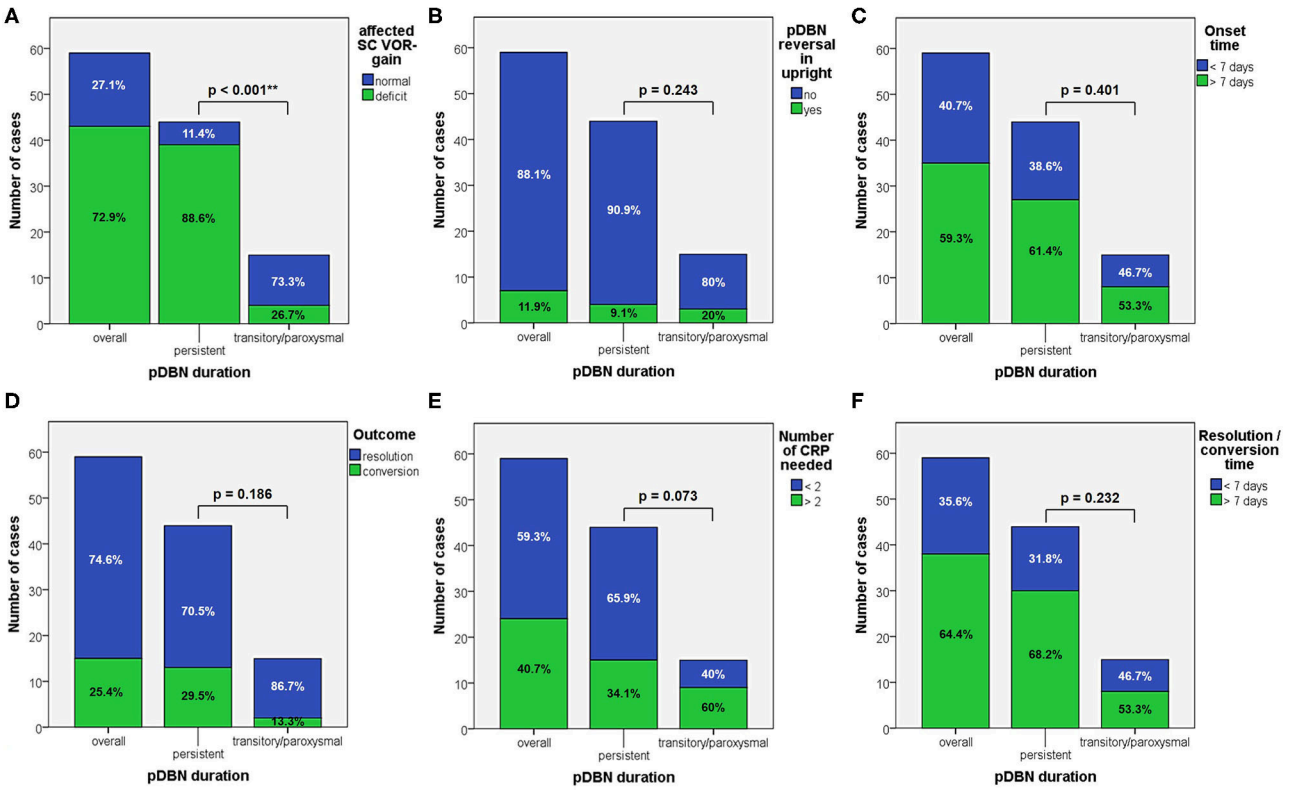

FIGURE 6 | Bar plots showing the amount of subjects among overall population, divided in paired subgroups depending on pDBN duration, exhibiting different instrumental, and clinical features. **(A)** Normal or hypoactive SC VOR-gain for the affected canal at presentation. **(B)** Reversal of pDBN in upright position. **(C)** Different onset times. **(D)** Different outcomes. **(E)** Different number of CRP needed for resolution or conversion. **(F)** Different time needed for resolution or conversion of pDBN. Relative percentages among subgroups are reported in each column. Statistically significant differences at the Fisher's exact test are reported. CRP: canalith repositioning procedure. pDBN, positional downbeat nystagmus; SC, semicircular canal; VOR, vestibulo-ocular reflex. Statistically significant differences at the Fisher's exact test are reported and highlighted with $^{**}p < 0.01$.

<5–10% of cases (1, 11, 12, 15, 51, 52). Moreover, despite it has been demonstrated by microscopic investigations how otoliths may either float within membranous ducts (*canalolithiasis*) or adhere to the cupula (*cupulolithiasis*) (53, 54), it has been also hypothesized that a consistent amount of otoconial fragments may sometimes aggregate in clots remaining entrapped within membranous ducts (*canalith jam*) (55, 56). Since several CRP have been described to treat each possible BPPV variant, precise localization of otoconia within the labyrinth is of pivotal importance for treatment outcome. As vestibular testing have a limited role in BPPV diagnosis, not being even recommended in current clinical practice guidelines (57, 58), otoconia siting has been predominantly relied on combining the above-mentioned notions with both the spatial orientation of the assumed SC involved and principles of gravitational fluid mechanics leading to nystagmus recorded during examination and throughout treatment.

The distinguishing feature of the typical variant of PSC-canalolithiasis (involving its ampullary arm) is represented by paroxysmal upbeat nystagmus with torsional components beating toward the undermost ear, referring to the upper corneal poles, evoked by ipsilateral DH maneuver. Geotropic upbeat nystagmus is disconjugated, with a weaker downward and stronger intorsional slow component in the eye of the pathologic side and a stronger downward and weaker extorsional slow component in the opposite eye, resulting from the transitory activation of ipsilateral PSC-ampulla, since debris within the ampullary arm move away from the cupula during diagnostic maneuvers (59). Resulting ampullofugal endolymphatic flows represent an excitatory stimulus for PSC according to Ewald's

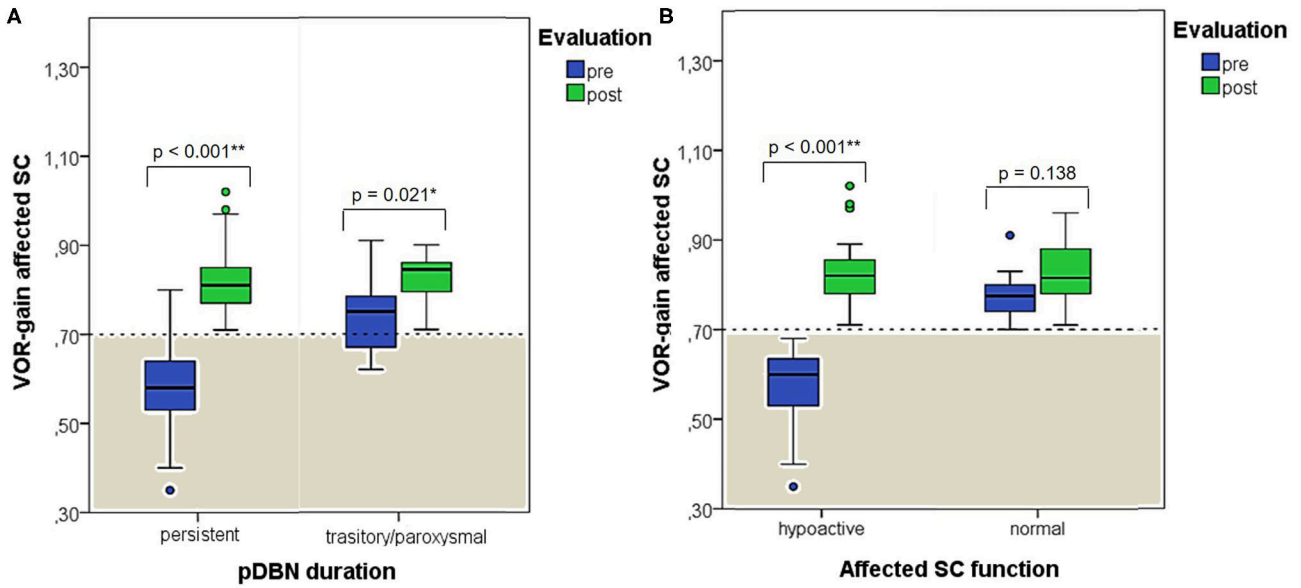

FIGURE 7 | Box plots correlating medians of VOR-gain values at presentation and following physical therapy for the affected SC among overall 53 subjects with identified pathologic canal divided according to pDBN duration **(A)** and affected SC function **(B)**. Horizontal dashed lines represent the border between normal and pathologic VOR-gain values for vertical canals (0.7) and values within gray areas represent abnormal measurements. Statistically significant differences at the Wilcoxon signed-rank test are shown. $p < 0.05$ and < 0.01 are marked with * and **, respectively. pDBN, positional downbeat nystagmus; post, post-treatment; pre, at presentation; SC, semicircular canal; VOR, vestibulo-ocular reflex. Values at a greater distance from the median than 1.5 times the IQR are plotted individually as dots (weak outliers).

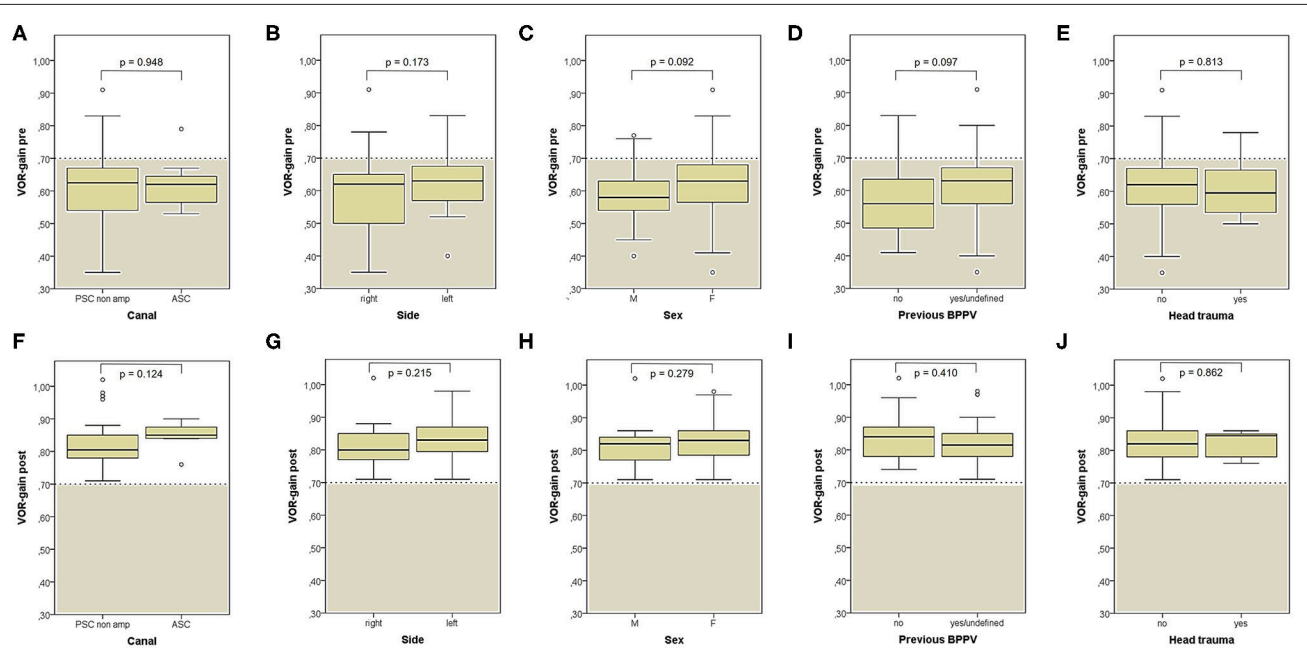

FIGURE 8 | Box plots correlating medians of VOR-gain values at presentation **(A–E)** and following physical treatment **(F–J)** for the SC involved by BPPV among overall subjects (53) with identified affected canal divided based on different details. **(A,F)** Affected semicircular canal. **(B,G)** Affected side. **(C,H)** Gender. **(D,I)** History of recent BPPV. **(E,J)** History of recent head trauma. Statistically significant differences at the Mann-Whitney *U*-test are reported. ASC, anterior semicircular canal; BPPV, benign paroxysmal positional vertigo; F, female; M, male; post, post-treatment; pre, at presentation; PSC non-amp, posterior semicircular canal non ampullary arm; SC, semicircular canal; VOR, vestibulo-ocular reflex. Values at a greater distance from the median than 1.5 times the IQR are plotted individually as dots (weak outliers).

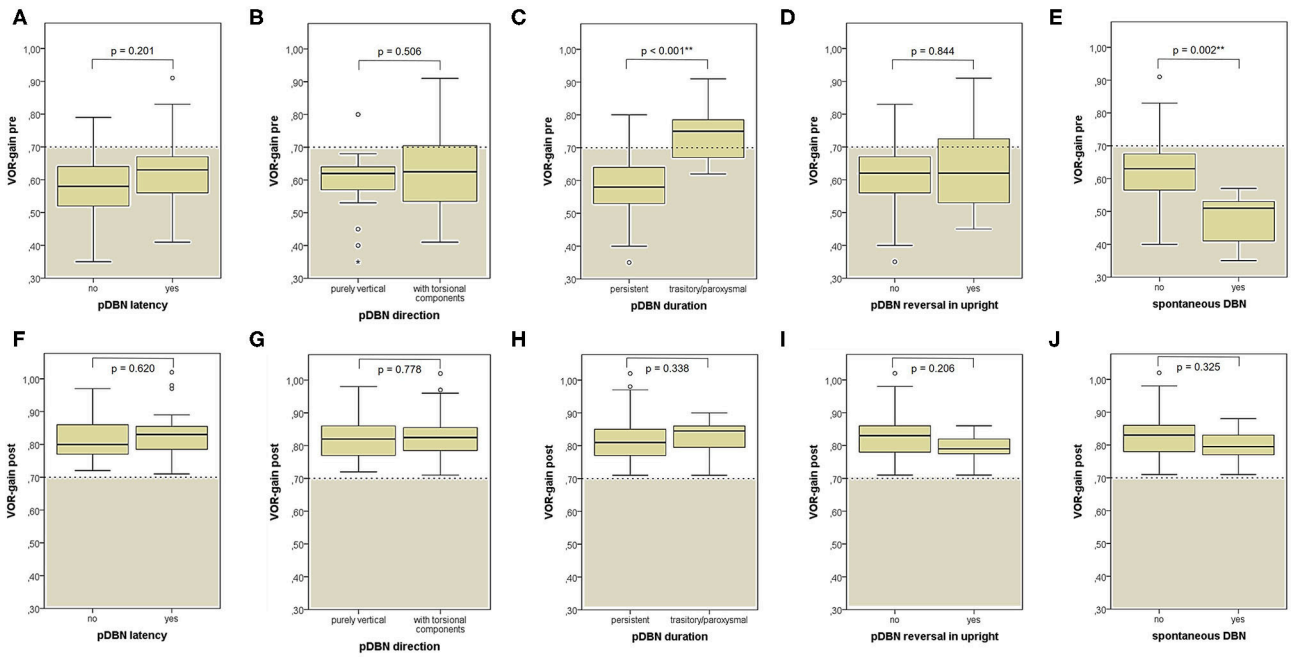

FIGURE 9 | Box plots correlating medians of VOR-gain values at presentation **(A–E)** and following physical treatment **(F–J)** for the SC involved by BPPV among overall subjects (53) with identified affected canal divided based on different VOG findings at presentation. Statistically significant differences at the Mann-Whitney *U*-test are reported and highlighted with $^{**}p < 0.01$. BPPV, benign paroxysmal positional vertigo; post, post-treatment; pre, at presentation; pDBN, positional downbeat nystagmus; SC, semicircular canal; VOG, video-oculography; VOR, vestibulo-ocular reflex. Values at a greater distance from the median than 1.5 times and 3 times the IQR are plotted individually as dots (weak outliers) and asterisks (strong outliers), respectively.

laws, explaining the aligning plane and the direction of resulting positional nystagmus. It usually exhibits both a typical crescendo-decrescendo course and limited duration as it recedes once debris have reached the undermost position. Moreover, it shows direction reversal with analogous time characteristics once returning to the upright position due to reflux of otoconia toward PSC ampulla. In accordance with Ewald's laws, the latter nystagmus shows lower amplitude than the former, as it results from ampullopetal flows inhibiting PSC afferents (1, 2). Canalolithiasis involving HSC lead to oculomotor patterns exhibiting similar time features to PSC, though it is mainly elicited by head movements along the yaw plane in the supine position (1, 2). Whereas, HSC-cupulolithiasis has been widely investigated, resulting in persistent direction-changing positional nystagmus aligning with the horizontal plane due to a continuous deflection of the overloaded cupula in lateral positionings, cupulolithiasis involving PSC has been rarely described (60–62). It has been related to persistent positional nystagmus elicited in recumbent positionings with either downbeat or upbeat direction depending on anatomy and head-bending angle, similarly to migrainous subjects with supposed modified density ratio between PSC-cupula and surrounding endolymph (63).

Nevertheless, most authors have advocated BPPV involving ASC ampullary arm as underlying mechanism for pDBN (**Figures 13A–D**). In this condition, debris are thought to move away from ASC ampulla resulting in ampullofugal cupular deflection with an excitatory discharge of the superior ampullary nerve [(1, 9, 28, 52); **Figure 13C**]. Morphological characteristics of pDBN resulting from such a physiological event should exhibit a fast phase torsional components directed toward the affected ear as nystagmus is generated by the contraction of ipsilateral superior rectus and contralateral inferior oblique muscles. Nevertheless, interpretation of pDBN still represent a challenging topic, as patients with ASC-BPPV usually present with atypical positional nystagmus mimicking central pDBN (1–3, 9). In fact, it is rarely evoked only by ipsilateral positioning and it usually exhibits longer time constant compared to typical BPPV-like nystagmus, lacking of both crescendo-decrescendo course and torsional components (3, 9–15). Moreover, it has been recently hypothesized that the same pDBN could also be generated by particles gravitating through the distal portion of the non-ampullary tract of PSC, close to the common crus [(16–27); **Figures 14A–D**]. In this condition, provoking maneuvers should move debris toward PSC-ampulla leading to an inhibitory discharge of PSC-afferents, which in turn results in pDBN with torsional components beating toward the contralateral ear (**Figure 14C**). Likewise ASC-BPPV (9), even in this case the non-ampullary arm of each PSC aligns with gravity enough to move debris in ampullopetal direction in both DH bilaterally and SHH positionings (20). Therefore, the same positional nystagmus resulting from activation of ASC-afferents could be also generated inhibiting contralateral posterior ampullary nerve, which drive contractions of the same ocular muscles (18, 28). Though comparison of amplitude between nystagmus evoked in

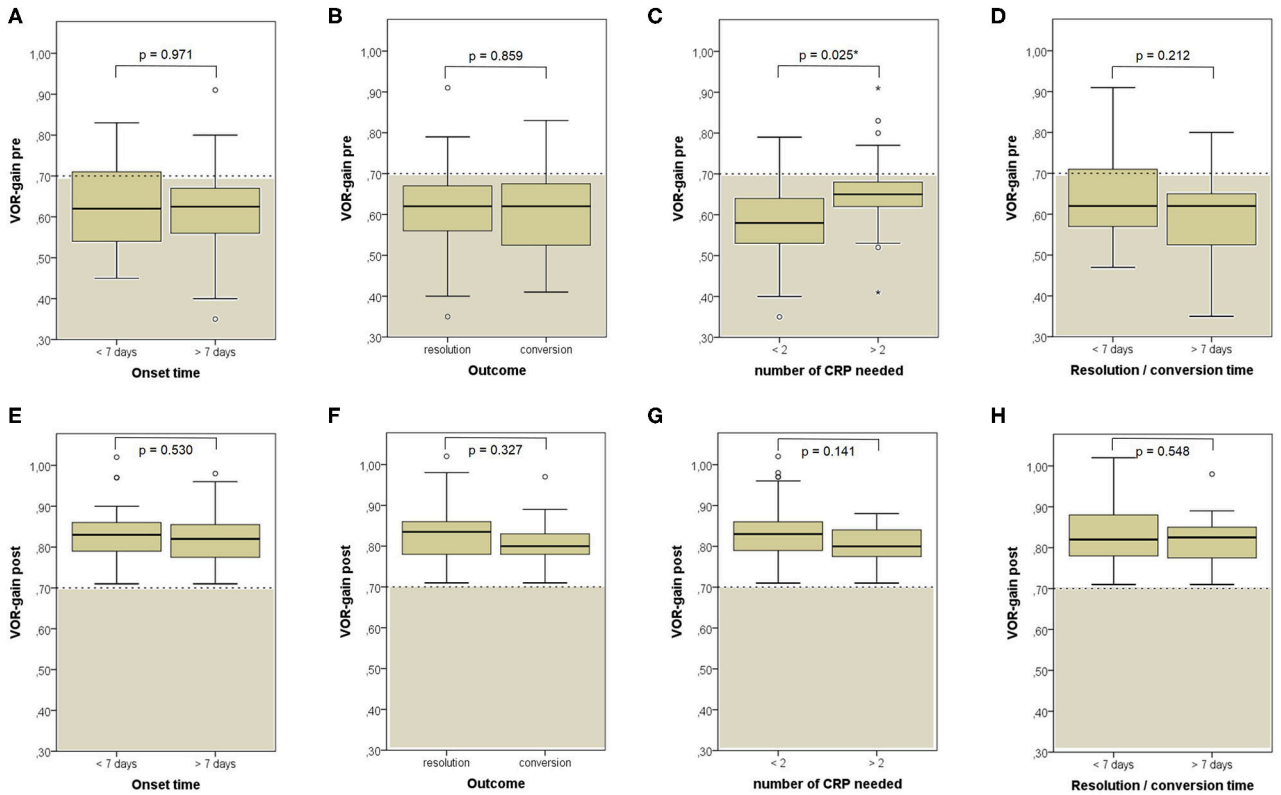

FIGURE 10 | Box plots correlating medians of VOR-gain values at presentation **(A–D)** and following physical treatment **(E–H)** for the SC involved by BPPV among overall subjects (53) with identified affected canal divided based on different details. **(A,E)** Onset time. **(B,F)** Outcome. **(C,G)** Number of CRP needed to restore or convert pDBN. **(D,H)** Time needed for resolution or conversion of pDBN. Statistically significant differences at the Mann-Whitney *U*-test are reported and highlighted with $*p < 0.05$. BPPV, benign paroxysmal positional vertigo; CRP, canalith repositioning procedure; pDBN, positional downbeat nystagmus; post, post-treatment; pre, at presentation; SC, semicircular canal; VOR, vestibulo-ocular reflex. Values at a greater distance from the median than 1.5 times and 3 times the IQR are plotted individually as dots (weak outliers) and asterisks (strong outliers), respectively.

recumbent positionings and reversed nystagmus once returned upright should theoretically distinguish the two forms, as in each case nystagmus could result either from the excitation (stronger nystagmus) of a SC or inhibition (weaker nystagmus) of contralateral canal and viceversa, in both BPPV variants pDBN do not usually reverse in sitting position. This atypical aspect may be due to the reduced movement of the clot in a restricted tract of the SC laying in an almost horizontal plane with the patient upright [(18); **Figures 13B**, **14B**]. Additionally, pDBN often lacks of torsional components in both ASC-BPPV and apogeotropic PSC-BPPV. Authors advocated several explanation for this finding (8, 9, 11, 19, 20, 64). Basically, they stated that since in the human skull, on average, ASC is closer to the sagittal plane (on average only 41°) than PSC (56°) (65, 66), a much smaller torsional component is expected from ASC stimulation. Additionally, calculations of angular eye velocity vectors derived from known canal geometry show the existence of an upwards bias in vertical slow phase eye velocity (67) Thus, more downbeat than torsional nystagmus is expected from ASC-BPPV (9). The same geometrical and neurophysiological considerations have been considered for pDBN resulting from apogeotropic PSC-BPPV, as PSC likely rotates its axis proceeding from the ampullary to non-ampullary arm, so that the latter becomes closer to the sagittal plane (20). Moreover, as the torsional gain of the human VOR is less than unity, about 0.75 and 0.28–0.5 in response to high- and low-frequency roll head rotations, respectively, torsional components of VOR responses should be smaller than the horizontal and vertical components (64). Nevertheless, even though peripheral pDBN is unanimously accepted to align with a more vertical than torsional plane and not to reverse while upright in the majority of cases, these aspects need to be better clarified yet.

According to our original series of 93 patients, most pDBN recognize a peripheral origin confirming previous studies (8, 9, 15). Despite confirming that ASC-canalolithiasis represents a rare entity, it is actually possible to occur. Nevertheless, unlike other reports (19), its prevalence is much smaller than apogeotropic PSC-BPPV, accounting for <12% of pDBN due to BPPV compared to 78% for apogeotropic PSC-BPPV (**Table 1**). Unlike previously reported series (19), ratio of pDBN with latency, with purely vertical direction and with a persistent course did not significantly differ among subgroups, resulting in challenging differential diagnosis when relying only in the interpretation of pDBN characteristics (**Figure 2**). It is noteworthy that in our

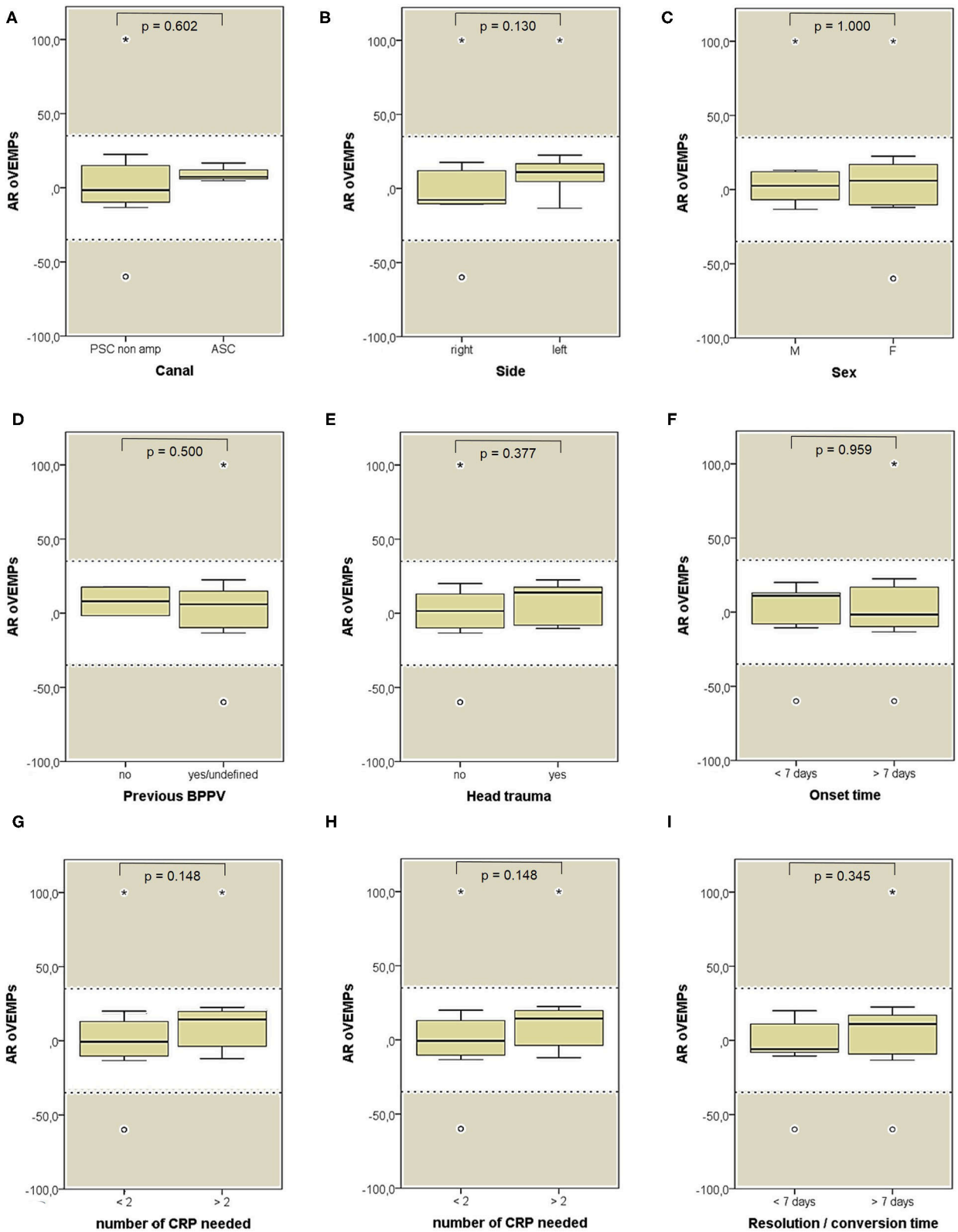

FIGURE 11 | Box plots correlating medians of AR values for air-conducted ocular VEMPs values among 26 patients submitted to electrophysiological testing, divided according to different features. **(A)** Affected semicircular canal. **(B)** Affected side. **(C)** Gender. **(D)** History of recent BPPV. **(E)** History of recent head trauma. **(F)** Onset time. **(G)** Outcome. **(H)** Number of CRP needed to restore or convert pDBN. **(I)** Time needed for resolution or conversion of pDBN. No statistically significant

(Continued)

FIGURE 11 | differences at the Mann-Whitney *U*-test are reported. Horizontal dashed lines represent the border between normal and pathologic AR values for ocular VEMPs (35%) and values within gray areas represent abnormal measurements. AR, asymmetry ratio; ASC, anterior semicircular canal; BPPV, benign paroxysmal positional vertigo; CRP, canal repositioning procedures; F, female; M, male; oVEMPs, ocular vestibular-evoked myogenic potentials; pDBN, positional downbeat nystagmus; PSC non-amp, posterior semicircular canal non-ampullary arm. Values at a greater distance from the median than 1.5 times and 3 times the IQR are plotted individually as dots (weak outliers) and asterisks (strong outliers), respectively.

series otoconia entrapped within the non-ampullary branch of PSC were more likely to result in persistent positional nystagmus than ASC (**Figure 2C**). This may be due to the fact that in general population the tract of the posterior canal approaching the common crus could be more frequently narrow than ASC ampullary arm. According to our result, pDBN could be always evoked in bilateral DH and SHH tests in case of ASC involvement compared to PSC where positional nystagmus was detectable only in one DH positioning in 21.7% of cases (**Figure 1B**).

Despite specific rehabilitative treatments for these BPPV-variants have been designed reporting good results (12, 14, 19, 20, 24, 28, 45, 46, 68, 69), uncertainty regarding the involved SC represents a dilemma when deciding the best therapeutic approach. Authors have proposed to use the efficacy of appropriate physical therapy or the conversion into a classical ipsilateral canalolithiasis to identify the involved canal (18–20, 24). Others have advocated the use of the so-called "pendular maneuver" aiming to shift otoconia toward PSC ampullary arm to detect the affected canal and proceed later with proper repositioning (70).

The importance of a precise detection of the affected SC is reflected in higher number of CRP needed to restore patients with undefined affected SC compared to cases with identified pathologic canal in our series (**Figure 1D**), with obvious prognostic sequel and related patient's discomfort. Conversely, irrespective to the canal affected, number of CRP needed, outcome and time required for resolution or conversion did not differ among ASC- and apogeotropic PSC-BPPV (**Figure 1**). High prevalence of efficacy in two-step maneuvers could be explained assuming that partially entrapped otoliths might fragment during the first maneuver and then return back to the utricle following prolonged positionings.

Although objective measures of canal function would be of extreme help in such cases, diagnostic usefulness of vestibular tests in BPPV remains controversial. Previous investigations assessing the feasibility of VEMPs (71–73) and other tests measuring ampullary activity in different frequency domains (74–77) to detect the ear or the canal involved in patients with typical PSC-canalolithiasis have not achieved univocal consensus. Recently, vHIT has been used to assess high-frequency SCs function in a subsample of patient presenting with persistent pDBN due to the vertical SC-BPPV. Whereas VOR-gain proved to be reduced for the involved canal at presentation, it normalized following proper CRP aimed to release the affected canal from otoconia or to transform pDBN in typical paroxysmal upbeat nystagmus (37). Authors have hypothesized that, unlike typical canalolithiasis involving PSC ampullary tract, where particles are free to float along the membranous duct with minimal effect on cupular dynamics during high-frequency testing (75, 77), in cases with ASC-BPPV and apogeotropic PSC-BPPV presenting with persistent pDBN debris could alter endolymphatic dynamics and cupular response mechanisms, resulting in high-frequency VOR deficit for the involved canal. This condition is thought to occur whenever otoconia settle in physiological narrow portions of the canal lumen [such as the distal portion of the non-ampullary branch of PSC, close to the common crus (20)] or in particular sites of altered canal anatomy due to possible structural changes in SCs orientation (9, 13, 46) or to acquired stenosis of membranous ducts [as demonstrated for ASC ampullary arm (10, 78)] or even to irregularities in membranous walls. Given that hydrodynamic models of fluid-filled SC have demonstrated how a pressure amplification occurs as otoconia enter a narrow section of the canal (79, 80), in particular situations it could likely result in an *incomplete canalith jam* (18, 20) leading to impaired ampullary responses for high-frequency range (37). Namely, this condition would behave as a *"low-pass filter"* allowing the cupula to be activated by low-frequency stimuli (otoconial shifts producing pDBN) while impeding the ampullary receptor to respond to high-frequency inputs (head impulses leading to impaired vHIT data). Partial embedment of debris within narrower portion of membranous duct may also account for the usual persistent course of pDBN with smaller frequency compared to typical PSC-canalolithiasis. In fact, hypothesizing that otoconia could remain incompletely entrapped in these canal tracts, a small amount of endolymphatic reflux is expected and fluid column may continue to press against ampullary receptor, resulting in a slower return of the ampullary crest to the resting position than typical BPPV (20). Finally, considering that some patients with refractory BPPV submitted to surgical plug have recently been found to have, on microscopic examination, fragments of otolith membrane and otoconia encased in their gelatinous matrix rather than simply free-floating otoconia (54), it is not hard to assume how these large materials could be trapped in various locations inside membranous SC dampening endolymphatic flows.

These hypothetical conditions significantly diverge from presenting scenario in typical PSC-canalolithiasis, where dislodged debris prove to be freely moving within the canal by the transitory paroxysmal nystagmus with crescendo-decrescendo course evoked in both recumbent positionings and in return upright. In fact, according to investigations on SCs model, when debris enters the membranous canal from ampulla, a transcapular pressure is generated resulting in cupular displacement and nystagmus onset. Once debris settle on canal walls, they have no more effects on the ampullary receptor, unless the clot fills the portion of the canal with a consequent greater effect on cupular dynamics (80). Whereas, the former mechanism may account for the lack of persistent dynamic perturbation of canal activity by dislodged otoconia in classical PSC-canalolithiasis, with

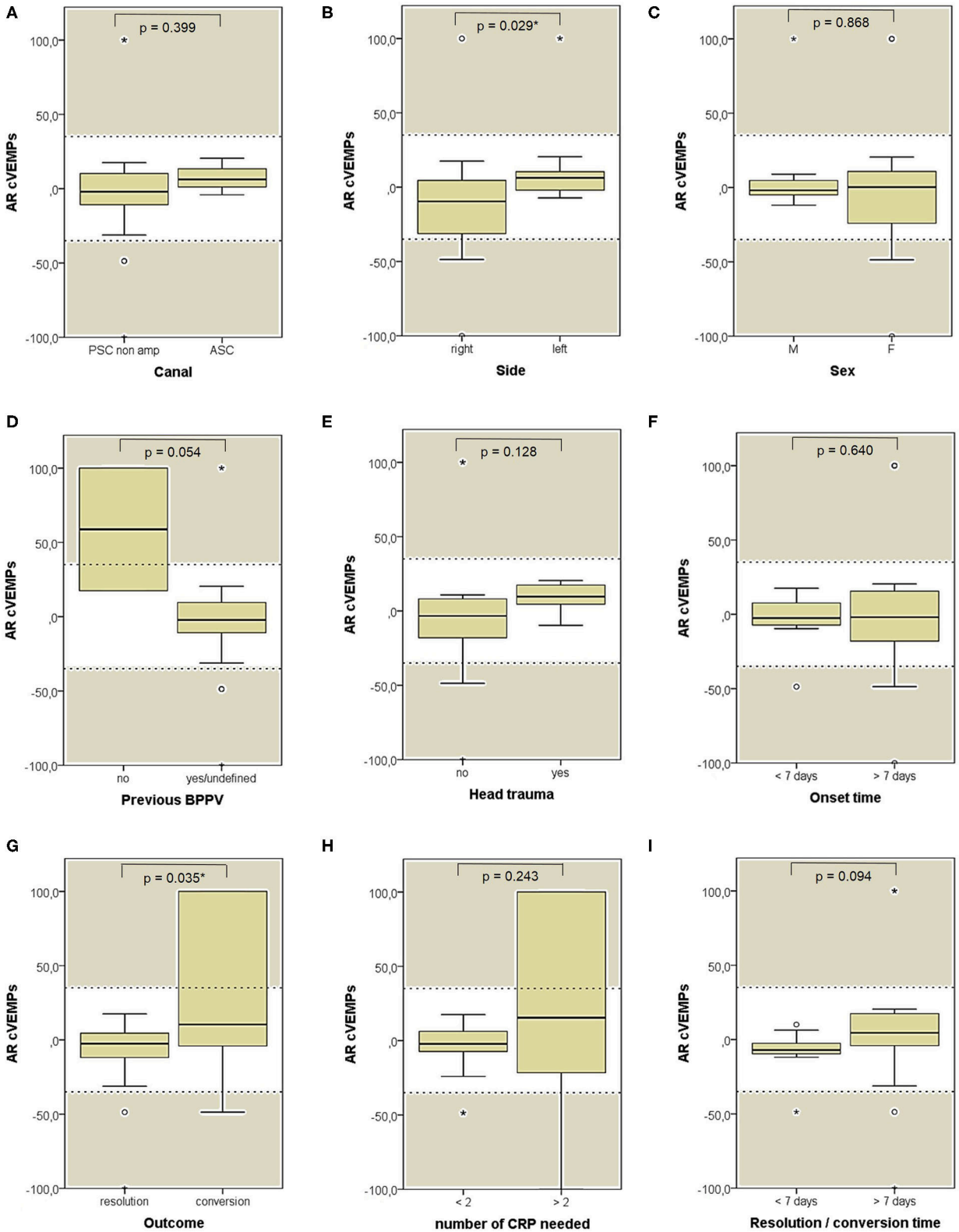

FIGURE 12 | Box plots correlating medians of AR values for air-conducted cervical VEMPs values among 26 patients submitted to electrophysiological testing, divided according to different features. **(A)** Affected semicircular canal. **(B)** Affected side. **(C)** Gender. **(D)** History of recent BPPV. **(E)** History of recent head trauma. **(F)** Onset time. **(G)** Outcome. **(H)** Number of CRP needed to restore or convert pDBN. **(I)** Time needed for resolution or conversion of pDBN. Statistically significant

(Continued)

FIGURE 12 | differences at the Mann-Whitney *U*-test are reported and highlighted with for $p < 0.05$. Horizontal dashed lines represent the border between normal and pathologic AR values for cervical VEMPs (35%) and values within gray areas represent abnormal measurements. AR, asymmetry ratio; ASC, anterior semicircular canal; BPPV, benign paroxysmal positional vertigo; CRP, canal repositioning procedures; cVEMPs, cervical vestibular-evoked myogenic potentials; F, female; M, male; pDBN, positional downbeat nystagmus; PSC non-amp, posterior semicircular canal non-ampullary arm. Statistically significant differences at the Mann-Whitney U-test are reported and highlighted with * for $p < 0.05$. Values at a greater distance from the median than 1.5 times and 3 times the IQR are plotted individually as dots (weak outliers) and asterisks (strong outliers), respectively.

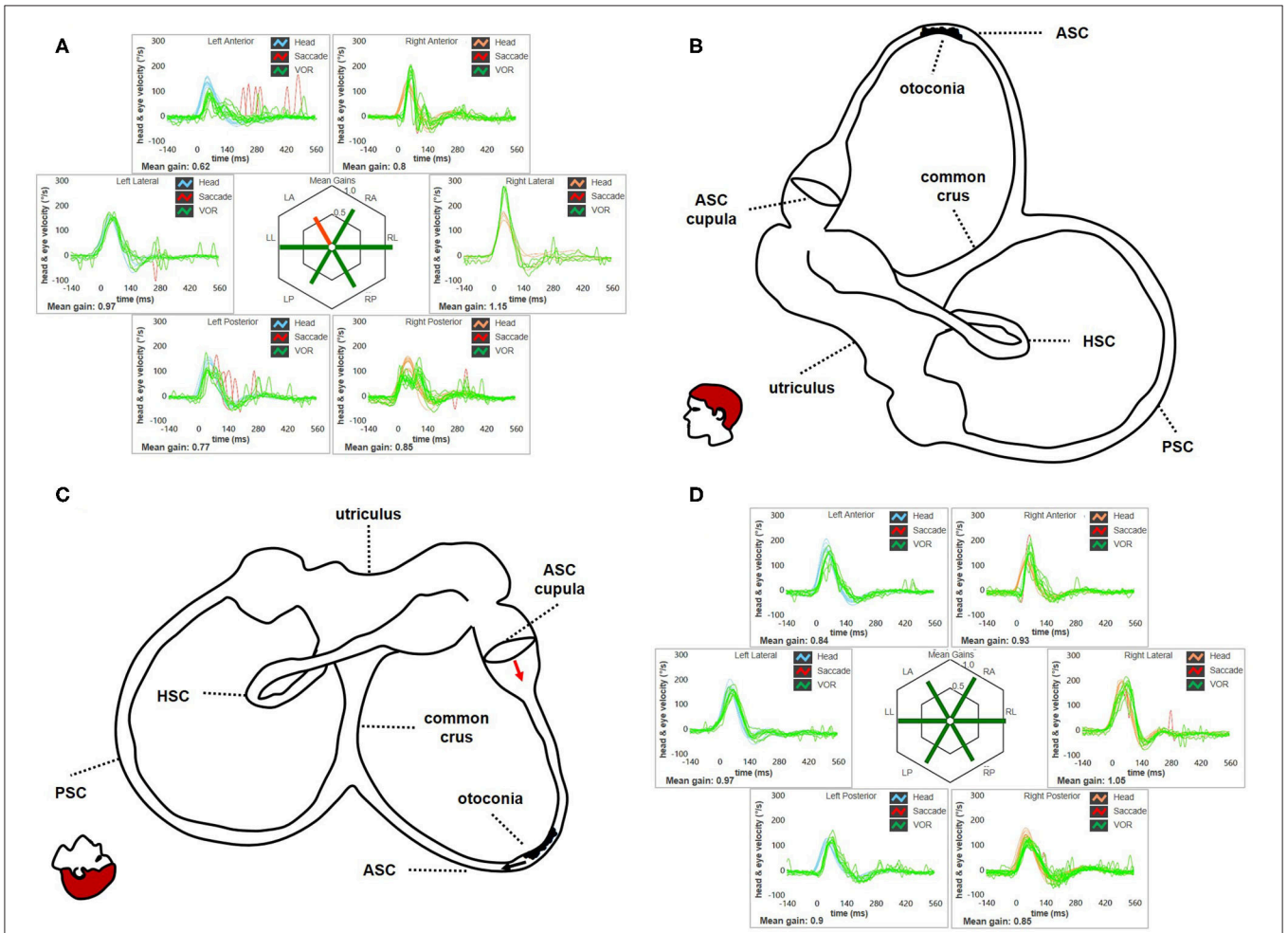

FIGURE 13 | (A) Presenting vHIT of subject # 45 affected by BPPV involving the ampullary arm of left ASC. Mean value of VOR-gain (eye velocity/head velocity) is reported for each canal. The hexagonal plot in the center of the figure summarizes mean VOR-gains for each canal; normal gains are shown in green and deficient gains are in red. Selective slight deficient VOR-gain for left ASC (0.62) with scattered overt saccades can be observed. **(B)** Representation for left membranous labyrinth and patient's head along the sagittal (pitch) plane in upright position to explain the site settled by otoconia at presentation. Debris are located within a nearly horizontal tract of the canal, where possible narrowing or irregularities could allow them to settle without resulting in nystagmus in upright position. In this condition, otoliths are thought to partly occlude the canal lumen resulting in an incomplete canalith jam acting as "low-pass filter" for ampullary receptor, thus preventing high-frequency stimuli as detect by vHIT. **(C)** Representation of the disposition of otoconia after SHH test. In this position, otoconia may slowly shift toward the non-ampullary tract of the canal below (black arrow) due to gravity. Resulting excitatory endolymphatic movement should lead ASC cupula to bend ampullofugally (red arrow), accounting for pDBN in recumbent positions. **(D)** vHIT findings after performing CRP for ASC-BPPV leading to return of particles within the utriculus and resolution of symptoms and signs. VOR-gain value for left ASC is back within normal range (0.84). ASC, anterior semicircular canal; BPPV, benign paroxysmal positional vertigo; CRP, canalith repositioning procedure; HSC, horizontal semicircular canal; LA, left anterior; LL, left lateral; LP, left posterior. pDBN, positional downbeat nystagmus; PSC, posterior semicircular canal; RA, right anterior; RL, right lateral; RP, right posterior; SHH, straight head hanging; vHIT, video-head impulse test; VOR, vestibulo-ocular reflex.

consequent missing abnormalities in vestibular tests assessing canal function (75, 77), the latter finding could likely explain the transient VOR-gain impairment for the affected SC in case of pDBN (37).

In our opinion, this hypothetical mechanism represents the most likely explanation for our findings. In fact, abnormal VOR-gain values were detected in 43/59 cases with pDBN due to vertical SC-BPPV, with a sensitivity of vHIT in detecting

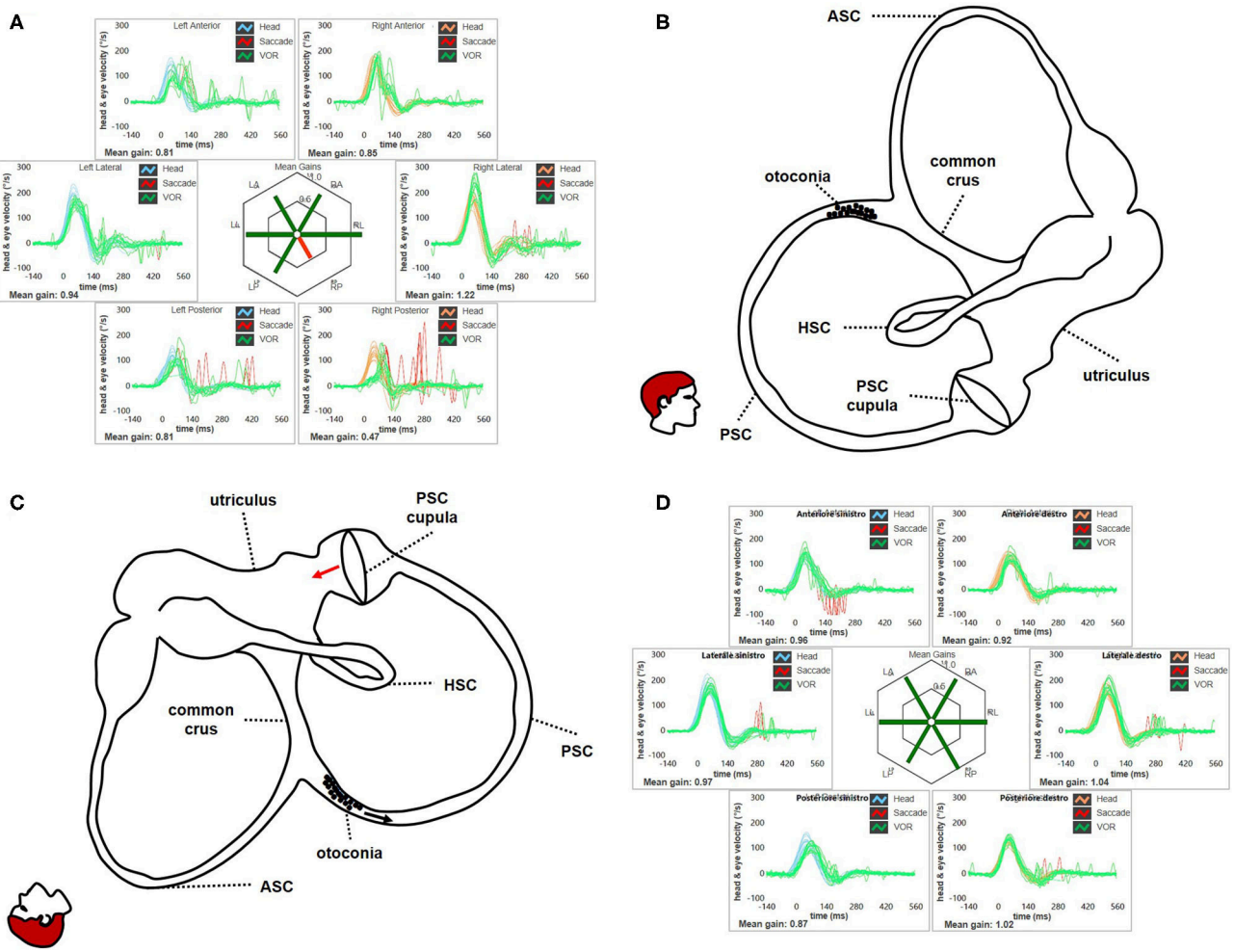

FIGURE 14 | (A) Presenting vHIT data for subject # 18 affected by right apogeotropic PSC-BPPV showing selectively impaired VOR-gain values for right PSC (0.47) with both covert and overt saccades. **(B)** Even in this case, otoliths are partially entrapped within a narrow tract of the non-ampullary branch of the canal nearly aligning with the horizontal axis, explaining the lack of spontaneous nystagmus. Likewise ASC, even in this condition the canal is thought to be partially plugged by otoconia, explaining high-frequency VOR-gain impairment for the involved canal. **(C)** Once diagnostic head hanging position is obtained, gravity vector should slowly move debris toward the ampullary tract of the canal below, leading to an ampullopetal endolymphatic flow (black arrow). Resulting cupular bending (red arrow) should generate an inhibitory discharge for PSC afferents, accounting for pDBN. **(D)** vHIT measurement following CRP for apogeotropic PSC-BPPV confirming complete restoration for the impaired PSC VOR-gain. BPPV, benign paroxysmal positional vertigo; CRP, canalith repositioning procedure; HSC, horizontal semicircular canal; LA, left anterior; LL, left lateral; LP, left posterior; pDBN, positional downbeat nystagmus; PSC, posterior semicircular canal; RA, right anterior; RL, right lateral; RP, right posterior; vHIT, video-head impulse test; VOR, vestibulo-ocular reflex.

the affected SC of 72.9%, irrespective to the canal involved (**Figure 4A**). In all 43 cases, SC presenting with deficient VOR-gain values matched with the canal involved by BPPV, except for subject #12 who was affected by ASC-canalolithiasis despite presenting with ipsilateral impaired PSC VOR-gain. In this case, transitory pDBN with left-torsional components was related to left ASC-BPPV rather than contralateral apogeotropic PSC-BPPV as the patient was treated few days before for a typical variant of left PSC-canalolithiasis. Moreover, she developed deficient VOR-gain value for left PSC, normalizing after proper CRP for ASC-BPPV, suggesting that otoliths, though eliciting superior ampullary afferents, could have dampened dynamic responses for ipsilateral PSC. We hypothesized a common crus-canalolithiasis for this patient, where geometrical abnormalities in canal disposition, such as ASC with large-sized diameter prevailing over PSC in common crus constitution, could occur. Nevertheless, 25.4% of overall patients presented with transitory nystagmus (**Figure 2C**), suggesting that otoconia may also be freely moving within either ASC or PSC non-ampullary lumen in some cases. Among them, only 26.7% of cases presented with VOR-gain value <0.7 (**Figure 6A**), confirming how pDBN with longer time constant is mostly related to the "incomplete jam" theory. The two different mechanisms theorized (*canalolithiasis* vs. *incomplete jam*) could likely account for different behavior of pDBN and affected SC activity in these BPPV variants, explaining also how vertical SCs

function could have been normal in a series of patient diagnosed with AC-BPPV presenting with mainly transitory pDBN (81). In fact, examining only data of 44 patients presenting with persistent pDBN, where an incomplete jam is thought to happen, diagnostic sensitivity of vHIT increased up to 88.6% (39/44 cases) (**Figure 6A**). Additionally, when analyzing pDBN features, VOR-gain values for affected SC presenting with persistent pDBN were found significantly more impaired than cases with transitory/paroxysmal pDBN, further confirming different behavior for high-frequency ampullary responses depending on the degree of otoconial entrapment (**Figure 9C**). Moreover, in all cases (43/59) presenting with impaired VOR-gain for the affected SC, canal function normalized after proper CRP with either resolution or conversion into a typical BPPV, irrespectively to the underlying diagnosis (**Figure 5**), confirming a strong linkage between abnormalities for high-frequency canal activity and dislodged otoconia consistently with the "incomplete plug" theory. These assumptions are also in accordance with the significant improvement for VOR-gain detected only for SC exhibiting deficient VOR-gain at presentation, whereas normally active SC did not significantly modify VOR measurements after repositioning (**Figure 7B**).

It is noteworthy that medians of overall VOR-gain values highly significantly improve not only for the affected SC, but also for the contralateral vertical canal functionally coupled with the involved SC, despite presenting with VOR-gain within normal ranges (**Figure 5**). This is in line with studies on contralesional canal activity following acute vestibular loss showing, on average, slightly reduced VOR-gain also in the healthy side. It is still matter of debate whether only peripheral phenomena may account for this finding (mainly a functional loss of the "push-pull" mechanism) or if also central compensation (mainly cerebellar "shut-down") could reduce canal activity on the healthy side (82–84). Probably, the latter phenomenon may likely explain reduced VOR-gain values detected also in the other vertical SC contralaterally to the lesion side and in those patients with long-lasting symptoms (the majority in our cohort). Additionally, canal function, despite normal, resulted to slightly improve even for ipsilateral SCs among cases with involved ASC (**Figure 5C**). Despite this finding may be a result of casualty, given the small-sized cohort of ASC-BPPV cases, it may be assumed that ASC-BPPV could more likely result in a global labyrinthine perturbation compared to apogeotropic PSC-BPPV.

Nevertheless, no differences were found among presenting VOR-gains for the affected SC according to the canal and side involved, to the patients' gender and to previous history of BPPV or head trauma (**Figures 8A–E**). Similarly, neither different onset time, outcome nor time needed for resolution or conversion of pDBN in paroxysmal nystagmus were found to impact on presenting function for the involved SC (**Figures 10A,B,D**). Significantly higher VOR-gain at presentation for the affected SC in patients requiring more than 2 CRP to recover or convert into a typical BPPV compared to those treated with a two-steps maneuver could be explained with the fact that cases in the former group were more likely to have normal VOR-gain, resulting in a more difficult localization of otoconia with vHIT (**Figure 10C**). On the other hand, the routine use of high-frequency measurement of canal function to detect the canal involved may account for the smaller amount of cases with canal switch in our cohort (**Figures 1C**, **6D**) compared to other series where conversion into a typical BPPV variant was used as a diagnostic tool (19, 20, 24, 70). Interestingly, no significant differences in terms of VOR-gain values following CRP could be found among patients exhibiting different time of symptoms onset, outcomes, number of physical treatments and time required for pDBN resolution or conversion (**Figures 10E–H**), proving how possible residual dizziness in these patients may be ascribed to other than peripheral causes (85).

As previously mentioned, persistent positional vertical/torsional nystagmus (either upbeat or downbeat, depending on anatomy) evoked in DH or SHH positions has been related to PSC-cupulolithiasis (60–62) or to modified density ratio between the PSC-cupula and surrounding endolymph (63). Therefore, it might be reasonable to assume that presenting findings in some patient from our cohort could be ascribed to such mechanism. Nevertheless, we found some discordant issues between VOG/vHIT findings and cupulolithiasis/buoyancy theory that made us leaning toward BPPV involving non-ampullary arm of PSC resulting in an incomplete jam. Firstly, we did not detect any direction-changing nystagmus by modifying head-bending angle in upright position or in contralateral DH positioning. We could only record slight transient nystagmus reversal when returning upright from head hanging positionings in a small subset of patients of our cohort. In a hypothetical case of PSC-cupulolithiasis, we would have expected to find the above-mentioned findings if PSC-cupula had been overloaded by attached otoliths and bent downward (either toward the canal or toward the ampulla, depending on anatomy, and head-bending angle), persistently exciting or inhibiting, respectively, PSC afferents (60, 61). Moreover, unlike what observed, we would also expected to record a neutral head position where the axis of the affected cupula is supposed to align with gravity, suppressing positional nystagmus (60, 63). Additionally, most cases presenting with hypoactive PSC recovered following CRP properly designed for BPPV involving PSC non-ampullary arm, without canal conversion. Conversely, in case of otoconia attached on the side of cupula overlooking the long arm of the canal, whichever maneuver should always be expected to convert pDBN in paroxysmal upbeating nystagmus as debris should necessarily detach and become freely floating within the membranous PSC before returning within the utricle. Moreover, according to mathematical model, cupulolithiasis resulted to require much greater amount of particles compared to canalolithiasis (79, 80), so its conversion into a canalolithiasis should result in strong positional nystagmus that could hardly go unnoticed by patients. Alternatively, debris hypothetically either settling on the opposite side of the cupula or shifting within PSC short arm should theoretically result in worse symptoms while upright rather than in evident nystagmus in DH positioning, unlike what recorded in our cohort of patients (62, 86). Finally, those cases presenting with reduced VOR-gain for ASC normalizing after CRP should have necessarily exhibited endolymphatic perturbations altering the activity of the superior

ampullary receptor rather than PSC-cupulolithiasis. Although other possible explanations could be assumed, in our opinion all these findings suggested that PSC-cupulolithiasis was less likely to occur than apogeotropic PSC-BPPV.

Finally, when considering different VOR behavior for the affected canal between cases exhibiting spontaneous DBN or not, the former group presented with highly reduced function compared to the latter (**Figure 9E**). This data are in accordance with the assumed mechanism consistent with a canalith jam, where an otoconial clot is thought to completely plug a narrow portion of the membranous duct, blocking endolymphatic flows (56). In this condition, a continuous alteration of hydrostatic pressure between the otoliths clump and the cupula may occur, leading to a persistent cupular deflection thus explaining sudden conversion of positional nystagmus in stationary nystagmus irrespective to head positions occurring during physical treatment (55, 56). As already described for HSC-canalith jam (87, 88), this mechanism may prevent both high- and low-frequency responses for the SC affected (namely head impulses and otoconial shifts, respectively) by blocking endolymphatic flows, likewise surgical plugging (89), thus explaining severe impairment of canal VOR-gain. Though canalith jam has been described for HSC in several reports, occurring either spontaneously (87, 88, 90, 91) or as a result of inappropriate CRP (92–94), a similar condition involving PSC has been recently implied as the hypothetical pathomechanism for spontaneous DBN receding after proper physical treatment (95). Whereas, spontaneous nystagmus resulting from HSC-canalith jam overlaps presenting signs of acute vestibular loss, spontaneous VOG findings due to a PSC involvement should be mainly torsional/vertical aligning with vertical SC axis, thus mimicking CNS pathologies. In these conditions, instrumental equipment for vestibular testing may play a key role in the differential diagnosis, since other end-organs dysfunctions or additional signs of central origin should always coexist with VOR-gain impairment for vertical SC in CNS disorders (36). In **Table 2** each possible scenario (*regular canalolithiasis* vs. *incomplete jam* vs. *complete canalith jam*) accounting for different patterns of pDBN due to BPPV and vHIT measurements with corresponding assumed pathomechanism is summarized.

Despite our instrumental assessment included both cervical and ocular-VEMPs to air-conducted sounds, they were neither routinely performed to search for possible AR differences among patients nor they were routinely tested both before and after CRP to look for amplitudes changes following proper repositioning. Moreover, due to the lack of bone-conducted stimuli in our equipment, a reliable measurement of both saccular and utricular function could not be obtained. On the other and, analysis of variations in VEMPs amplitudes among BPPV patients would have gone beyond the aim of our investigations. These methodological bias could likely account for the lack of statistically significant results among VEMPs data (**Figures 11**, **12**).

Our investigation presents some other limitations. First of all, being a multicentre investigation, each involved otoneurologist collected data by him/herself, and an inter-observer agreement for ambiguous cases (in particular for three-dimensional evaluation of nystagmus) was never used. Then, despite corrective saccades were always checked to avoid artifacts inclusion in hypoactive VOR-gain plots, our analysis on vHIT

TABLE 2 | Table summarizing each of the three possible scenarios accounting for different patterns of pDBN in BPPV and vHIT measurements with corresponding hypothetical pathomechanisms.

	Oculomotor findings	VOR-gain for the affected SC on vHIT	Assumed underlying mechanism	Endolymphatic flows	
				Low-frequency	High-frequency
Regular canalolithiasis	Transient paroxysmal pDBN in DH or SHH, usually reversing in upright	Usually normal	Debris are free to float along the SC	Preserved as debris can move in both directions along the canal	Preserved as debris neither aggregate nor occlude the canal lumen, thus do not impair cupular responses
"Incomplete" (or "functional" or "positional") canalith jam	Persistent pDBN in DH or SHH, rarely reversing in upright	Slightly reduced	Otoliths are partly entrapped in a narrower canal tract, partially plugging the affected SC lumen	Likely preserved as otoliths, despite partly blocked, are allowed to slowly move toward the cupula in DH or SHH	Impaired as otoliths likely prevent high acceleration flows dampening head impulse responses (behaving as a "low-pass filter")
Complete canalith jam	Spontaneous DBN, slightly increasing in DH and SHH	Greatly reduced	An otolith clot is completely entrapped within a narrower tract of the canal, entirely plugging the affected SC lumen	Impeded due to a continuous endolymphatic pressure constantly displacing the cupula of the affected SC	Impeded due to a continuous endolymphatic pressure constantly displacing the cupula of the affected SC

BPPV, benign paroxysmal positional vertigo; DBN, downbeat nystagmus; DH, Dix Hallpike; pDBN, positional downbeat nystagmus; SC, semicircular canal; SHH, straight head hanging; vHIT, video-head impulse test; VOR, vestibulo-ocular reflex.

data focused almost solely on SC VOR-gain values, whereas morphological study of saccades (covert vs. overt, latency, distribution, peak velocity and inter-aural differences, etc.) was not pursued, being beyond the aims of this study. Moreover, we considered as deficient only VOR-gains below normative data without considering gain asymmetry between coupled pairs of SC. In addition, the subgroup of patients with ASC involvement was significantly smaller than population with apogeotropic PSC-BPPV, leading to possible misleading conclusions when comparing subsamples data. The inclusion in the analysis of 6 subject where the affected SC could not be identified could also have altered final results of our investigation. Though they presented with pDBN exhibiting the same characteristics of the remainder of cases with BPPV and restored with positionings, it could not be excluded they were not affected by vertical SC-BPPV. Finally, despite our cohort size with pDBN collected in a 1-year period was similar to others series, the small-sized sample analyzed does not permit to achieve definitive conclusions on the sensitivity of vHIT in detecting the affected canal in these patients. Further prospective investigations with a more significant number of subjects with pDBN will be needed to better determine the role of vHIT in vertical canals BPPV presenting with pDBN.

CONCLUSIONS

According to our data, vHIT may play a key role in the diagnosis of the affected canal in BPPV involving vertical SC presenting with pDBN. In fact, conversely to typical BPPV with paroxysmal positional nystagmus, where particles are free to move along the membranous ducts, in case of persistent pDBN an *incomplete jam* is likely to occur. Unlike complete canalith jam, where otoconia are thought to plug the entire canal lumen impeding endolymphatic flows for both high- and low-frequency domains due to a continuous pressure exerted by the clot on a persistently displaced cupula, in these conditions particles partially entrapped within a narrow portion of the canal likely behave as a *"low-pass filter"* for the ampullary receptor. This phenomenon may actually impair high-frequency dynamic responses for the affected canal while allowing low-frequency endolymphatic movements, thus explaining reduced VOR-gain for the affected SC on vHIT despite pDBN, respectively, and normalization of head impulse data following symptoms resolution or pDBN conversion into a typical paroxysmal nystagmus. These findings should encourage clinicians to routinely use the vHIT in case of pDBN, including high-frequency testing of canal function in the test battery for these patients, particularly in cases lacking of torsional components, where detection of the affected canal and differential diagnosis with CNS disorders may be challenging.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Area Vasta Nord Emilia Romagna Institutional Review Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AC, PM, and SM led the conception of the study and conducted most data acquisition, interpretation and made significant contributions to the writing, and editing of the manuscript. AC conducted data analysis and creation of figures. CB and MR were involved in project conception and manuscript editing. SD, SQ, ER, and EA contributed to data acquisition and manuscript review. EA, MM, AG, and GL were involved in manuscript review. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.578588/full#supplementary-material

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ORIGINAL RESEARCH
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Unhealthy Lifestyle Is an Important Risk Factor of Idiopathic BPPV

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Background: Benign paroxysmal positional vertigo (BPPV) is a self-limiting and recurrent disease but the cost is considerable. The number of patients with BPPV increased significantly under the quarantine policy in Hangzhou. The unhealthy lifestyle risk factors of BPPV have not yet been investigated. Thus, the objective is to analyze whether an unhealthy lifestyle is a risk factor of BPPV.

Methods: One hundred and sixty three patients with idiopathic BPPV aged 22–87 years (BPPV group), and 89 aged 23–92 years sex-matched control subjects (non-BPPV group) were enrolled in this study. All BPPV patients received a definitive diagnosis which excluded secondary BPPV. Non-BPPV cases excluded BPPV, sudden deafness, Meniere's disease, ear or craniofacial surgery, vestibular neuritis, and head trauma history. We obtained a blood lipids profile, serum uric acid, total bilirubin, and related diagnostic information through the electronic medical record system. To get the time of physical activities and recumbent positions, we asked the patient or their family from February 2020 to June 2020, and the rest of the patient's information was acquired by phone or WeChat.

Data Analyses: The *t*-test or chi-squared test, univariate, and multiple logistic regression analyses were performed for the two groups. For each factor, odds ratios were calculated with 95% confidence intervals (CIs). Moreover, test equality of two or more receiver operating characteristic (ROC) analyses were applied to the physical activities, and recumbent position time; area under curve (AUC) measures were calculated with 95% CIs and compared with each other.

Results: The BPPV group had unhealthy lifestyles such as poor physical activities, prolonged recumbent position time, and low rate of calcium or VD supplementation in univariate logistic regression analyses ($P < 0.05$). Poor physical activities and prolonged recumbent position time were independently associated with BPPV in multiple logistic regression models (OR = 18.92, 95% CI: 6.34–56.43, $p = 0.00$ and OR = 1.15, 95% CI: 1.01–1.33, $p < 0.04$). In the comparison of ROC curves of recumbent position time and physical activities in identifying BPPV, AUCs were 0.68 (0.61–0.74), and 0.68 (0.63–0.73), respectively.

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Conclusion: We conclude that poor physical activities and prolonged recumbent position time may be independent risk factors for BPPV patients, but hypertension, hyperuricemia, hyperlipidemia, hemoglobin, diabetes, serum bilirubin, CHD, and CI, may not be.

Keywords: BPPV-benign paroxysmal positional vertigo, risk factors, physical activity, quarantine policy, recumbent position time

BACKGROUND

Vertigo is one of the most common symptoms in neurological illness and the cost of evaluating dizziness is considerable. Benign paroxysmal positional vertigo (BPPV) is the most common peripheral vertigo disease (1). It amounts to 20% of all vertigo patients (2). BPPV has a recurrence rate of about 15% every year (3). Some studies have found that the age, gender, hypertension, hyperuricemia, hyperlipidemia, diabetes, and osteoporosis may be the risk factors of BPPV (4, 5). There are few studies on the unhealthy lifestyle and BPPV.

After the quarantine policy was performed to prevent COVID-19 in Hangzhou, it was found that the number of BPPV diagnoses increased more rapidly than in the same period in 2019 (**Figure 1**). Therefore, in this study, we aimed to (1) investigate the risk factors of BPPV; and (2) explore the association between an unhealthy lifestyle and BPPV. We hypothesized that the onset of BPPV is associated with people's unhealthy lifestyles.

METHODS

Object of Study

A retrospective observational study was conducted in the Department of Neurology in Tongde Hospital of Zhejiang Province from June 16, 2018 to June 30, 2020. The study included 163 patients with idiopathic BPPV aged 22–87 years (BPPV group), and 89 aged 23–92 years sex-matched control subjects (non-BPPV group). The BPPV group patients received a definitive diagnosis and CRM treatment, and excluded secondary BPPV. The non-BPPV group enrolled patients who after an annual physical examination in our hospital excluded diagnoses for BPPV, sudden deafness, Meniere's disease, ear or craniofacial surgery, vestibular neuritis, and head trauma. We obtained a blood lipids profile, serum uric acid, total bilirubin, and related diagnostic information through the electronic medical record system. To get the time of physical activities and recumbent position we asked the patients or their family from February 2020 to June 2020, and the rest of the patient's information was acquired by phone or WeChat.

Diagnostic Criteria

This references the diagnosis standard of BPPV in the 2014 New England Journal (6). All the patients were examined by Dix-Hallpike and roll-tested.

Abbreviations: BPPV, Benign paroxysmal positional vertigo; SD, standard deviation; CHD, coronary heart disease; CI, cerebral infarction; AUC: area under curve; ROC, receiver operating characteristic; MD, Meniere's disease.

The definition of hyperuricemia is based on the laboratory standard of our hospital that states that serum uric acid in female patients must be higher than 340 μmol/L and in male patients higher than 400 μmol/L. Hyperlipidemia is defined when low-density lipoprotein is higher than 3.2 mmol/L, total cholesterol is higher than 5.7 mmol/L, or triglyceride is higher than 1.95 mmol/L. Lack of physical activity is defined as <5 exercises per week and <20 min at a time. The prolonged recumbent position time is defined as when the daily lying time is longer than or equal to 10 h, including the time of falling asleep and not falling asleep.

If the patient had suffered from the following diseases, it will be classified as secondary benign paroxysmal positional vertigo and will be excluded. Such as sudden deafness, Meniere's disease, ear or craniofacial surgery, vestibular neuritis within 1 year, or head trauma within 1 year.

Data Analyses

The measurement data in accordance with normal distribution are expressed by $\bar{x} \pm S$, and the comparison between groups is expressed by the *t*-test; the numeration data were statistically analyzed with the chi-squared test. When $p < 0.05$, the differences between the two groups were deemed to be statistically significant (**Table 1**). Multivariable logistic regression was performed to identify the risk factors of BPPV in all of the patients (**Table 2**). The comparison of ROC curves of recumbent position time and physical activities are shown in (**Figure 1**). For each factor, odds ratios were calculated with 95% confidence intervals (CIs). All statistical analyses were performed using the STATA statistical software version 15.1.

RESULTS

Univariate analysis of BPPV related risk factors of the two group's patients were summarized in **Table 1**. No significant difference was found between the two groups with respect to age, MD, sudden deafness migraine, hypertension, hyperlipidemia, CHD, CI, and diabetes ($P > 0.05$). Although lifestyles including prolonged recumbent position time (≥10 h) (OR = 3.12, 95% CI: 1.75–5.61, $P = 0.00$), and poor physical activities (OR = 24.57, 95% CI: 8.12–98.22, $P = 0.00$) reached statistical significance in patients with BPPV compared with controls.

To identify the predictors of BPPV, multiple logistic regression analyses were performed. Due to the strong correlation, recumbent position time and poor physical activities values were found to be independently associated with BPPV in the multiple logistic regression model (**Table 2**). Multivariable logistic regression revealed that prolonged recumbent position

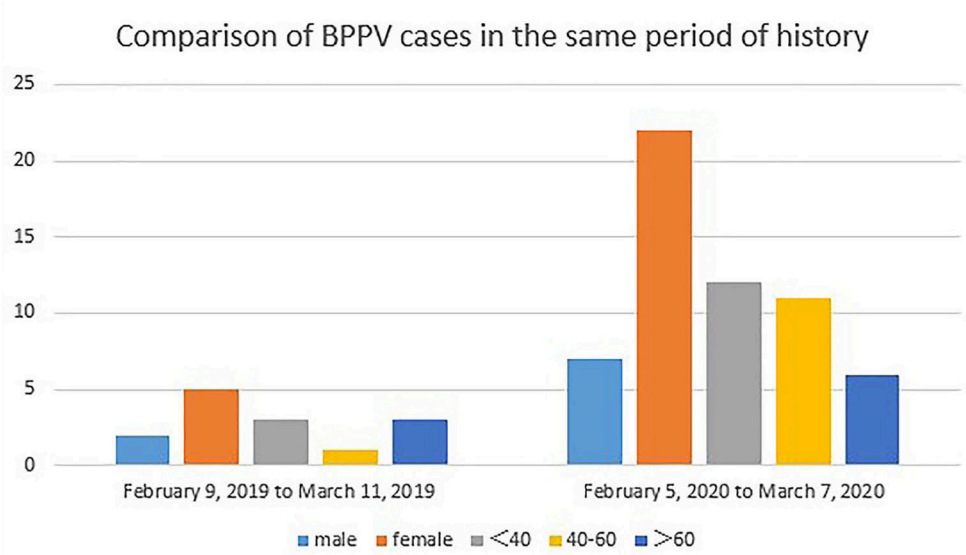

FIGURE 1 | The BPPV of young and middle-aged and total cases increased significantly during the period of 30 days in the quarantine policy of COVID-19 than in the same period last year.

TABLE 1 | Univariate analysis of BPPV related risk factors ($N = 252$).

Variables	BPPV group ($n = 163$)		Non-BPPV group ($n = 89$)		Odds ratio	95% CI	*p*-value
	Total (*N*)	Column (%)	Total (*N*)	Column (%)			
Age, years (mean ± SD)	56.46 ± 15.67		54.47 ± 18.37			53.69–57.82	0.37
Female	105	64.42	60	57.42	0.88	0.49–1.56	0.63
Hypertension	46	28.22	29	32.58	0.81	0.45–1.49	0.47
Low-density lipoprotein	2.73 ± 0.80		2.79 ± 0.76			2.65–2.85	0.58
>3.2 mmol/L	43	26.38	23	25.84	1.03	0.55–1.95	0.93
Total cholesterol	4.50 ± 1.09		4.54 ± 1.08			4.38–4.65	0.78
>5.7 mmol/L	21	12.88	12	13.48	0.95	0.42–2.25	0.91
Triglyceride	1.59 ± 1.43		1.40 ± 0.79			1.37–1.68	0.25
>1.95 mmol/L	37	22.70	17	19.10	1.24	0.63–2.53	0.51
Hemoglobin	131.21 ± 17.67		132.58 ± 18.39			129.47–133.92	0.56
Diabetes	14	8.59	8	8.99	0.95	0.35–2.73	0.91
Osteoporosis	3	1.84	4	4.49	0.40	0.06–2.42	0.22
Serum uric acid	311.46 ± 87.10		307.67 ± 91.44			299.14–321.10	0.745
Male > 400 μmol/L.	10	6.13	4	4.49	1.39	0.39–6.24	0.59
Female > 340 μmol/L	39	23.93	20	22.47	1.09	0.57–2.13	0.79
Serum bilirubin	13.80 ± 6.14		14.87 ± 6.55			13.40–14.96	0.20
Vitamin D supplement	3	1.84	7	7.87	0.22	0.04–1.00	0.02*
Calcium supplement	3	1.84	8	8.99	0.19	0.03–0.82	0.01*
Fracture of history	4	2.45	4	4.49	0.53	0.97–2.95	0.37
CHD	10	6.13	9	10.11	0.58	0.20–1.69	0.25
CI	13	7.98	9	10.11	0.77	0.29–2.14	0.57
Poorphysical activities	159	97.55	55	61.80	24.57	8.12–98.22	0.00*
Recumbent position Time (mean ± SD)	10.37 ± 2.78		8.98 ± 2.36			9.54–10.22	0.0001*
≥10 h	96	58.90	28	31.46	3.12	1.75–5.61	0.00*

**Prolonged recumbent position time, poor physical activities, Vitamin D and Calcium supplement reached statistical significance ($P < 0.05$). SD, standard deviation; CHD, coronary heart disease; CI, cerebral infarction.*

TABLE 2 | Multiple logistic regression analysis to identify the predictors of risk factors for BPPV.

Variables	Odds ratio	95% confidence interval	*p*-value
Age	1.01	0.99–1.03	0.43
Low-density lipoprotein	0.82	0.46–1.46	0.51
Total cholesterol	0.93	0.59–1.47	0.75
Triglyceride	1.27	0.87–1.87	0.22
Serum uric acid	1.00	0.99–1.00	0.78
Calcium supplement	0.11	0.01–1.38	0.09
Vitamin D supplement	0.66	0.04–10.38	0.77
Poor physical activities	18.92	6.34–56.43	0.00*
Recumbent position Time (mean ± SD)	1.15	1.01–1.33	0.04*

**Poor physical activities and prolonged recumbent position time were significance predictors of BPPV.*

time (OR = 1.15, 95% CI: 1.01–1.33, $p < 0.04$), and poor physical activities (OR = 18.92, 95% CI: 6.34–56.43, $p = 0.00$) may be important risk factors for BPPV (**Table 2**).

Receiver operating characteristic analyses were applied to recumbent position time and physical activities variables. AUCs were 0.68 (0.61–0.74), and 0.68 (0.63–0.73), respectively (**Figure 2**).

DISCUSSION

As we all know, age, gender, sex hormones, osteoporosis, hypertension, hyperlipidemia, diabetes, plasma vitamin D level, and hyperuricemia are all considered as risk factors for BPPV (4, 5, 7–10). According to a previous study, cerebrovascular risk factors influence BPPV onset (9, 11). In addition, some studies have found that age does not increase the recurrence rate of BPPV (11) and seasonal vitamin D deficiency in winter is not enough to cause BPPV (12). The risk factor of BPPV needs further analysis. In theory, with the increase of age, the function of human organs gradually declines and cardiovascular risk factors increase with age. As a part of the inner ear structure, the metabolism, absorption, and regeneration of otoliths are affected, and can easily fall off and lead to BPPV. Previous studies have found that the high morbidity of BPPV in women may be related to widespread osteoporosis (6). It may also be related to the abnormal hormone metabolism in post-menopausal women. We found that there was no obvious correlation to the common BPPV related risk factors in this study, such as hypertension, hyperuricemia, hyperlipidemia, diabetes, serum bilirubin, CHD, and CI.

We found that the numbers of idiopathic BPPV was significantly higher than the same period a year earlier under the quarantine policy in Hangzhou from January 2020 to March 2020. This may correlate with the unhealthy lifestyle of patients during the COVID-19 spread. To verify this hypothesis, we expanded the sample size of idiopathic BPPV and set up a non-BPPV health checker as a control group.

As to the lifestyle of the BPPV group, the majority of patients had the following characteristics, poor physical activities and prolonged recumbent position time. It can be seen that prolonged recumbent position time and poor physical activities may be important pathogenic factors for BPPV. Van WE confirmed that 11% of the dizziness symptoms in Parkinson's patients are likely to be BPPV, which is also considered to be related to poor physical activities (13). It has been suggested that a prolonged recumbent position may promote calcium carbonate deposition and otolith relaxation in the elliptical capsule (4). The author believes that this view can explain the mechanism of the significant increase of BPPV patients in our study. Studies have found that poor physical activities is one of the most important risk factors for BPPV in women and the morbidity of women who do not exercise is 2.62-fold that of women who regularly exercise (14). Regular physical exercise may be a good choice to prevent BPPV.

Some studies found that the decrease in the plasma vitamin D level is directly related to BPPV (9, 10). We believe that prolonged recumbent position time and poor physical activities can lead to sunlight insufficiency, which in turn leads to vitamin D deficiency.

Through this clinical study, we hypothesized that the broken otolith of the endolymph in healthy people may be continuous, which may be absorbed and dissipated due to regular exercise and suitable recumbent position time. For those who have prolonged recumbent position time or poor regular physical activities, the deposition is affected by gravity, and when they move position such as getting up from a resting position or turning over, it may result in BPPV. This finding may explain why BPPV occurs several days after trauma, rather than immediately after trauma.

The movement of the body and head may promote the circulation of the endolymph in the semicircular canal, and the degenerative otolith also dissolves and dissipates with the circulation. However, prolonged recumbent position time or poor regular physical activities will slow down the circulation. The otolith particles in the membranous labyrinth will also increase due to the unhealthy lifestyle. The three-dimensional movement of the body and head may promote the formation of the normal structure and functional remodeling of otoliths on the utricle. However, an unhealthy lifestyle may lead to otolith structural disorder, which may lead to the otolith falling off easily.

CONCLUSION

This study found that idiopathic BPPV had no obvious relationship with hypertension, hyperuricemia, hyperlipidemia, hemoglobin, diabetes, serum bilirubin, CHD, or CI. In this study, poor physical activities and prolonged recumbent position time are important predictors for BPPV. Changing unhealthy lifestyles may be the solution to decrease the morbidity of BPPV. The authors speculate that BPPV is associated with poor physical activities and prolonged recumbent position time which may be the independent risk factors.

The limitations of the study are that it failed to assess the anxiety and depression of all patients. Sleep quality was not included in the analysis (15). BPPV styles were not classified. Osteoporosis information was obtained only through asking the patient for their medical history, lacking relevant examinations.

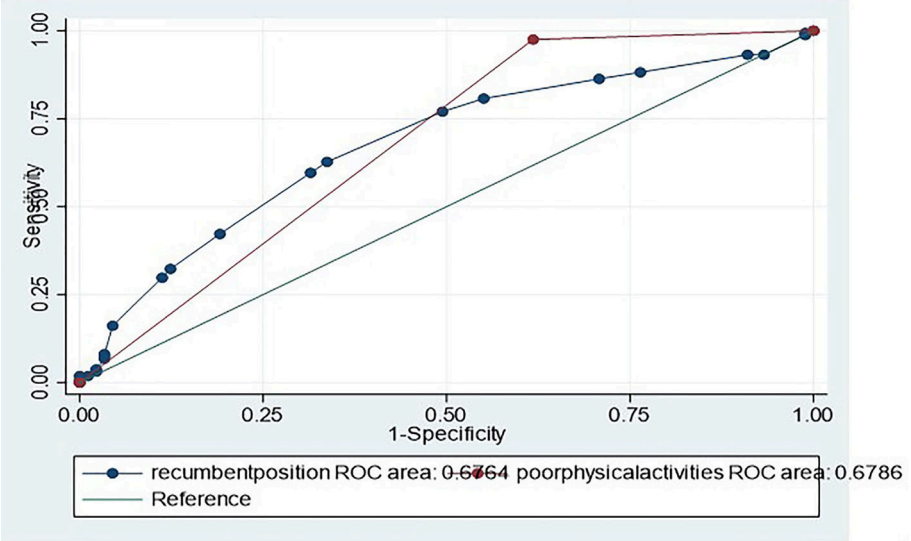

FIGURE 2 | Comparison of ROC curves of recumbent position time and poor physical activities in identifying BPPV. AUCs were 0.68 (0.61–0.74), and 0.68 (0.63–0.73), respectively.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/Supplementary Material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Tongde Hospital of Zhejiang Province. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

C-yF conceived the study and design, conducted the experiment, and wrote the manuscript. F-lY prepared manuscript, and revised this manuscript. Z-zZ, JC, and SJ conducted the acquisition of subjects and the interpretation of data. All authors contributed to the article and approved the submitted version.

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REVIEW
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Benign Paroxysmal Positional Vertigo Risk Factors Unique to Perimenopausal Women

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Many investigations have found common occurrences of benign paroxysmal positional vertigo (BPPV) in women, and clinical experience has shown that BPPV can develop due to increased hormonal fluctuations, especially during menopause. Therefore, knowledge about neurochemicals and their involvement with BPPV is imperative for the management of neurological issues in women. This review will discuss appropriate gender-based considerations of BPPV based on experimental and clinical evidence. The studies describe 2 lines of evidence regarding the association of perimenopause in women and the development of BPPV: (1) experimental evidence: the existence of estrogen receptors in the inner ear, otoconial malformations in osteopenic/osteoporotic rats, changes in otoconin 90 caused by hormone replacement therapy, and impaired calcium absorption following estrogen deprivation corrected by estrogen replacement therapy and (2) clinical evidence: epidemiological aspects, osteoporosis and estrogen deficiency. Future studies are necessary to validate the effects of hormonal replacement therapy and phytoestrogen in women with recurrent BPPV.

Keywords: vertigo, estrogen, women, otoconia, perimenopause

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INTRODUCTION

Known as the most common cause of recurrent vertigo (1), benign paroxysmal positional vertigo (BPPV) is an important health problem affecting more than 420 million adults worldwide, based on an international consensus that BPPV has a lifetime prevalence of 10% (2). BPPV increases with age, especially during menopause, in a ratio of 2-3.2:1 for women and men aged 40–60 years (3–8). In particular, hormonal changes, external estrogens, and pregnancy exposure are only experienced by women. Further understanding of possible contributors to the predominance of BPPV in women could make a significant contribution to our understanding of the causes of BPPV and may provide new methods for prevention. Therefore, the present study will review the current state of knowledge on BPPV risk factors specific to women.

PERIMENOPAUSE PERIOD

There are three stages of perimenopause in the executive summary of the Stages of Reproductive Aging Workshop: "early menopausal transition (early perimenopause), characterized by irregularities in the menstrual cycle, late menopausal transition (late perimenopause), characterized by an interval of more than 60 days of amenorrhea in the previous 12 months; and early postmenopause, which is the first year following the last menstrual period (9)." Physiologically,

TABLE 1 | The Kupperman scale*.

Items		Factor	Severity	Numerical Conversion (Factor * Severity)
1	Hot flashes	4		
2	Sweating	2		
3	Paresthesia	2		
4	Insomnia	2		
5	Nervousness	2		
6	Melancholia	1		
7	Vertigo	1		
8	Fatigue	1		
9	Myalgia	1		
10	Headache	1		
11	Palpitation	1		
12	Vaginal dryness	1		
Menopausal index (sum of each numerical conversion)				(0–57)

*Severity: O—None = 0, S—Slight = 1, M—Moderate = 2, +–Marked = 3 *The Kupperman scale described by Morrie M. Gelfand in 2002.*

estrogen declines sharply during this period, which occurs over several years and is characterized by marked fluctuations in sex hormone levels. The fluctuations during this period are more severe than those during the menstrual cycle (10). Regarding personal aspects, menopause occurs during the time in life when women are actively involved in raising a family and/or full-time work, during which time women may also be responsible for caring for elderly parents. Most menopausal women experience uncomfortable symptoms, and menopause is related to an increased risk for metabolic syndrome, in addition to obesity and osteoporosis (11). In the field of gynecology, menopausal symptoms are assessed using the "Kupperman rating scale" (**Table 1**) (12–14). The inclusion of vertigo items in one menopausal symptom index suggests that vertigo is also a frequent complaint in gynecology clinics. Although the nature of vertigo has not been precisely elucidated, postmenopausal hormone replacement therapy (HRT) was superior to placebo when assessed by the "Kupperman scale including the item addressing vertigo (15)." Additionally, many neurotology studies have shown an increased incidence of BPPV in women, and experience with older people suggests that hormonal fluctuations, particularly during menopause, may increase, resulting in the development of BPPV (3–8). Cooperative management between neurotologists and gynecologists could be helpful in the management of dizziness in women who experience it.

EXPERIMENTAL EVIDENCE

Anatomical Differences

Differences in the peripheral vestibular system between men and women have been reported. To our knowledge, no reports have described the direct comparison of otoconial morphology between women and men. However, in the anteroposterior dimension, the width of the peripheral vestibular system is significantly smaller in women (16), which could suggest a difference in otoconial morphology, such as differences in the bones according to sex. Further validation studies are needed.

Hormone Changes

Physiologically, testosterone levels are more stable than estrogen levels throughout a woman's life and are relatively constant at ages 30–70 (17). Estrogen decreases steeply during the climacteric period. The female sex hormone estrogen 17β-estradiol (E2) is well-known to perform many tasks and contributes to various roles, such as reproductive organ differentiation and function, memory processes and bone metabolism (18, 19). Clinically, E2 and progesterone levels are clearly reduced in women with BPPV (20, 21); however, no difference in testosterone was found between the postmenopausal and control groups (21). Similar to other sex steroids, estrogen acts on target cells by attaching to nuclear hormone receptors such as estrogen receptor (ER)α and β (22). Thus, the ER level is an important determinant that influences estrogen signaling to the cell.

Estrogen Receptors in the Inner Ear

Estrogen functions have been suggested to influence hearing and vestibular function (23, 24). In addition, the expression of ERα and β decreases with increasing age (25). A previous double-staining study found that in the inner ear, ERα and β were generally co-expressed (25). However, ERβ predominates in type II spiral ganglion neurons or inner ear strial marginal cells (24, 26–28). These findings support the role of estrogen in the inner ear.

TRPV6 and Estrogen

BPPV is described as the process of otoconia debris removal from the otoconial membrane (29). Because otoconia are calcium carbonate crystals, initial crystal formation in the proteinaceous core needs a local increase in Ca^{2+} and carbonate (CO_3^-) concentrations (30). Importantly, low Ca^{2+} levels must be maintained in the endolymph of vestibular organs to prevent unnecessary mineralization (31). Several Ca^{2+} channel structures primarily act on the temporospatial control of Ca^{2+} concentrations in the endolymph to preserve a circumstance suitable for stable Ca^{2+} equilibrium. Previous reports indicate that the epithelial Ca^{2+} channels TRPV5 and TRPV6 manifest in the semicircular canal, which are important Ca^{2+}-binding proteins for the maintenance of low Ca^{2+} concentrations in the endolymph. Moreover, ERα has been demonstrated to tightly regulate uterine TRPV6 transcription. An experimental study also showed that E2 regulates TRPV6 through an ERα-dependent pathway (32). In a previous study, decreased ERα levels in aged animals could induce a decrease in TRPV6, resulting in otoconial malformation and a decrease in the number of otoconia (25). Therefore, a sharp decrease in estrogen during menopause, especially a decrease in ERα, may impair otoconial metabolism and lead to a higher prevalence of BPPV (25).

Estrogen and Otoconia

Estrogen may also play an important role in otoconial metabolism. Bilateral ovariectomized osteopenic/osteoporotic rats had larger otoconia with a reduced density compared to controls (33).

Estrogen and Otoconin 90

An animal study conducted by Yang et al. demonstrated that bilateral ovariectomy in rats receiving female HRT reversed the reduction in the level of otoconin 90, the main protein that preserves the normal morphology and growth of otoconia (20, 34).

Estrogen and Vitamin D

Recent reports have shown that reduced serum levels of vitamin D are associated with the occurrence of BPPV (4, 35–40), and supplementation of vitamin D with/without calcium reduces recurrent events in BPPV patients (41–44). Estrogen treatment prevents the loss of intestinal Ca^{2+} absorption and bone density caused by ovariectomy in the premenopausal period (45). Experimental studies have shown that impaired Ca^{2+} absorption following estrogen deprivation is caused by a decreased response to 1,25 dihydroxycholecalciferol, the main regulator of intestinal absorption, and that estrogen treatment, rather than short-term replacement with 1,25 dihydroxycholecalciferol, can amend this abnormality. Therefore, combined hormone replacement and vitamin D management could be more effective for the prevention of further attacks of vertigo in perimenopausal women with BPPV. However, further validation studies are needed (45).

CLINICAL EVIDENCE

Susceptibility of Women to BPPV

Several factors increase the susceptibility to BPPV, including older age, head and neck trauma, inactivity, and other ear problems or surgery. Many studies have shown a common occurrence in women, and clinical experience with older people has shown that BPPV can develop due to increased hormonal fluctuations, especially during menopause (3–8).

BPPV and Oral Contraceptives

A previous study reported that recurrent BPPV was related to oral contraceptives (46). It has been postulated that oral contraceptives may induce disturbances in the water and electrolyte balance, variances in endolymph pH and abnormalities in carbohydrate or lipid metabolism, which may cause otoconial degeneration and subsequent otoconial detachment and BPPV (46).

BPPV in Pregnancy

Although the link between BPPV and pregnancy is still unclear, some pregnant women have been first diagnosed with BPPV during pregnancy (47).

Osteoporosis

A characteristic feature of osteoporosis is a decrease in bone mass due to an imbalance between bone resorption and formation. Loss of reproductive function and aging are the two most significant factors developing this condition. After ∼30–40 years, both women and men experience 0.3–0.5% bone loss per year (48, 49). After menopause, the rate of bone loss can increase 10 fold. In Western countries, one-third of women with menopause experience osteoporosis (50). There are two types of osteoporosis: primary osteoporosis and secondary osteoporosis (51). Type I primary osteoporosis occurs during the postmenopausal period when estrogen output and the bone formation rate are reduced and bone loss is accelerated (51). Type II primary osteoporosis is a senile process with a reduction in the synthesis of active vitamin D in the elderly, which reduces gastrointestinal absorption of Ca^{2+}, bone cell activity and bone development. Secondary osteoporosis is caused by specific conditions and drugs and occurs in all age groups irrespective of sex. Fractures and injuries due to osteoporosis could harm a person's life and incapacitate

TABLE 2 | Evidence of the relationship of estrogen to the pathogenesis of benign paroxysmal positional vertigo.

	References	Findings
Experimental	(26)	In general, co-expression of ERα and β in the inner ear.
	(32)	TRPV6 is an important Ca^{2+} binding protein for maintenance of low [Ca^{2+}] in the vestibular endolymph. Estradiol regulate TRPV6 via an ERα-dependent pathway.
	(33)	In rats by ovariectomy, the density of otoconia with larger size compared to the controls.
	(25)	Otoconial malformation and decreased the number of otoconia in older animals with ERα deficiency.
	(20)	The recovery of the otoconin 90, which preserves the normal morphology and growth of otoconia in bilateral ovariectomy in rats receiving female sex hormone replacement therapy
Clinical	(8)	Perimenopausal women with BPPV are the predominant patient type in dizziness clinics.
	(3)	
	(5)	
	(6)	
	(4)	
	(7)	
	(45)	Estrogen supplement, not short-term treatment with vitamin D, can repair calcium ion malabsorption occurring after estrogen deprivation.
	(46)	Recurrent BPPV is related to oral contraceptive treatment.
	(47)	Pregnant women with first attack of BPPV
	(6)	In the Taiwanese population, estrogen care for menopausal syndromes significantly lower incidence of BPPV.
	(20)	The lower level of estradiol in the postmenopausal women with idiopathic BPPV than those in the control subjects ($p < 0.001$).

BPPV, benign paroxysmal positional vertigo.

their ability to live independently. Therefore, bone fractures related to decreased bone density can increase mortality (51). In addition, decreased bone mineral density is related to the occurrence/recurrence of BPPV. Patients with BPPV had lower bone density among both women and men compared to controls (52). Although both men and women may develop osteoporosis, women are more susceptible to osteoporosis than men due to their smaller size with lower bone mass and decreased estrogen secretion during menopause (53, 54). In a previous study on bone mineral density and BPPV, women over the age of 45 in the relapse group had lower T scores than those in the *de novo* group (52). To examine osteoporosis in menopausal women, ovariectomized rats have been investigated in several studies (55, 56). Estrogen spares the human skeleton from bone loss by slowing down the process of bone remodeling and maintaining an equilibrium between bone formation and absorption (57, 58). In women undergoing rapid bone loss after menopause (59, 60), bone resorption and urinary Ca^{2+} excretion are increased, and these changes are reversed by estrogen replacement therapy (61, 62). Considering that estrogen loss is a causal factor for bone loss during perimenopause, a specific ER modulator could be used to treat postmenopausal BPPV patients.

Hormone Replacement Therapy

HRT to combat estrogen depletion in menopause has also been successfully used to treat vasomotor symptoms and is assumed to be neuroprotective compared to women not using HRT. Although the nature of vertigo has not been precisely elucidated, women using postmenopausal HRT had better scores than the placebo group on the "Kupperman scale" (sweating, hot flashes, myalgia, and vertigo) (15). The hormonal fluctuation of ovarian neurosteroids might trigger the occurrence/recurrence of BPPV during the perimenopausal period. In the Taiwanese population, a study revealed that the incidence of BPPV was significantly lower in patients taking estrogen for menopausal syndrome in two age groups (ages 45–65 and ages 65 and over) (6). These findings support the efficacy of estrogen supplementation to decrease the occurrence of BPPV in women with menopause. The possible mechanisms include complete, more reliable estrogen blood levels that induce protective effects, estrogen effects on autophagy and possible epigenetic modulation (5, 6, 20, 63). However, chronic use of HRT increases the risk of breast cancer (64), stroke (64), and venous thrombosis. Therefore, many postmenopausal women rely on other non-steroidal estrogen mimetics or natural remedies to solve the problems associated with the symptoms of estrogen deficiency. Phytoestrogen could be an alternative to HRT. Phytoestrogens, including soy isoflavones, are non-steroidal, diphenolic substances that can bind to ERs and have activity similar to that of estrogen (65). To date, there have been no reports on the effectiveness of phytoestrogens on BPPV recurrence.

CONCLUSION

The biochemical pathway is a key factor in some medical illnesses. Thus, investigation into the biochemical causes of neurotological problems could be guaranteed to produce results and can be cost effective. In particular, hormonal changes, external estrogens, and pregnancy exposure are only experienced by women. It is not fully understood why postmenopausal women show a higher prevalence of BPPV. However, in menopause, the rapid decrease in ERs, especially ERα, due to the sudden decrease in estrogen can lead to the disturbance of otoconial metabolism, which can increase the prevalence of BPPV. Additionally, HRT can reverse the low otoconin 90 levels and reduce the incidence of BPPV (**Table 2**). Adoption of a customized approach considering the neurochemical changes in perimenopause will be extremely helpful for the management of BPPV in women. Cooperative management among neurotologists, endocrinologists, and gynecologists is also important as a focus for neurotological disorders, including BPPV, in women.

AUTHOR CONTRIBUTIONS

S-HJ acquired and analyzed the data, and drafted the manuscript.

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Analysis of the Skew Deviation to Evaluate the Period of Onset of a Canalolithiasis After Macular Damage

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Benign paroxysmal positional vertigo (BPPV) is the most common peripheral vestibular end-organ disease, and it is one of the first causes of access to the emergency room. The moment of migration of the otoconial debris in a semicircular canal does not necessarily coincide with the moment of detachment of the debris themselves. Consequently, the paroxysmal positional vertigo could arise with a variable delay with respect to the mechanical damage suffered by the macula. The aim of this work is to try to identify objective criteria to establish whether a canalolithiasis is synchronous or diachronic to the damage. The analysis of skew deviation in the context of ocular tilt reaction in patients with canalolithiasis could provide useful information to understand if macular damage occurred at the origin of the disease and when the damage may have occurred. In this study, 38 patients with BPPV were analyzed based on the type of skew deviation that was presented. We found that if the eye on the side of the canalolithiasis is hypotropic the damage of the utriculus is likely recent (last 10 days), if it is hypertropic the damage is not recent (20 days before) and finally if the eyes are at the same height it could be an utricular damage in compensation (occurring the last 10–20 days) or a secondary labyrinth canalolithiasis, without associated utricular damage. Our results show that the evaluation of skew deviation in patients suffering from BPPV could be useful to evaluate: (a) if a positional paroxysmal nystagmus can be related to an previous relevant injury event (for example a head injury that occurred days before the crisis); (b) if it is a BPPV of recent onset or a re-entry of the debris into the canal.

Keywords: vertigo, benign paroxismal positional vertigo, ocular tilt reaction, skew deviation, vestibular disorder (VD)

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common peripheral vestibular end-organ disease and it is characterized by a sudden, transient vertigo which is accompanied by the typical paroxysmal positional nystagmus. Symptoms are provoked by positional changes of the head with respect to gravity and can range in severity from mild dizziness to debilitating episodes that may induce nausea or vomiting, and significantly reduced quality of life (1). BPPV is caused by otoconia that have become detached from the utricular maculae. The otoconia could enter the semicircular canal and can move in the endolymph (canalolithiasis) or become attached to the cupula (cupulolithiasis). Nowadays, the availability of neurophysiological tests such as cervical

and ocular Vestibular Myogenic Potentials, provide the possibility to detect the functionality of the utricular and saccular maculae. By the above-mentioned tests, a damage of the utricular and saccular macula could be detected in BPPV (2, 3). Skew deviation (SD) is a vertical misalignment of the eyes caused by damage to prenuclear vestibular input to ocular motor nuclei. It is usually accompanied by binocular torsion, torticollis, and a tilt in the subjective visual vertical. This constellation of findings has been termed as ocular tilt reaction (OTR). SD can result from any acute injury within the posterior fossa, the majority of cases are seen in association with brainstem stroke. A tonic ipsiversive ocular tilt reaction, not associated to a central nervous system damage, could be related to a damage to one utricle or other lesions involving the human labyrinth and vestibular nerve (4, 5). An injury of one utricular macula could produce an otolithic detachment but the moment of migration of the otoconial debris in a semicircular canal does not necessarily match with the moment of detachment of the debris themselves. We hypothesize that the study of the skew deviation could give important information regarding the timing of the onset of a paroxysmal positional vertigo. The aim of this paper is to identify objective criteria to establish whether a BPPV occurs at the same time as the damage of utricle or subsequently.

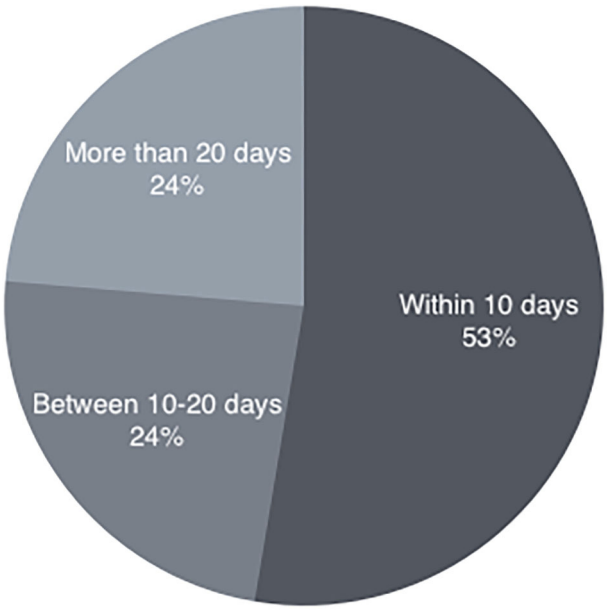

FIGURE 1 | Time of onset of BPPV.

METHODS

In the period from January 2018 to January 2020 we consecutively evaluated 120 patients with BPPV. Our inclusion criteria were based on the presence of recurrent short-lasting episodes of positional vertigo, on the positivity of the provocation maneuvers, and on nystagmus characteristics (latency, fatigue and direction) compatible with BPPV. The diagnosis of posterior canal BPPV was made using the Dix–Hallpike test that elicited a mixed vertical– torsional Paroxysmal positional nystagmus with the vertical component beating toward the forehead, and the upper pole of the eyes beating toward the affected (lower) ear. We used the Pagnini-McClure maneuver to diagnose horizontal semicircular canal BPPV. This was considered positive when a horizontal direction-changing nystagmus (geotropic or apogeotropic) appeared; the directions of lying-down nystagmus and head-bending nystagmus have been used to correctly evaluate the affected side (6). All the patients were carefully asked to clearly verify the exact day of onset of the symptomatology. They were successfully treated for complete resolution of nystagmus after appropriate repositioning maneuver; anamnesis of the exact day of the onset of the BPPV symptoms. We included in our study 38 subjects (16 males and 22 females, mean age 58 years, ranging from 15 to 90 years) successfully treated with the repositioning maneuver. Twenty-seven subjects, suffering from posterior canal BPPV were treated with the Semont's maneuver and 11 subjects, suffering from lateral canal BPPV were treated with the Gufoni's maneuver. We excluded patients who presented with multiple canal BPPV, with a prevalent downbeating nystagmus, or patients with no immediate response to the therapeutic maneuver. We excluded patients with associated vestibular pathology (such as previous acute unilateral loss, Menière's Disease) or signs of central nervous system involvement and patients affected with ophthalmological diseases. The selected patients were divided into three groups (**Figure 1**): (a) canalolithiasis recently occurred: within 10 days before clinical observation (b) canalolithiasis not recently occurred: between 10 and 20 days before clinical observation (c) canalolithiasis that occurred late: more than 20 days before clinical observation. The evaluation of the skew deviation has been performed with Frenzel Goggles and its measurement with the Eye Alignment Test. The test includes these steps: (1) The patient is seated and wears Frenzel's glasses, without resting his back or his arms. (2) The examiner takes a photo of the eyes: the camera is equipped with "a level" to keep it perfectly horizontal. (3) The angle between the interpupillary line and the horizontal line is measured on the photo (**Figure 2**). Some "vector graphics software" can be used. The inclination of the interpupillary line is measured and it is considered pathological if the result is an angle $>2.5^{\circ}$ (7). The side from which the eye is lower is identified and the records relating to each patient were noted. The examiner who carried out the measurement of the eyes was different from the examiner who had carried out the diagnosis of canalolithiasis and did not know which was the pathological side. All patients underwent routinely-performed tests only, without invasive or experimental procedures. Informed consent was obtained from all participants and the study was performed in accordance with the Declaration of Helsinki.

RESULTS

We evaluated the congruence between the BPPV affected side and the skew deviation. Out of 20 subjects in whom

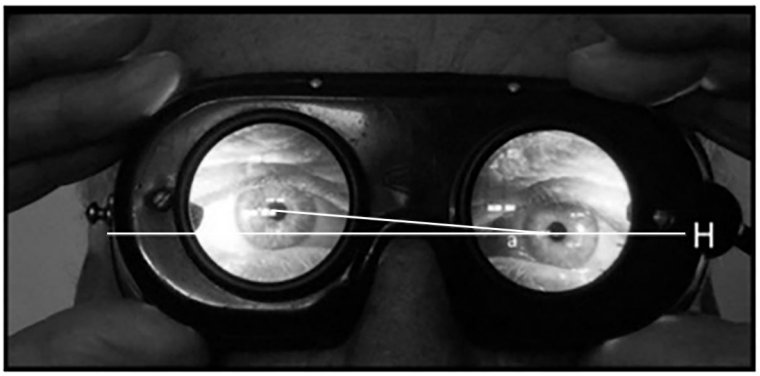

FIGURE 2 | Evaluation of the angle "a" between interpupillary line and horizon: in this case the angle is 5°.

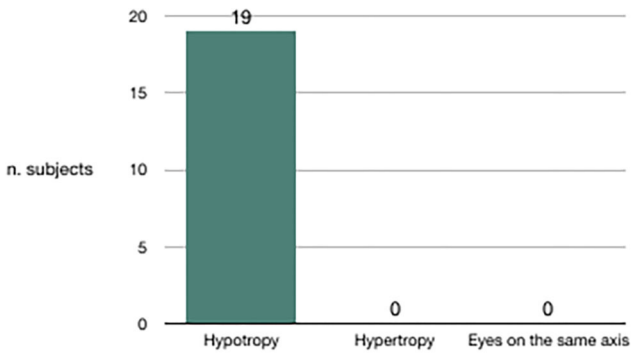

FIGURE 3 | Subjects with BPPV occurred within 10 days before clinical observation.

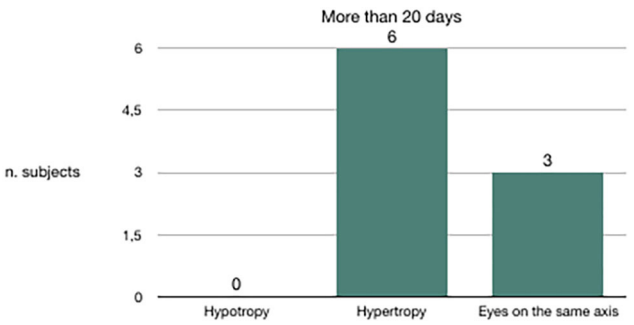

FIGURE 4 | Subjects with BPPV occurred more than 20 days before clinical observation.

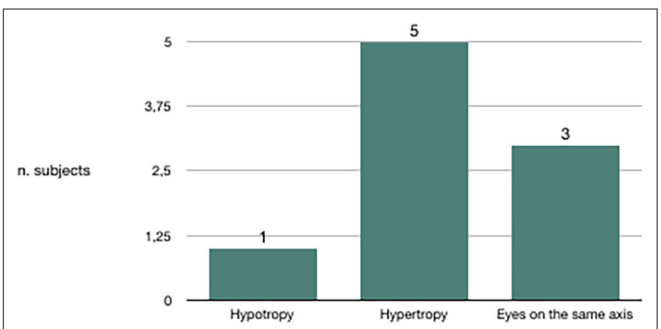

FIGURE 5 | Subjects with BPPV occurred 10–20 days before clinical observation.

canalolithiasis had occurred 10 days before clinical observation, 19 had hypotropia of the eye on the same side of the affected vestibule (**Figure 3**). Out of nine subjects in whom canalolithiasis had occurred 20 days before clinical observation, six had hypertropia of the eye on the same side of the affected vestibule (**Figure 4**). Out of 9 subjects in whom canalolithiasis had occurred between 10 and 20 days before clinical observation: three had compensated skew deviation (eyes on the same axis), one had uncompensated skew deviation (hypotropia of the eye on the same side of the affected vestibule), five had hyper compensated skew deviation (hypertropia of the eye from the sick side) (**Figure 5**). A comparison was made (Chi-squared test) for the presence of hypertropia of the eye from the side of the damaged labyrinth between two groups: a group with recent onset of canalolithiasis (<10 days) and a group with canalolithiasis present for at least 20 days. The difference was statistically significant ($p = 0.00033$) allowing the zero hypothesis of belonging to the same group to be rejected.

DISCUSSION

From the evidence of this study, it therefore seems possible to trace the age of onset of macular damage on the basis of the degree of compensation of the ocular tilt reaction, with particular reference to skew deviation. If the eye on the side of the canalolithiasis is hypotropic the damage of the utriculus is likely recent: last 10 days. If the eye on the side of the canalolithiasis is hypertropic, the damage of the utriculus is not recent: dates back to at least 20 days before. If the eyes are at the same height it could be: (a) a secondary labyrinth canalolithiasis, without associated utricular damage. (b) utricular damage in compensation: occurring in the last 10–20 days. In

literature, OTR is assessed using different methods, which have as their purpose the measurement of at least one of the three signs that compose it (ex/inciclotorsion, hyper/hypotropia of the eye, lateral flexion of the head). One method is the evaluation of the subjective visual vertical (SVV) (8): the angle at which a light line in the dark is perceived to be perfectly vertical is measured. A dynamic SVV toward the affected side was recorded in all subtypes of BPPV with a statistically significant difference from those of the controls (9). A variant that does not require instrumentation is the "Bucket test" (7). Using this method, a reduction of the deviation of SVV was detected immediately after the repositioning maneuvers (10). A complete study of OTR should be based on the evaluation of the three signs of OTR at the same time, including the exiclo and inciclo torsion of the eyes. This component of OTR is not uniquely considered an expression of macular damage (11–15) and could generate a "bias" in the evaluation of the utricular function. The ocular Vemps (oVemps) are generated from the utricle and carried along the otolith-ocular crossed neural pathways (3). A recent meta-analysis indicated that in patients with BPPV, oVemps showed an abnormal asymmetry ratio reflecting a difference between affected and not affected sides (2). However, the same authors suggested that this method is not suitable for clinical application.

Our study has several limitations: firstly, the sample size is too small to drive a definitive conclusion; secondly, comparing the results of OTR in our patients with the results of o-Vemps would have provided more detailed information about the presence of a utricular dysfunction. Nevertheless, the aim of our study was not the evaluation of the functionality of the utricular macula, but to obtain reliable data about the restoration of the macular damage.

CONCLUSIONS

Analyzing skew deviation in the context of ocular tilt reaction in patients who come to our clinical attention with canalolithiasis can provide extremely useful information to help understand if macular damage occurred at the origin of the disease and when the damage may have occurred. We are of the opinion that this method can be useful to evaluate if a positional paroxysmal nystagmus can be related to an anamnestically relevant injury event or if it is a new BPPV or a re-entry in the channel of pre-existing otoliths.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG: study concept, design, acquisition of data, analysis, interpretation of data, drafting of the manuscript, and study supervision. MV: acquisition of data, drafting of the manuscript, administrative support, and technical and material support. AC: study concept, design, analysis, interpretation of data, drafting of the manuscript, and study supervision. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Ocular vs. Cervical Vestibular Evoked Myogenic Potentials in Benign Paroxysmal Positional Vertigo: A Systematic Review and Meta-Analysis

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Objective: To compare utricular dysfunction with saccular dysfunction in benign paroxysmal positional vertigo (BPPV), based on ocular vestibular evoked myogenic potentials (oVEMP) and cervical VEMP (cVEMP), respectively.

Materials and Methods: We performed a literature search exploring utricular and saccular dysfunction in BPPV patients through June 2020 using oVEMP and cVEMP, respectively. The databases included Pubmed, Embase, CENTRAL, CNKI, Wan Fang Data, and CBM. The literatures were limited to Chinese and English. Inclusion criteria and exclusion criteria were defined. We adopted abnormal rate as the outcome. All statistical processes were conducted through software Review Manager. Considering the air-conducted sound (ACS) and bone conducted vibration (BCV) may have different mechanisms, and three types of diagnostic criteria for abnormal VEMP were available, sub-group analysis was performed simultaneously according to the sound stimuli and the diagnostic criteria of abnormal VEMP.

Results: We retrieved 828 potentially relevant literatures, and finally 12 studies were included for meta-analysis of abnormal rate after duplication removal, titles and abstracts screening, and full-text reading. The abnormal rate of oVEMP was not significantly different from cVEMP (OR = 1.59, 95% CI = 0.99–2.57). But the abnormal rate was obviously different between the subgroups adopting ACS oVEMP and BCV oVEMP. In studies adopting ACS oVEMP, the abnormal rate of oVEMP was higher than cVEMP (OR = 1.85, 95% CI = 1.38–2.49). The abnormal rate of oVEMP was also higher than cVEMP when adopting asymmetry ratio (AR) and no response (NR) as diagnostic criteria (OR = 2.16, 95% CI = 1.61–2.89).

Conclusion: The meta-analysis reveals that utricular dysfunction may be more predominant in BPPV compared with saccular dysfunction.

Keywords: vestibular evoked myogenic potentials, benign paroxysmal positional vertigo, saccule, utricle, meta-analysis

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INTRODUCTION

Vestibular evoked myogenic potentials (VEMPs) have been widely adopted as a practical and effective measure of function of otolith pathway in central and peripheral vestibular disorders (1, 2). VEMPs can be recorded from the contracted sternocleidomastoid muscle (cervical VEMPs or cVEMPs) (3) and the inferior oblique muscle (ocular VEMPs or oVEMPs) (4). Generally, cVEMPs mainly represent the inhibitory vestibulo-collic reflex and reflect the functions of ipsilateral saccule and inferior vestibular nerve, while oVEMPs commonly represent the active vestibulo-ocular reflex and reflect predominantly the functions of contralateral utricle and superior vestibular nerve (5, 6).

VEMPs are short-latency alterations of myogenic activity in response to various stimuli. Loud air-conducted sound (ACS) (7) and bone conducted vibration (BCV) (8) are the most common stimulation modes adopted in clinical practice. The mechanisms of ACS and BCV may be different (9). In most cases, ACS is the best stimulus for cVEMP, while BCV oVEMP is better for detection of utricular dysfunction (5).

Benign paroxysmal positional vertigo (BPPV) is an episodic and brief vertigo or dizziness triggered by the sudden change of head position relative to gravity. BPPV is the most common cause of peripheral vertiginous disorders. So far the theories of canalolithiasis (10) and cupulolithiasis (11) have been widely regarded as the pathophysiology of BPPV. But the cause of otoconia detaching from macula of otolith organ remains unclear. In idiopathic BPPV, otolith dysfunction derived from degeneration of the utricular or saccular macula may be responsible for the dislodging of otoconia (12). Head trauma or inner ear diseases (13, 14) may especially damage the otolith organ, resulting in secondary BPPV. Due to the close anatomical relations, utricle is regarded as the principle source of otoconia debris and utricular dysfunction may be responsible for BPPV (15). However, a few of previous studies showed that otoconia may originate from the saccule and saccular dysfunction was correlated with BPPV occurrence and prognosis (16, 17).

There have been many studies which compared utricular function using oVEMP testing with saccular function using cVEMP testing in BPPV patients, and most studies confirmed that utricular dysfunction was more frequent (18, 19), but the conclusions were still contradictory (20, 21). Part of the reason may be different acoustic stimuli or different criteria for abnormal VEMP used by different studies. So we systemically retrieved all eligible studies and performed subgroup analysis simultaneously to compare the utricular and saccular dysfunctions in BPPV patients using oVEMP and cVEMP testing, respectively. The study aims to investigate whether utricular or saccular dysfunction may be predominant in BPPV.

MATERIALS AND METHODS

Literature Search Strategy

We performed a literature search which explored utricular and saccular dysfunction in BPPV patients through June 2020. The databases we systemically searched included Pubmed, Embase, CENTRAL, CNKI, Wan Fang Data, and CBM. The language was limited to Chinese and English. The search strategies were "vestibular evoked myogenic potential or VEMP" and "benign paroxysmal positional vertigo or BPPV." We sequentially screened titles and abstracts, and then read full-text to identify literatures for meta-analyze. Additionally we screened all references of eligible literatures. The flowchart is presented in **Figure 1**.

Study Selection Criteria

Inclusion criteria: (1) observation studies assessing utricular and saccular function in BPPV patients using oVEMP and cVEMP testing respectively; (2) diagnosis of BPPV relied on brief and recurrent vertigo and characteristic nystagmus in positional tests, such as Dix-Hallpike test and supine Roll test; (3) number of patients with response of oVEMP and cVEMP, or/and number of patients with abnormal oVEMP and cVEMP, were clearly stated.

Exclusion criteria: (1) insufficient data of oVEMP or cVEMP available resulting in incomparability; (2) absence of definite criteria for abnormal VEMP; (3) patents with conductive hearing loss, or other inner ear diseases, or neurological diseases; (4) unpublished studies, case reports, comments, practice guidelines, reviews, or letters.

Outcome Synthesis

There has been no international consensus on diagnostic criteria for abnormal VEMP. Delayed peak latency might be attributed to the reducing nerve conduction velocity consequent on demyelination. Enlarged asymmetry ratio (AR) with VEMP response might indicate various degrees of damage involving the sensory organ of saccule and utricle, while absent VEMP response might mean the damage is extensive (21). Most relevant studies used abnormal rate of oVEMP and cVEMP to assess the functions of utricle and saccule. So in our meta-analysis, abnormal rate was adopted to compare utricular dysfunction with saccular dysfunction in BPPV patients.

Data Extraction

Two authors (GC and XD) independently extracted all data through a uniform tool. Agreement was reached by consensus between the two authors. We extracted the data as follows: first author, country, publication year, age, gender, type of acoustic stimuli, criteria for abnormal VEMP, number of BPPV patients included, and number of patients with abnormal oVEMP and cVEMP.

Statistical Analysis

All statistical processes of this systematic review were conducted using software Review Manager (RevMan), version 5.3. Dichotomous variables were analyzed by Odds ratios (OR) and its 95% confidence interval (CI). Statistical heterogeneity was evaluated by X^2 and I^2 index. The random-effects model was used if $I^2 > 50\%$, indicating significant heterogeneity, otherwise we chose fixed-effects model. Considering the ACS and BCV may have different mechanisms, the sub-group analysis according to acoustic stimulus was conducted. Besides, another sub-group analysis according to diagnostic criteria was conducted because three types of diagnostic criteria for abnormal VEMP were available.

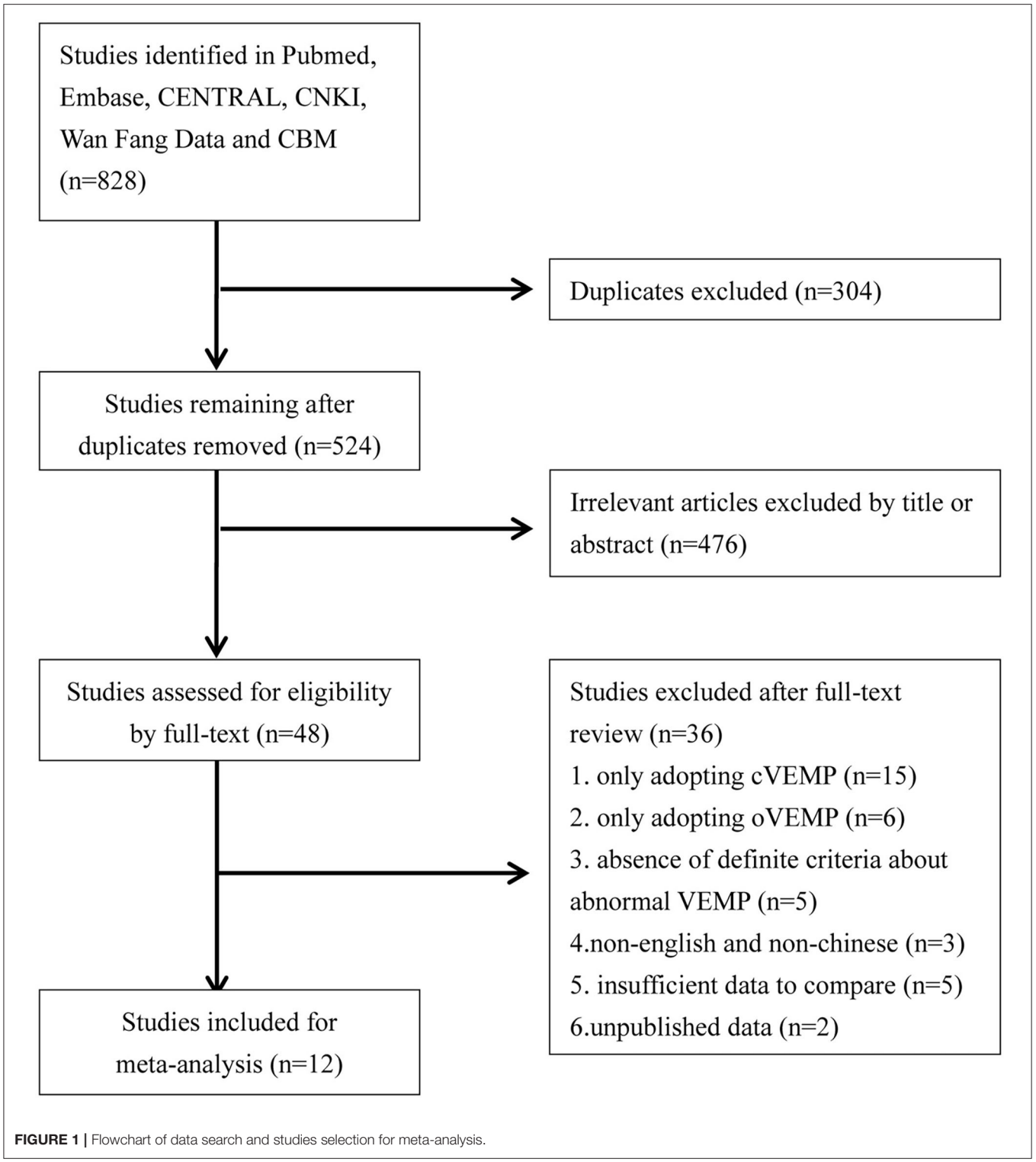

FIGURE 1 | Flowchart of data search and studies selection for meta-analysis.

RESULTS

Literature Screening

We retrieved 828 potentially relevant literatures, and 304 literatures were removed for duplication, and 476 literatures were excluded for irrelevance to our purpose after screening titles and abstracts. Of the remaining 48 literatures needing a full-text reading, 15 were excluded for only adopting cVEMP, 6 were excluded for only adopting oVEMP, 3 were excluded for non-English and non-Chinese publication, 5 were excluded for

absence of definite criteria for abnormal VEMP while comparing abnormal rate, 5 were excluded for insufficient data to compare through their studies, and 2 were excluded for unpublished data. Finally, we confirmed 12 studies for meta-analysis (18–29) (**Figure 1**).

Characteristics of Studies Included

Of the 12 studies, 790 BPPV patients were involved, and 5 (25–29) were from China, and 4 (25, 27–29) were published in Chinese. All cVEMP testing in 12 studies and oVEMP testing in 11 studies were evoked by ACS, while oVEMP testing in 1 study (22) was evoked by BCV. Four studies (19, 21, 22, 24) adopted delayed latency and AR and no response (NR), and six studies (18, 23, 25, 27–29) adopted enlarged AR and NR, and two studies (20, 26) only adopted NR as their criteria for abnormal VEMP, respectively. The characteristics of included articles are described in **Table 1**.

Meta-Analysis Results

Abnormal Rate of cVEMP vs. oVEMP in BPPV Patients

Twelve studies assessed the abnormal rate of cVEMP vs. oVEMP in BPPV patients. Random-effects model was selected because of a significant heterogeneity ($p < 0.00001$, $I^2 = 77\%$, **Figure 2**). The abnormal rate of oVEMP in BPPV patients was not significantly different from cVEMP according to the forest plot (OR = 1.59, 95% CI = 0.99–2.57, $p = 0.06$, **Figure 2**).

In the sub-group analysis according to the sound stimuli, the result indicated a significant difference existed ($p < 0.00001$, $I^2 = 96.8\%$, **Figure 2**) between the one study adopting BCV oVEMP (OR = 0.28, 95% CI = 0.16–0.51, **Figure 2**) and eleven studies adopting ACS oVEMP (OR = 1.85, 95% CI = 1.38–2.49, **Figure 2**). In the subgroup adopting ACS oVEMP, the abnormal rate of oVEMP was significantly higher than cVEMP with mild heterogeneity ($p < 0.0001$, $I^2 = 31\%$).

In the sub-group analysis according to the diagnostic criteria of abnormal VEMP, the result indicated no significant difference existed between the three groups ($p = 0.27$, $I^2 = 24.7\%$, **Figure 3**). In the first subgroup adopting delayed latency and enlarged AR and NR as diagnostic criteria (OR = 0.91, 95% CI = 0.33–2.51, $p = 0.86$, **Figure 3**), and the third subgroup adopting NR (OR = 1.64, 95% CI = 0.46–5.88, $p = 0.45$, **Figure 3**), the abnormal rate of oVEMP in BPPV patients was not significantly different from cVEMP. But six studies adopted enlarged AR and NR in the second subgroup (OR = 2.16, 95% CI = 1.61–2.89, $p < 0.00001$, **Figure 3**), and the abnormal rate of oVEMP in BPPV patients was significantly higher than cVEMP with no heterogeneity ($I^2 = 0\%$).

DISCUSSION

Several previous studies have compared oVEMP and cVEMP testing in BPPV patients. But the results varied widely. The abnormal rate of oVEMP ranged from 9.8% (24) to 66.7% (19), while cVEMP ranged from 13.4% (24) to 60.6% (22). The differences including the age of included individuals, stimulation

TABLE 1 | The basic characteristics of all eligible studies.

References	Country	No. of BPPV	Gender (M:F)	Age (years) (mean ± SD)	Acoustic stimuli		Diagnostic critera of abnormal VEMP	No. with abnormal response	
					cVEMP	oVEMP		cVEMP	oVEMP
Lee et al. (20)	Korea	36	NA	48.52 ± 10.06	ACS 90 dB nHL 500 Hz TB	ACS 95 dB nHL 500 Hz TB	NR	7	6
Nakahara et al. (19)	Japan	12	5:7	Mean 65.5	ACS 125 dB SPL 500 Hz TB	ACS 125 dB SPL 500 Hz TB	Latency + AR + NR	3	8
Talaat et al. (24)	Egypt	112	52:60	46.2 ± 10.2	ACS 95 dB nHL 500 Hz TB	ACS 95 dB nHL 500 Hz TB	Latency + AR + NR	15	11
Kim et al. (21)	Korea	102	48:54	62.8 ± 13.1	ACS 100 dB nHL 1,000 Hz TB	ACS 100 dB nHL 1,000 Hz TB	Latency + AR + NR	29	35
Zhou et al. (27)	China	59	13:46	48.35 ± 11.81	ACS 95 dB nHL 500 Hz TB	ACS 95 dB nHL 500 Hz TB	AR + NR	22	37
Xu et al. (26)	China	30	12:18	Mean 45.5	ACS 90 dB nHL 500 Hz TB	ACS 90 dB nHL 500 Hz TB	NR	9	17
Rao et al. (28)	China	40	7:33	51.36 ± 9.21	ACS 95 dB nHL 500 Hz TB	ACS 95 dB nHL 500 Hz TB	AR + NR	13	23
Fujimoto et al. (22)	Japan	99	32:67	63.0 ± 14.2	ACS 135 dB SPL 500 Hz TB	BCV 128 dB re 1 Mn 500 Hz TB	Latency + AR + NR	60	30
Tian et al. (25)	China	97	32:57[a]	NA	ACS 100 dB nHL 500 Hz TB	ACS 100 dB nHL 500 Hz TB	AR + NR	25	40
Martínez et al. (23)	Spain	67	16:51	Mean 58.06	ACS 100 dB 500 Hz TB	ACS 100 dB 500 Hz TB	AR + NR	33	41
Semmanaselvan et al. (18)	India	36	24:12	Mean 38.9	ACS 100 dB nHL 500 Hz TB	ACS 100 dB nHL 500 Hz TB	AR + NR	8	18
You et al. (29)	China	100	28:72	48.7 ± 5.8	ACS 100 dB nHL 500 Hz TB	ACS 100 dB nHL 500 Hz TB	AR + NR	44	30

BPPV, benign paroxysmal positional vertigo; VEMP, vestibular evoked myogenic potentials; cVEMP, cervical VEMP; oVEMP, ocular VEMP; NA, not available; SD, standard deviation; No., number; AR, asymmetry ratio; NR, no response; ACS, air-conducted sound; BCV, bone-conducted vibration; TB, tone bursts.

[a]eight patients with bilateral absence of cVEMP or oVEMP waveform were not included.

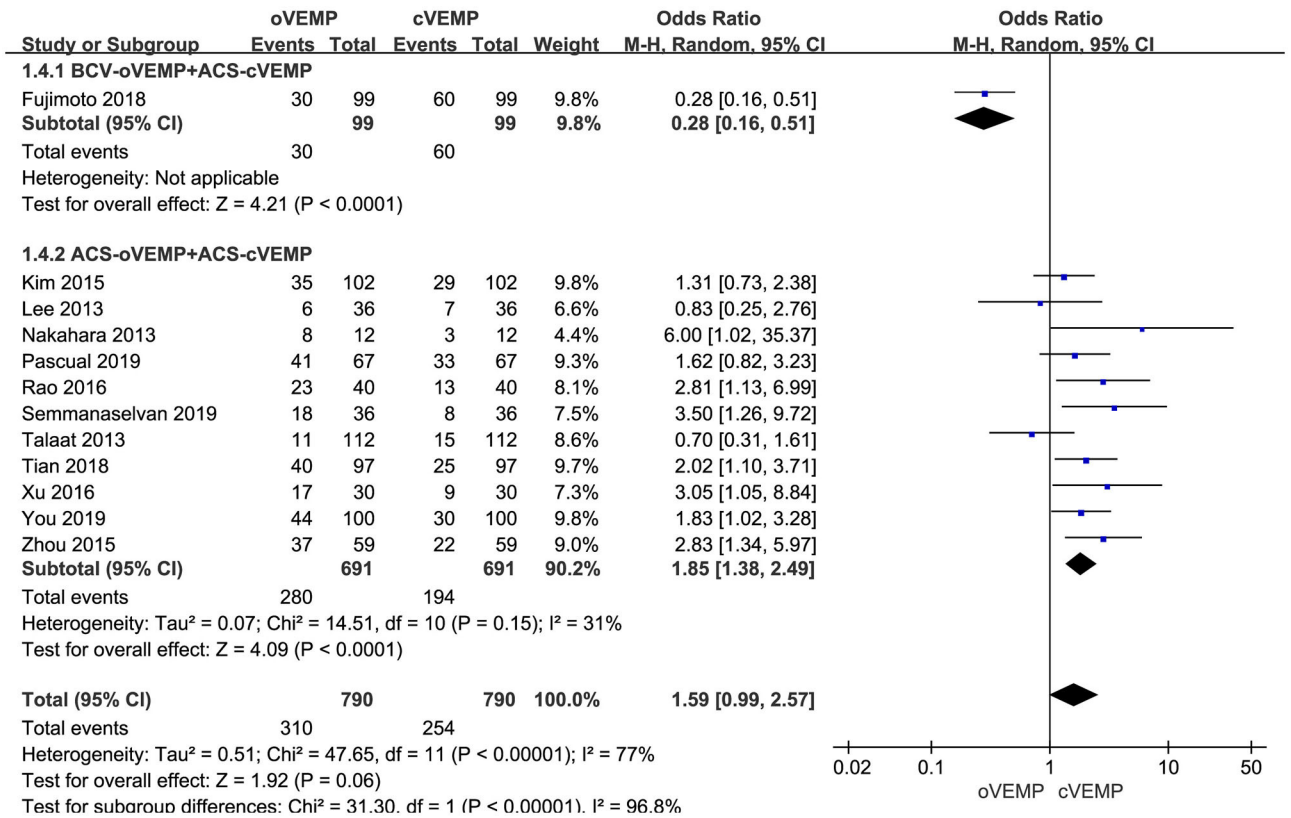

FIGURE 2 | Meta-analysis of abnormal rate of vestibular evoked myogenic potential (VEMP) in benign paroxysmal positional vertigo (BPPV) patients based on sound stimuli.

mode, and diagnostic criteria for abnormal VEMP among each study may partly account for these.

Many studies (18, 19, 25) reported that the abnormal rate was higher compared with cVEMP in BPPV patients. From these studies, we may speculate that utricular dysfunction seems to be predominant in BPPV. But the argument is still under controversy. Semmanaselvan et al. (18) reported the opposite conclusion that the abnormal rate was lower compared with cVEMP. Talaat et al. (24) found that the proportion of abnormal cVEMP (13.4%) was higher than oVEMP (9.8%) although the difference was not statistically significant. Therefore, we conducted the meta-analysis and subgroup analysis to compare the abnormal rate of oVEMP with cVEMP in BPPV, and to investigate whether utricular or saccular dysfunction may be predominant in BPPV.

According to our meta-analysis, the difference of abnormal rate between cVEMP and oVEMP in BPPV patients was not significant, but the heterogeneity was very large ($I^2 = 77\%$). ACS and BCV are the most common acoustic stimuli modes adopted for cVEMP and oVEMP testing. In sub-group analysis according to the type of sound stimuli, the abnormal rate for oVEMP presented an expressive difference in the comparison between ACS and BCV. Only one included study (22) adopted BCV oVEMP, partly resulting in heterogeneity. Besides, the more important reasons for this huge difference may be that ACS and BCV have different stimulus translation mechanisms (9). Some otolith irregular neurons only respond to BCV, so BCV could evoke larger oVEMP responses (30). In detecting oVEMP abnormalities, ACS is more sensitive than BCV, while BCV shows a higher specificity (31). Therefore, we must be cautious about comparisons between ACS oVEMP and BCV oVEMP (9). In subgroups adopting ACS cVEMP and ACS oVEMP, the abnormal rate of oVEMP was higher than cVEMP with mild heterogeneity. This may indicate that utricular dysfunction may be more frequent in BPPV. Rosengren et al. (32) found the response rate of ACS cVEMP (96%) was higher than ACS oVEMP (81%) in normal subjects. The difference in the strength of ACS cVEMP and ACS oVEMP reflex pathways may account for this phenomenon. So we should consider this phenomenon in normal subjects or adopt normal controls in the further study about otolith dysfunction of BPPV patients.

There has been no international consensus on diagnostic criteria for abnormal VEMP, and the studies included in our meta-analysis adopted three types of diagnostic criteria. There was no difference about abnormal rate between them according to subgroup analysis, but the heterogeneity was large. Besides the large heterogeneity, few studies were included in the first subgroup adopting latency and AR and NR, and the third subgroup adopting NR, so we could not come to a convincing conclusion about the comparison of abnormal rate in the first and

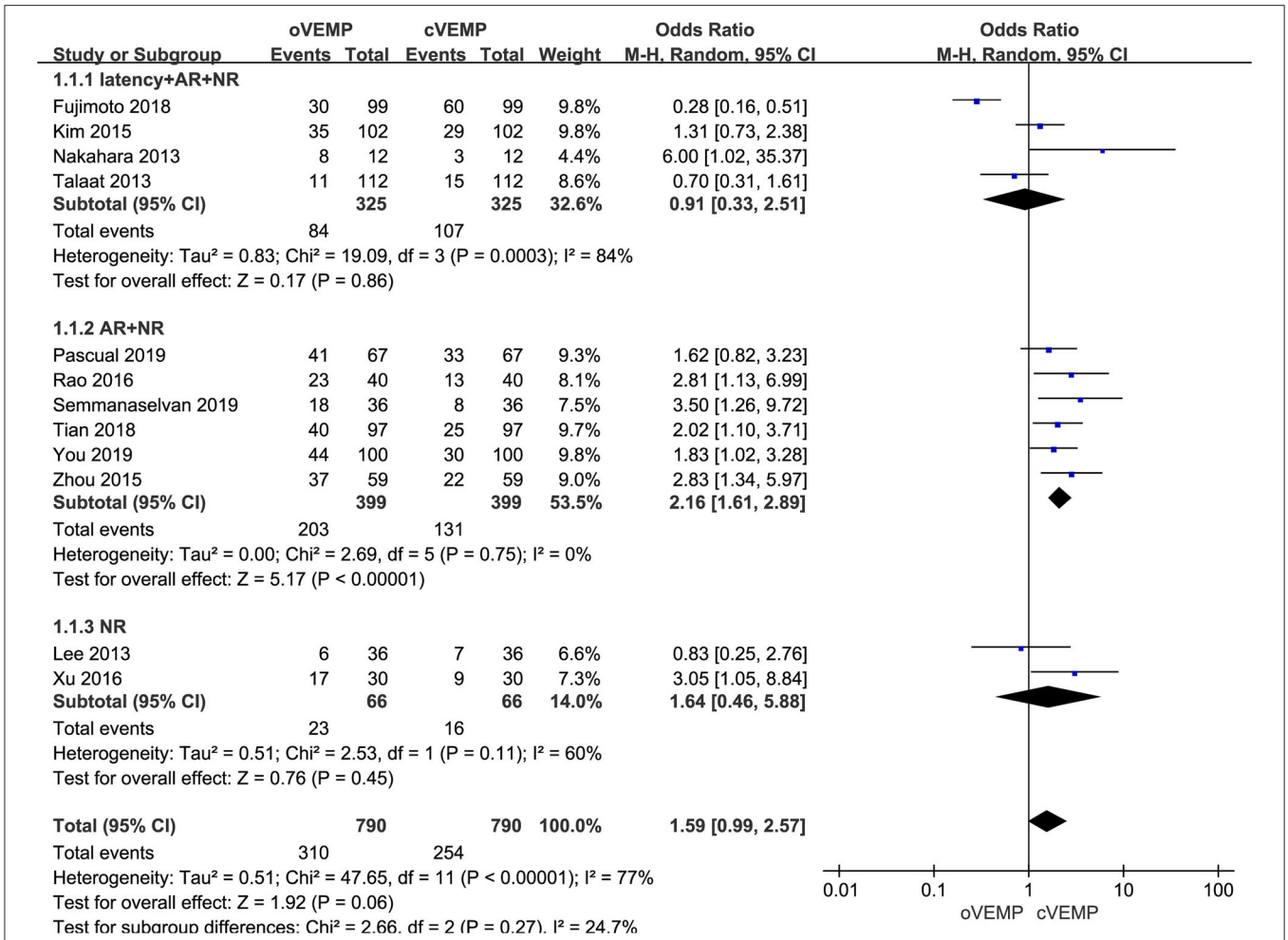

FIGURE 3 | Meta-analysis of abnormal rate of vestibular evoked myogenic potential (VEMP) in benign paroxysmal positional vertigo (BPPV) patients based on diagnostic criteria of abnormal VEMP.

third subgroups. In the second subgroup adopting AR and NR as diagnostic criteria, six studies were included, and the abnormal rate of oVEMP was higher than cVEMP with no heterogeneity. This may also suggest that utricular dysfunction may be more common in BPPV, and the studies have comparability if adopting AR and NR as diagnostic criteria. In cVEMP testing of BPPV patients, latency of p13 was prolonged regardless of the age (33). But the latency parameter of VEMP waveform is particularly affected by rise time and stimulus shape (5). Two studies used latency criteria from their own normal controls, while two studies adopted latency criteria from other researchers. These may add the heterogeneity when including latency as diagnostic criteria. We should verify the reliability of using delayed latency as diagnostic criteria in future studies with large sample and uniform parameters of VEMP testing.

A few limitations still remain be considered in our study. First of all, a part of the studies adopted different stimulation modes, such as ACS and BCV. Even if they all adopted ACS, the intensity and frequency of acoustic stimuli may have a little difference. And only one study on BCV oVEMP was included in our meta-analysis. Secondly, the different diagnostic criteria for abnormal VEMP resulted in large heterogeneity. Thirdly, the mean ages of BPPV individuals in the included articles were different from each other, and normal control group was absent. Therefore, we should conduct well-designed studies with large sample and normal control group and uniform parameters of VEMP testing to further investigate the otolith dysfunction of BPPV patients.

CONCLUSION

In oVEMP, the abnormal rate has been higher using ACS when compared to BCV, showing that BCV seems to be more specific for the evaluation of utricular dysfunction. And in studies adopting ACS cVEMP and ACS oVEMP, the abnormal rate of oVEMP was higher than cVEMP. And the abnormal rate of oVEMP in BPPV patients was also higher than cVEMP with no heterogeneity if adopting AR and NR as diagnostic criteria. It is inferred that utricular dysfunction may be more predominant

in BPPV compared with saccular dysfunction. Well-designed studies with large sample and normal control group and uniform parameters of VEMP testing should be conducted to further investigate the otolith dysfunction of BPPV patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

GC and XD contributed to the study design, statistical analysis, and manuscript draft. All authors helped to perform the analysis and to revise the manuscript with constructive discussions.

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ORIGINAL RESEARCH
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Upright BPPV Protocol: Feasibility of a New Diagnostic Paradigm for Lateral Semicircular Canal Benign Paroxysmal Positional Vertigo Compared to Standard Diagnostic Maneuvers

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Background: The diagnosis of benign paroxysmal positional vertigo (BPPV) involving the lateral semicircular canal (LSC) is traditionally entrusted to the supine head roll test, also known as supine head yaw test (SHYT), which usually allows identification of the pathologic side and BPPV form (geotropic vs. apogeotropic). Nevertheless, SHYT may not always allow easy detection of the affected canal, resulting in similar responses on both sides and intense autonomic symptoms in patients with recent onset of vertigo. The newly introduced upright head roll test (UHRT) represents a diagnostic maneuver for LSC-BPPV, supplementing the already-known head pitch test (HPT) in the sitting position. The combination of these two tests should enable clinicians to determine the precise location of debris within LSC, avoiding disturbing symptoms related to supine positionings. Therefore, we proposed the upright BPPV protocol (UBP), a test battery exclusively performed in the upright position, including the evaluation of pseudo-spontaneous nystagmus (PSN), HPT and UHRT. The purpose of this multicenter study is to determine the feasibility of UBP in the diagnosis of LSC-BPPV.

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Methods: We retrospectively reviewed the clinical data of 134 consecutive patients diagnosed with LSC-BPPV. All of them received both UBP and the complete diagnostic protocol (CDP), including the evaluation of PSN and data resulting from HPT, UHRT, seated-supine positioning test (SSPT), and SHYT.

Results: A correct diagnosis for LSC-BPPV was achieved in 95.5% of cases using exclusively the UBP, with a highly significant concordance with the CDP ($p < 0.000$, Cohen's kappa = 0.94), regardless of the time elapsed from symptom onset to diagnosis. The concordance between UBP and CDP was not impaired even when cases in which HPT and/or UHRT provided incomplete results were included ($p < 0.000$). Correct diagnosis using the supine diagnostic protocol (SDP, including SSPT + SHYT) or the sole SHYT was achieved in 85.1% of cases, with similar statistical concordance ($p < 0.000$) and weaker strength of relationship (Cohen's kappa = 0.80).

Conclusion: UBP allows correct diagnosis in LSC-BPPV from the sitting position in most cases, sparing the patient supine positionings and related symptoms. UBP could also allow clinicians to proceed directly with repositioning maneuvers from the upright position.

Keywords: BPPV, horizontal semicircular canal BPPV, upright head roll test, lateral semicircular canal BPPV, head pitch test, upright BPPV protocol

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) involving the lateral semicircular canal (LSC) is the second most common subtype of BPPV, accounting for <15% of all BPPV (1–3). It accounts for vertigo spells provoked by head position changes in the sitting and supine positions, and it is accompanied by positional and direction-changing horizontal nystagmus elicited by turning the head to either side (4, 5).

Canalolithiasis and cupulolithiasis are the most commonly accepted pathomechanisms underlying LSC-BPPV (4, 5). In canalolithiasis, free-floating otoliths within the canal can modify cupula sensitivity to accelerations, whereas in cupulolithiasis, debris are attached to the cupula overloading the cupula itself. In both cases, the cupula becomes sensitive to linear accelerations such as gravity and linear vectorial components induced by brisk head movements aligning with the plane of the involved canal (4–10).

The most widely used diagnostic test for LSC-BPPV is the supine head roll test, also named the "McClure–Pagnini maneuver" (1, 2, 11, 12), consisting of turning the patient's head 180° to either side while supine. Since it is performed along the yaw plane, it should be most properly called the "supine head yaw test" (SHYT) (13).

Depending on the direction of nystagmus evoked by SHYT, two variants of LSC-BPPV can be distinguished. In geotropic form, the paroxysmal nystagmus beats horizontally toward the undermost ear in both sides, since free-moving debris gravitate along the posterior arm of LSC toward the ampulla, thus exciting the ampullary receptor (1–13). Conversely, in an apogeotropic variant, particles can settle in the ampullary arm of the canal or adhere to the cupula, resulting in either paroxysmal or persistent nystagmus, respectively, beating toward the uppermost ear, as resulting endolymphatic displacement is ampullofugal, thus inhibiting the afferent resting firing rate (1–13).

Detection of the affected ear and involved arm is pivotal for successful repositioning. The first clinical sign used for the diagnosis of the affected side was nystagmus amplitude evoked by SHYT. In accordance with Ewald's second law, postulating that excitatory responses prevail over inhibitory outputs, the nystagmus elicited by SHYT beats with greater intensity toward the impaired ear compared to the contralateral side. Therefore, the affected side is where the nystagmus is more intense in geotropic variants, whereas the involved ear is the side where the nystagmus is weaker in apogeotropic forms (1, 2, 4–8).

Nevertheless, the diagnosis of the affected ear using the sole SHYT could be challenging, as differences in nystagmus amplitude and intensity could sometimes be hardly detected, despite the use of a video-oculography system possibly helping in this task (14). Additionally, keeping repeating SHYT could further reduce its sensitivity as nystagmus intensity may be altered by fatigability, and patients with recent onset of BPPV may experience significant discomfort and intense autonomic symptoms, potentially impeding diagnosis and treatment.

Some additional signs of laterality, listed as "secondary signs of lateralization" (14), could be sought to determine the precise location of debris in LSC-BPPV (14–28). These signs were firstly systematized into a diagnostic algorithm known as "minimum

Abbreviations: BPPV, benign paroxysmal positional vertigo; CDP, complete diagnostic protocol (PSN + HPT + UHRT + SSPT + SHYT); HPT, head pitch test; LSC, lateral semicircular canal; MSS, minimum stimulus strategy; PSN, pseudo-spontaneous nystagmus; SDP, supine diagnostic protocol (SSPT + SHYT); SHYT, supine head yaw test; SSPT, seated-supine positioning test; UBP, upright BPPV protocol (PSN + HPT + UHRT); UHRT, upright head roll test.

stimulus strategy" (MSS), with the aim to analyze changes in direction and/or intensity of the nystagmus as a function of head positions in space (13, 15, 29). MSS represents a three-step algorithm performed with the aid of video Frenzel goggles to monitor the plane and direction of the nystagmus (nystagmus-guided approach), aiming to result in the lowest discomfort possible.

It includes, as the first step, the evaluation of pseudo-spontaneous nystagmus (PSN) and nystagmus behavior during the head pitch test (HPT) performed in the sitting position. PSN is purely horizontal and differs from the direction-fixed nystagmus as its direction changes according to the head-bending angle (13, 15–18). HPT (or bow-and-lean test) consists of changing the angle between LSC and the horizontal plane by moving the patient's head along the pitch plane. During neck flexion, geotropic forms result in ampullopetal endolymphatic flows, evoking nystagmus beating toward the affected side, whereas resulting ampullofugal endolymphatic flows generate nystagmus toward the healthy ear in apogeotropic variants. Conversely, during neck extension, HPT determines reversed endolymphatic flows resulting in nystagmus beating opposite to previously reported movements (13–15, 19–22, 29).

The second step of MSS is the seated-supine positioning test (SSPT or lying-down test), consisting of bringing the patient down from the sitting to the supine positions. In LSC-BPPV, SSPT should evoke nystagmus beating toward the unaffected ear in geotropic forms and toward the opposite side in apogeotropic forms (8, 13, 15, 23–27, 29). Finally, the third and last step of MSS is SHYT. MSS is described in **Figure 1**.

The upright head roll test (UHRT) has been recently described in order to improve the diagnostic sensitivity of MSS (30). UHRT is performed in the upright position, and the patient' head is bent laterally toward one side, on the roll plane. This maneuver allows the gravity vector to move debris within LSC. Once horizontal nystagmus (either geotropic or apogeotropic) has been elicited, the head is slowly brought back to the center, and then the same procedure is repeated contralaterally (30).

UHRT has been conceived as a complementary test to HPT so that the affected side and LSC-BPPV variant could be determined from the upright position by matching nystagmus evoked by these two tests, sparing the patients troublesome symptoms.

We combined the tests performed in the upright position (PSN, HPT, and UHRT) into a new diagnostic protocol named "upright BPPV protocol" (UBP), aiming to diagnose LSC-BPPV in the sitting position, causing the least possible discomfort to patients, like MSS. UBP is described in **Figure 2**.

The aim of this study is to determine the feasibility of UBP in the diagnosis of LSC-BPPV, comparing its outcomes with those obtained using the complete diagnostic protocol (CDP) including both upright and supine tests (PSN + HPT + UHRT + SSPT + SHYT). We also compared UBP results with those achieved with the supine diagnostic protocol (SDP, consisting in SSPT + SHYT) and the sole SHYT. Moreover, we aimed to check whether the concordance of correct diagnoses provided with UBP and CDP remains high over time, when diagnostic tests may likely produce partially incomplete or unclear results, compared to diagnoses provided with either SDP or with SHYT.

MATERIALS AND METHODS

The study was conducted in eight centers from June 2019 to February 2020 and was approved by the local ethics committees (approval number for the promoter institution: 237/2020/OSS/AUSLRE). All experimental procedures were performed in accordance with the Helsinki declaration and its amendments for human experimentation. Whereas, only one otoneurologist in each center was involved in patients' assessment and data collection, overall data were then analyzed by specialists of all 20 different institutions involved.

Study Design

Chart review of adult patients diagnosed with LSC-BPPV was carried out. All patients enrolled in the study were evaluated with monocular or binocular video Frenzel goggles with a three-step diagnostic test battery according to the following order:

1. UBP: PSN, HPT, and UHRT
2. SSPT
3. SHYT

Collected clinical data included patient's personal information, time elapsed from symptom onset, direction of nystagmus observed during each maneuver, final diagnosis, and treatment performed with corresponding outcome.

Patients presenting with multiple semicircular canal involvement, with atypical forms of LSC-BPPV (i.e., canalith jam) or with coexistent vestibular disorders other than BPPV were excluded, as well as patients whose clinical chart was incomplete.

One hundred and thirty-four consecutive patients diagnosed with LSC-BPPV at different onset times were finally included in the study. Demographic data are summarized in **Table 1**. All data were systematically entered into a Microsoft Excel sheet (Microsoft Corporation, Redmond, Washington) shared by all centers involved in the study. Data were then collected and processed for statistical analysis.

Upright BPPV Protocol

The first step in UBP was the detection of PSN, defined as a horizontal long-lasting, non-paroxysmal nystagmus observed with the patient in the sitting position, with his head in axis with his body, so that LSC is 30° inclined with respect to the horizontal plane (upright position). If detectable, PSN direction was reported.

The second step consisted of observing nystagmus patterns during HPT. This maneuver was performed by slowly bending the patient's head 60° forward and then 30° backward with respect to the horizontal plane. The head was held still up to 30 s in both positions until nystagmus appears. In LSC-BPPV, the nystagmus elicited by HPT is purely horizontal and changes direction according to head positions. The direction of the nystagmus was recorded in both positions. HPT was classified as negative (if no nystagmus was detected), positive incomplete (if nystagmus was observed in only one position), and positive complete (if nystagmus was evoked in both positions).

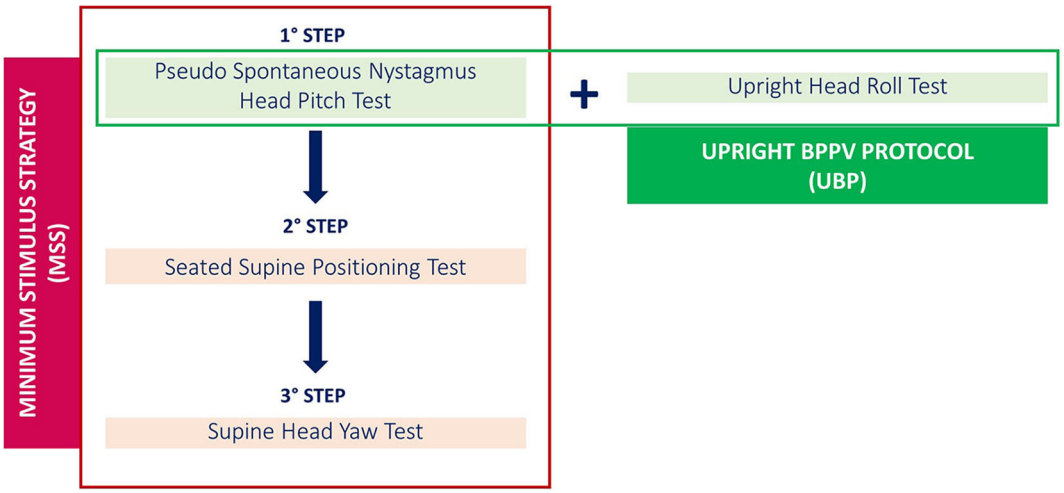

FIGURE 1 | Diagnostic algorithm for LSC-BPPV: minimum stimulus strategy (MSS) and upright BPPV protocol (UBP).

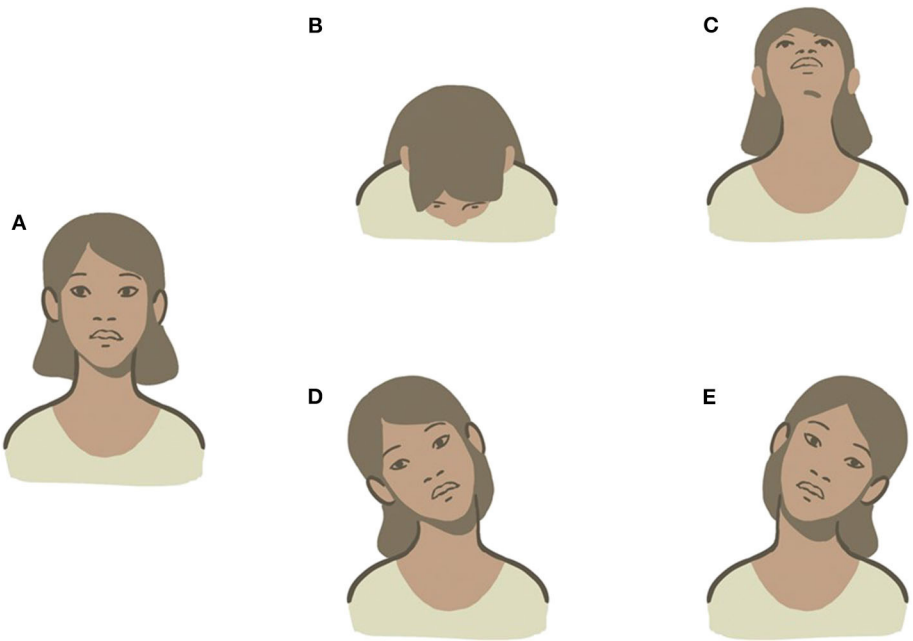

FIGURE 2 | UBP for BPPV-LSC. **(A)** Detection of pseudo-spontaneous nystagmus (PSN). **(B)** Head pitch test (HPT) with forward head bending. **(C)** HPT with backward head bending. **(D)** Upright head roll test (UHRT) with rightward head tilting. **(E)** UHRT with leftward head tilting.

UHRT represented the third step in UBP. First, the head of the patient was slowly bent about 30° laterally toward one side, in the roll plane, bringing the patient's ear closer to the shoulder on the same side. The head was held still up to 30 s in this position until nystagmus appears. Then, the head was slowly brought back to the center and held upright for an additional 30 s, to allow the resulting endolymphatic flows to restore. Thereafter, the same maneuver was performed toward the contralateral side. The direction of the nystagmus was recorded in both positions. UHRT was classified as negative (if no nystagmus was detected), positive incomplete (in case it was recorded in only one side), and positive complete (if it was detected in both sides). UBP is described in **Figure 2**.

SSPT

SSPT was performed quickly by bringing the patient from the sitting to the supine position and observing the resulting nystagmus. If nystagmus could be detected, its direction was recorded, indicating whether it was in accordance with the nystagmus evoked by SHYT.

TABLE 1 | Demographic data.

	Age	Onset time		Side		Geotropic forms	Apogeotropic forms
62 Males (46.26%)	56.82 ± 14.46 (range: 25–89)	<48 h	21 (15.67%)	Right	33 (26.62%)	21 (15.67%)	12 (8.95%)
		2–7 days	23 (17.16%)				
		>7 days	18 (13.43%)	Left	29 (21.64%)	20 (14.92%)	9 (6.71%)
72 Females (53.73%)	57.04 ± 15.58 (range: 22–85)	<48 h	20 (14.92%)	Right	39 (29.10%)	22 (16.41%)	17 (12.68%)
		2–7 days	34 (25.37%)				
		>7 days	18 (13.43%)	Left	33 (26.64%)	17 (12.68%)	16 (11.94%)
	56.94 ± 15.01 (range: 22–89)				134 (100%)	80 (59.70%)	54 (40.29%)

SHYT

SHYT was performed by turning the patient's head 180° to either side while supine. The direction of the nystagmus, either geotropic or apogeotropic, was recorded, specifying on which side the nystagmus was greater if asymmetry between positionings could be detected.

LSC-BPPV Treatment and Outcome

Several therapeutic strategies were adopted for LSC-BPPV with significant differences among different institutions. All therapeutic techniques performed in each patient were recorded and sorted according to the order of execution.

Therapeutic outcome was assessed by SHYT in the same session, 10–30 min after physical therapy or during a follow-up examination after 24–72 h, depending on protocols in use in the different centers and on patients' compliance. Outcomes were classified into resolution, resolution following conversion, failure, and unknown.

LSC-BPPV was considered as resolved if no nystagmus was evoked at the last follow-up SHYT, specifying whether a conversion in another form of BPPV occurred before resolution (i.e., conversion from apogeotropic to geotropic forms of LSC-BPPV or from LSC-BPPV to posterior semicircular canalolithiasis). Persistence of positional nystagmus at the second follow-up evaluation was classified as treatment failure. Outcome was classified as unknown if the patient did not attend the follow-up examination.

Statistical Analysis

Continuously distributed variables were described by median, mean, and SD; categorical variables were described by frequencies and percentages.

A chi-square test and Cohen's kappa statistics were performed to compare concordance between different protocols results. Thresholds of significance level were set to 0.05. Analyses have been processed using Sklearn, SciPy, and Pandas libraries in Python code (Python Software Foundation).

RESULTS

Clinical charts from 134 patients (62 males, 72 females, age: 22–89 years, mean 56.94 ± 15.01 years) with LSC-BPPV were considered for this study.

The time between symptom onset and diagnosis was <48 h in 41 patients (30.59%), ranged from 2 to 7 days in 57 cases (42.53%), and exceeded 7 days in 36 cases (28.86%), without significant differences according to age, involved ear, and LSC-BPPV form.

CDP was considered as reference for diagnosis (gold standard). The right side was involved in 72 cases (53.73%); canaliths were located in the non-ampullary arm of LSC in 43 cases (59.72%), whereas otoconial debris were in the ampullary arm in the remainder (40.27%). The left ear was affected in 62 patients (46.26%); geotropic forms were diagnosed in 37 cases (59.67%) and apogeotropic variants in 25 cases (40.32%). No differences were observed according to age, gender, and onset time.

PSN could not be detected in 63 cases (47.01%), whereas it always matched with the nystagmus detected in HPT with backward head bending in the remaining cases. HPT was classified as positive complete in 93 cases and positive incomplete in 35 (69.4 and 26.11%, respectively), whereas no nystagmus was detected in six subjects (4.47%). UHRT was positive in 133 (99.25%) cases (27 positive incomplete, 20.14%). Either UHRT or HPT was positive but incomplete in 50 cases (37.31%), while in 12 cases (8.85%), both tests were classified as positive incomplete, without statistical differences for age, gender, and affected side.

Associations between onset time and presence/absence of PSN and positivity for both HPT and UHRT tests were evaluated, but no statistically significant results were achieved. Only detectable PSN and onset time analysis achieved a significant p-value (0.014), but the strength of association was extremely weak (Cramer's $V = 0.0637$).

Nystagmus was observed with SSPT in 109 patients (81.34%), whereas this test was negative in 25 (18.65%) subjects, mostly presenting with apogeotropic forms (76%, $p < 0.001$).

TABLE 2 | Concordance between complete diagnostic protocol (CDP) and upright BPPV protocol (UBP) with positive incomplete outcomes of head pitch test (HPT) and upright head roll test (UHRT).

Cases	No. of cases	% concordance	Chi-square test	*p*-value	Cohen's kappa
Incomplete HPT	35	100.0%	105.0	<0.000	1.000
Incomplete UHRT	27	96.3%	81.0	<0.000	0.947
HPT and UHRT both incomplete	12	100.0%	36.0	<0.000	1.000

Furthermore, in five patients (4.48%), the direction of nystagmus did not comply with the nystagmus evoked by SHYT.

SHYT allowed diagnosis in 116 patients (86.56%), whereas in 18 (13.43%), it only allowed identification of the LSC-BPPV form despite failing to detect the affected side. Diagnosis was mainly missing in cases with apogeotropic variants (16 cases, 88.88%, $p < 0.001$). There were no statistically significant differences for age, gender, and involved side.

UBP protocols led to the same diagnosis obtained using CDP in 128 patients (95.5%). Statistical concordance between these protocols was significant ($p < 0.000$), as shown by high values of chi-square (376.4) and Cohen's kappa (0.94). CDP and UBP continued to show statistically significant concordant diagnosis even when analyzing cases in which HPT and UHRT provided positive incomplete outcomes, as shown in **Table 2**.

Similar outcomes could be found when comparing CDP and SDP outcomes, despite a weaker strength of relationship. CDP and SDP protocols provided identical diagnosis in 85.1% of cases (114 on 134), with statistically significant concordance (chi-square = 339.0, Cohen's kappa = 0.84, $p < 0.000$).

SHYT provided statistically significant concordant results ($p < 0.000$) with CDP (85.1% of cases), not lower than the results obtained using SDP.

In our series, 119 patients (88.80%) were successfully treated within two sessions with physical therapy. In 26 of them (21.84%), LSC-BPPV was converted into another BPPV form before resolution, whereas two patients (1.49%) did not attend the scheduled follow-up evaluation and therapeutic outcome was not assessed. In 13 subjects (9.70%) LSC-BPPV was not resolved within two sessions, and these cases were classified as "treatment failure." Among them, the apogeotropic form was diagnosed in 12 cases (92.03%).

The canalith repositioning procedure according to Gufoni et al. (31) was the most frequently used technique as first-line therapy, being applied in 65 patients presenting with geotropic variants (81.25%) and in 32 with apogeotropic variants (59.25%).

DISCUSSION

All tests proposed for the diagnosis of BPPV, regardless of the involved canal, are based on head movements on different planes of the space. With head movement, otoconial debris can gravitate within the semicircular canals, eliciting ocular movements or modifying underlying ongoing nystagmus. In light of the above, diagnostic tests can be properly described according to the axis around which the head moves and to patients' position (upright or supine).

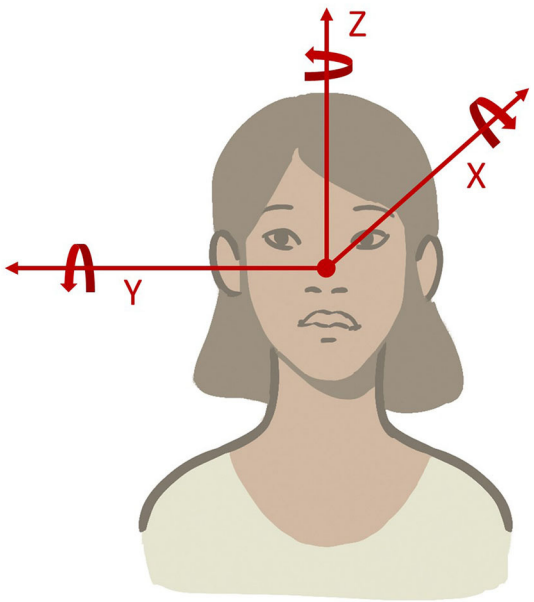

FIGURE 3 | Schematic overview of head rotations along three axes (X, Y, and Z). Axes are defined relative to the person, not to gravity.

The head can rotate around the X (roll), Y (pitch), and Z (yaw) axes originating at the intersection of the midsagittal plane with the interocular axis (the nasion) (**Figure 3**). Consequently, the following head movements were found:

a) Head movements in the yaw plane (i.e., around the rostral-caudal, yaw, or z-axis) are horizontal.
b) Head movements in the pitch plane (i.e., around the inter-aural, pitch, or y-axis) are vertical.
c) Head movements in the roll plane (i.e., around the naso-occipital, roll, or x-axis) are torsional.

Rotations around these axes can be performed slowly or rapidly. In the first case, debris are moved only by gravity, whereas inertia of otoconial fragments adds up to the gravitational vector if movements are brisk.

Diagnosis of LSC-BPPV is traditionally based on the features of nystagmus elicited by SHYT, which is performed in the supine position and evokes a direction-changing horizontal nystagmus according to head rotations around the z-axis. The nystagmus herein elicited may be paroxysmal or persistent, beating toward the ground (geotropic) or in the opposite direction (apogeotropic). The nystagmus direction suggests the

position of debris that may settle in the short arm, close to the cupula, or freely float in the non-ampullary arm. Diagnosis of the involved side (lateralization) can be achieved by comparing the intensity of the nystagmus evoked on each side. Nevertheless, determining the affected ear based on Ewald's second law and related asymmetrical outputs may be challenging in clinical practice, mostly because the intensity and amplitude of eye movements may be symmetrical. Our data showed that SHYT is unable to determine the involved side in 13.43% of patients, consistent with other studies aiming to define accuracy of lateralization in LSC-BPPV (14, 32).

In our study, most patients with non-diagnostic SHYT were affected by apogeotropic forms, exhibiting small-amplitude direction-changing nystagmus leading to hardly comparable responses on either side. This finding matched with the mathematical model proposed by Squires et al. suggesting that canalithiasis represents a mechanism likely stronger than cupulolithiasis in deflecting ampullary cupula. Therefore, a bigger amount of debris or larger otoconia is necessary to produce the same nystagmus intensity in cupulolithiasis as that in canalithiasis (33, 34).

Although sensitivity of SHYT may be improved using a video-oculography system, this technology is not always available in clinical practice. On the other hand, repeating the test to confirm the diagnosis may result in impaired paroxysmal nystagmus due to fatigue response and significant discomfort for patients with acute vertigo and intense autonomic symptoms (14, 29).

However, other findings may provide clues to determine the affected ear in LSC-BPPV without comparing intensities of direction-changing positional nystagmus with SHYT. PSN represents the easiest finding among secondary signs of lateralization as it can be observed directly in the neutral sitting position (14–19, 29). In fact, LSC acts as an inclined surface drawing a 30° front-open-angle with the horizontal plane, allowing otoconial debris to move along the canal (in canalolithiasis) or resulting in a persistent cupular displacement (in cupulolithiasis). Therefore, PSN, when detectable, is directed to the healthy side in geotropic forms and to the affected side in apogeotropic variants (13, 15–18). Although its pathophysiology is not yet fully understood, a long-lasting course of PSN elicited in both cases has been supposed to result from the action of different forces exhibiting similar amplitudes though acting in opposite directions on the otolith mass: gravity, which moves otoliths along the LSC, balanced by fluid viscosity and endolymphatic friction (15).

In our series, PSN was detectable in 53.09% of cases, mostly among patients with recent onset of symptoms. This finding suggested that disaggregation of the original, heavy otoconial cluster represents a time-dependent phenomenon occurring spontaneously and resulting in dispersion of several fragments. Therefore, otoconial debris dispersed along the canal and, adherent to walls of membranous canals, could become "silent" over time, namely, unable to induce cupular deflection in the absence of head movements (34).

Changes in PSN direction occur when performing HPT, consisting of neck flexion and extension. PSN usually disappears by bending the head 30° forward as LSC reaches a neutral position, almost parallel to the ground. Bending the head further 30° forward results in an ampullopetal endolymphatic flow in geotropic forms, accounting for nystagmus toward the affected side while accounting for an ampullofugal flow in apogeotropic BPPV, resulting in nystagmus toward the healthy side. An opposite endolymphatic flow could be obtained by bending the head 60° backward, resulting in a horizontal nystagmus toward the healthy side in geotropic forms and toward the affected side in apogeotropic variants (14, 15, 20–22, 29).

Our data show that the nystagmus evoked by HPT represents an almost constant finding, providing highly reliable information for lateralization. However, HPT alone does not allow clinicians to identify which LSC and canal arm are involved. Nevertheless, it allows us to restrict the diagnostic hypotheses to only two options: the geotropic variant of one side or apogeotropic variant involving the opposite LSC (30).

Considering a hypothetical case with LSC-BPPV as a practical example, evaluation of a patient in the upright position presenting with left-beating horizontal PSN can be assumed. When the patient's head is bent forward, the nystagmus first disappears and then reverses, becoming right beating. Moreover, when the head is bent backward, the nystagmus changes its direction returning to being left beating. In this case, only two options are possible: right geotropic LSC-BPPV or left apogeotropic LSC-BPPV.

Although it has been described how the evaluation of nystagmus intensity by moving the head on the pitch plane might distinguish geotropic from apogeotropic forms, identification of otolith location with only HPT is challenging in most cases (22).

Nystagmus evoked by UHRT appeared as a reliable lateralization sign in almost all cases, so that CDP and UBP protocols led to the same diagnosis in 95.5% of cases with extremely high levels of concordance, even higher than those achieved by SDP and SHYT alone. In UBP, indeed, UHRT is performed sequentially after HPT, aiming to complete the diagnostic workup in the sitting position, by simply tilting the patient's head sideways along the roll plane and observing the direction of nystagmus (geotropism) (30).

Considering the above-mentioned example, if left-beating nystagmus (apogeotropic) is elicited by tilting the head toward the right, debris can be easily localized within the ampullary arm of left LSC, consistent with left apogeotropic LSC-BPPV. When the patient's head is tilted toward the contralateral side, apogeotropic nystagmus (right beating) could be likely evoked again, thus confirming the diagnostic hypothesis (**Supplementary Video 1**). On the contrary, if geotropic nystagmus is elicited with UHRT on either side, otoliths should be considered as settling in the non-ampullary arm of the right LSC, thus allowing us to diagnose right geotropic LSC-BPPV (**Supplementary Video 2**). Other examples of LSC-BPPV diagnosed using UBP are reported in **Supplementary Videos 3**, **4**. **Figures 4**–**7** summarize how the nystagmus direction changes in relation to head positions with UBP in all possible four scenarios.

Although a first algorithm for nystagmus evaluation in the upright position was proposed by Frenzel (35), the use of tests in the sitting position for the diagnosis of BPPV is not

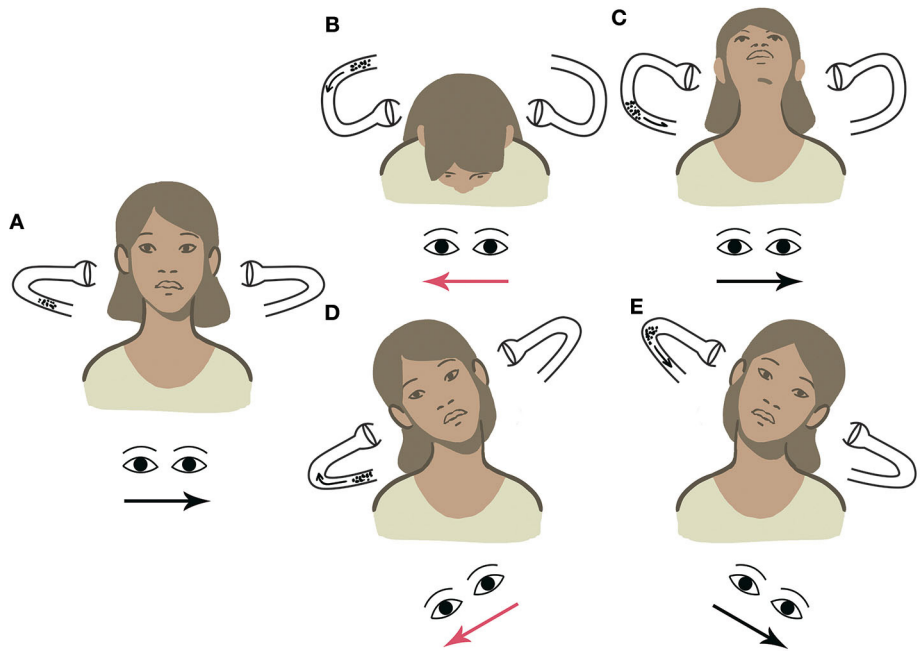

FIGURE 4 | UBP for right geotropic LSC-BPPV. Arrows within the canal represent the direction of endolymphatic flows, whereas arrows beneath the eyes represent the direction of the fast phase of nystagmus. Right-beating nystagmus is represented in red. **(A)** PSN: left beating. **(B)** HPT with forward head bending: right-beating nystagmus. **(C)** HPT with backward head bending: left-beating nystagmus. **(D)** UHRT with rightward head tilt: right-beating geotropic nystagmus. **(E)** UHRT with leftward head tilt: left-beating geotropic nystagmus.

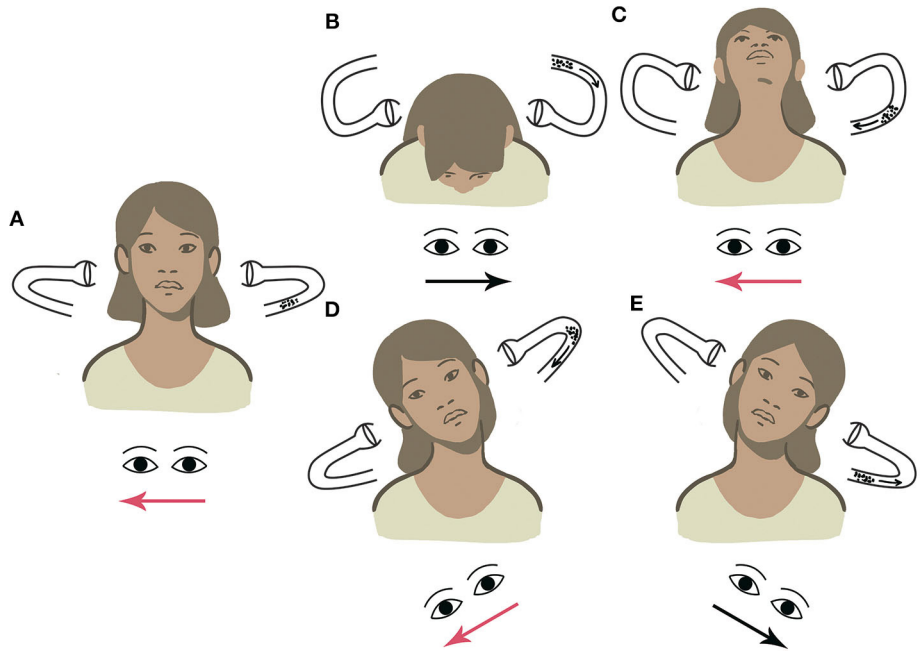

FIGURE 5 | UBP for left geotropic LSC-BPPV. **(A)** PSN: right beating. **(B)** HPT with forward head bending: left-beating nystagmus. **(C)** HPT with backward head bending: right-beating nystagmus. **(D)** UHRT with rightward head tilt: right-beating geotropic nystagmus. **(E)** UHRT with leftward head tilt: left-beating geotropic nystagmus.

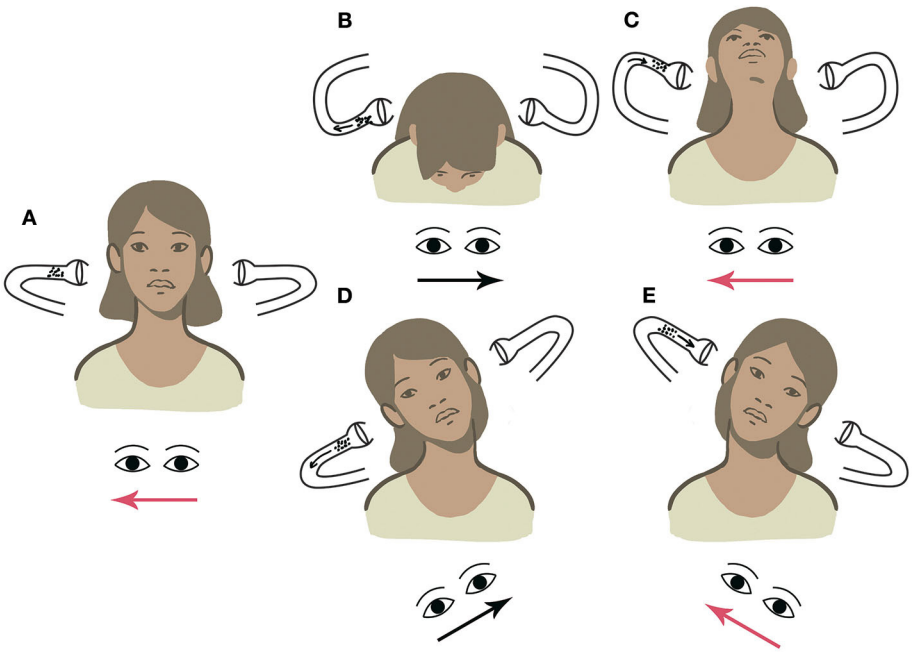

FIGURE 6 | UBP for right apogeotropic LSC-BPPV. **(A)** PSN: right beating. **(B)** HPT with forward head bending: left-beating nystagmus. **(C)** HPT with backward head bending: right-beating nystagmus. **(D)** UHRT with rightward head tilt: left-beating apogeotropic nystagmus. **(E)** UHRT with leftward head tilt: right-beating apogeotropic nystagmus.

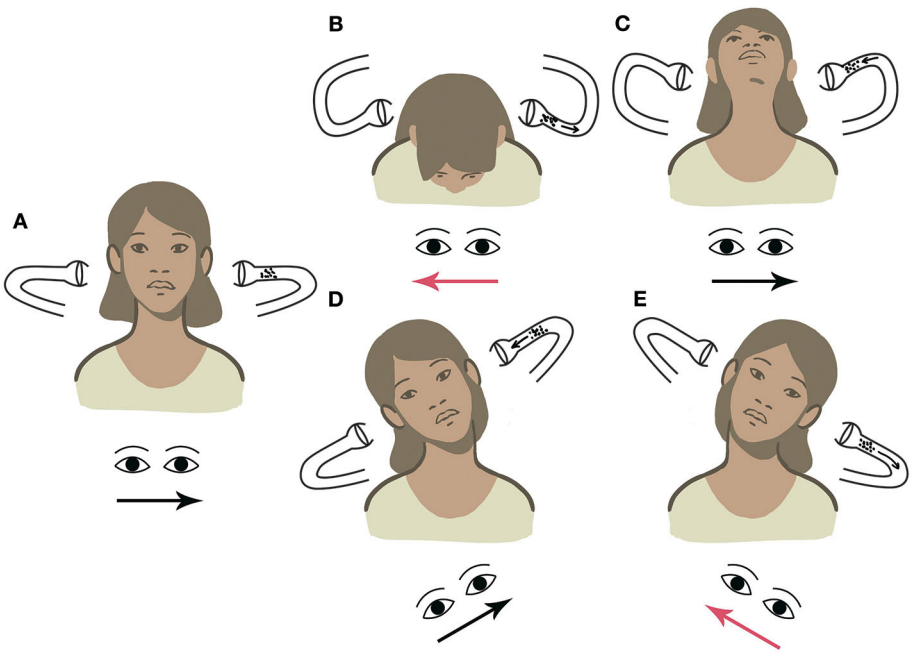

FIGURE 7 | UBP for left apogeotropic LSC-BPPV. **(A)** PSN: left beating. **(B)** HPT with forward head bending: right-beating nystagmus. **(C)** HPT with backward head bending: left-beating nystagmus. **(D)** UHRT with rightward head tilt: left-beating apogeotropic nystagmus. **(E)** UHRT with leftward head tilt: right-beating apogeotropic nystagmus.

widespread among clinicians. However, the opportunity to define the side and form of LSC-BPPV by only relying on maneuvers in the upright position may improve the tolerability of the diagnostic workup for patients, especially in the acute stage of the disease when they could be particularly susceptible to rotational movements and accelerations. Furthermore, UBP could also

result in a less time-consuming management of LSC-BPPV as patients can directly receive appropriate treatment from the upright position, immediately after diagnosis. The repositioning procedure proposed by Gufoni, which was the treatment of choice in our series, starts indeed with the patient in the sitting position with his legs out of the examination couch (31).

Although simple and easy to perform, UBP may be challenging in patients with reduced cervical range of motion, similar to other maneuvers for BPPV (36). Nevertheless, should the patient exhibit difficulties in head extension/flexion or in lateral tilting due to neck stiffness, his whole trunk may be slightly bent about 30° along the pitch or the roll planes to attain the same head positions with respect to gravity, keeping the diagnostic value of UBP unchanged (30).

As often observed in our series, UBP may produce incomplete responses since several factors could determine the lack of nystagmus during upright tests. In physiological conditions, the most relevant factors affecting detection of nystagmus during diagnostic maneuvers for BPPV are the plane aligning with the movement performed, imprinted accelerations, otolith size, and location. In fact, whereas larger fragments should float more quickly within the endolymph, producing more intense nystagmus than small-sized debris, interactions between canaliths and canal walls could also likely account for the considerable variability in duration and latency of nystagmus, assuming that debris settling closer to canal walls should result in less intense endolymphatic flows and nystagmus (33, 34). Then, the same diagnostic test could result in different outcomes according to the features of otoconial cluster, thus evoking weaker and long-latency nystagmus if small particles are dispersed along the canal walls, while accounting for more intense and prompt nystagmus if a single clumped stone floats in the canal lumen.

Although both HPT and UHRT, unlike SHYT, have been conceived for exploiting gravity to move otoconial fragments along LSC and elicit nystagmus, the sole gravitational vector may not be effective enough to displace the cupula in each position during UBP. Conversely, angular accelerations used in SHYT may likely break canal wall interactions mobilizing canaliths, thus explaining the reason that this test results in detectable nystagmus in most LSC-BPPV (33, 34).

Should nystagmus be missing at the upright tests, clinicians may increase UBP sensitivity by imparting slight accelerations to the patient's head by moving it quickly from a position to the other along the roll or the pitch plane. This way, inertial forces will likely help the gravity vector to generate endolymphatic flows, resulting in detectable nystagmus (30).

Nevertheless, according to our findings, proper diagnosis of LSC-BPPV could be achieved even if UBP test battery gives incomplete results, as shown in **Supplementary Video 4**. Theoretically, even if PSN was not detected, the side and form of LSC-BPPV could still be properly identified with at least only one nystagmus evoked each by HPT and UHRT.

Since nystagmus resulting from HPT and UHRT are often weak, the major limitation of UBP is differentiating BPPV subtypes with paroxysmal nystagmus (canalolithiasis) from variants with persistent nystagmus (cupulolithiasis). This aspect may be relevant in cases with direction-changing positional nystagmus due to central disorders mimicking BPPV, such as vestibular migraine (37, 38). Therefore, if clear nystagmus is not observed at least in one position for HPT and UHRT or in cases with atypical clinical history, diagnostic tests in the supine position are strongly recommended.

In addition to SHYT, SSPT was described to contribute to lateralization according to LSC geometry, as the canal plane changes alignment from about horizontal to vertical when the head moves from the sitting to supine positions. In apogeotropic variants, debris in the short arm of LSC cause ampullopetal deflection resulting in horizontal nystagmus toward the affected side. Conversely, in geotropic forms, canaliths within the non-ampullary arm move away from the cupula, eliciting an ampullofugal deflection and nystagmus toward the healthy side (26, 27).

Although SSPT may help clinicians to discriminate the involved ear, its sensitivity appears controversial (26, 39). Accordingly, in our series, this test did not lead to nystagmus in 18.65% of patients, and its lateralization rates were significantly lower in apogeotropic cases compared to geotropic forms. As discussed previously, these findings may be explained by the lower responsivity of LSC when otoconial matter is located in the short arm. Nevertheless, in our series, upright tests were scheduled as first tests according to the protocol (hence performed prior to supine maneuvers) and might have impaired SSPT sensitivity by dispersing canaliths along canals and reducing their "piston action" on the ampullary cupula (40). Finally, in our study, SDP and SHYT alone provided the same diagnostic concordance with CDP, indicating the limited role of SSPT in defining the diagnosis for LSC-BPPV.

Being a retrospective multicenter study, conclusions of our analysis present important limitations. They mainly include that it is not possible to ensure that observation of nystagmus has always been performed under the same conditions across all involved institutions, although only one otoneurologist in each center was involved in patients' assessment and data collection. Therefore, our data need to be confirmed by further studies with a prospective design and a common protocol shared by a larger amount of centers including larger cohorts.

CONCLUSIONS

According to our results, LSC-BPPV diagnosis can be obtained in the sitting position with upright diagnostic tests. Furthermore, UBP is a reliable algorithm to diagnose LSC-BPPV, and our detailed explanation of maneuvers proves that this study can be reproduced without difficulty. Then, in line with MMS principles, UBP can likely spare patients unpleasant maneuvers, allowing clinicians to proceed immediately with proper physical treatment. Nevertheless, SHYT is still required if oculomotor findings in the upright position are lacking or unclearly detectable or in cases where other vestibular disorders may mimic LSC-BPPV presenting with direction-changing positional nystagmus.

Further investigations following a prospective study, involving more centers, and including lager cohorts will be needed to

determine the sensitivity of UBP in detecting otolith location in LSC-BPPV.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Area Vasta Nord Emilia Romagna Institutional Review Committee (approval number: 237/2020/OSS/AUSLRE). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SM, PM, and AC led the conception of the study, conducted most data acquisition and interpretation, and made significant contributions to the writing and editing of the manuscript, they are designated co-first authors for this study. RP, VM, ASc, GA, and GAL equally contributed in data acquisition. SM conducted data analysis and creation of figures. BG, MR, VM, and GAL were involved in manuscript editing and review. All authors involved equally contributed to data interpretation and manuscript review, and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.578305/full#supplementary-material

Supplementary Video 1 | UBP for left apogeotropic LSC-BPPV.

Supplementary Video 2 | UBP for right geotropic LSC-BPPV.

Supplementary Video 3 | UBP for right apogeotropic LSC-BPPV.

Supplementary Video 4 | UBP for left geotropic LSC-BPPV.

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Low Antioxidant Status of Serum Uric Acid, Bilirubin, Albumin, and Creatinine in Patients With Benign Paroxysmal Positional Vertigo

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Objective: To investigate the roles of serum uric acid (UA), bilirubin (BIL), albumin (ALB), and creatinine (CRE) as major intravascular antioxidants, in benign paroxysmal positional vertigo (BPPV).

Methods: The serum levels of UA, BIL, ALB, and CRE were retrospectively analyzed in 70 patients with new-onset idiopathic BPPV and 140 age- and sex-matched healthy controls (HCs).

Results: Serum UA, BIL, ALB, and CRE levels were significantly lower in the BPPV group than the HC group. Furthermore, serum levels of BIL and ALB were significantly lower in the BPPV group when compared by sex. Multiple stepwise logistic regression revealed that a reduction in serum ALB was independently related to BPPV (odds ratio = 0.688; 95% confidence interval = 0.607– 0.780). Receiver operating characteristic analyses revealed a cut-off value of 45.15 g/L for ALB with a sensitivity of 74.29% (62.97– 83.07%) and specificity of 73.57% (65.71– 80.18%).

Conclusions: Serum levels of UA, BIL, ALB, and CRE were lower in BPPV patients, indicating a lower antioxidant status. Furthermore, a reduction in serum ALB was independently associated with BPPV. These results provide insights into the possible roles of oxidative stress in the pathogenesis of BPPV.

Keywords: benign paroxysmal positional vertigo, antioxidant status, uric acid, bilirubin, albumin, creatinine

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV), characterized by dizziness and vertigo, has a lifetime prevalence of more than 2.4% (1). The cause of BPPV is the detachment of otoconia (calcium carbonate crystals) that either float in the semicircular canal or attach to the cupule (2). However, at present, there are limited methods and techniques available to evaluate the condition of semicircular canals and vestibules, and the physiopathological explanations of BPPV are mainly speculative. Although most recover after positional maneuvers, up to 2/3 of patients may experience chronic, obstructive instability, dizziness, and discomfort, also known as residual dizziness (3). Meanwhile, the relapse rate of BPPV in the elderly is reportedly 23.5–50% (4). Hence, further studies of the mechanism underlying the onset of BPPV could provide new and efficient treatment regimens for residual dizziness and to decrease the recurrence rate.

It has been reported that Meniere's disease (MD) may be a systemic oxidative disorder, in which excessive free radicals and oxidative stress promote microvascular damage and participate in the development of endolymphedema (5). Recent studies have shown that some of the symptoms of BPPV are similar to those of MD and can occur at any stage, including the age of onset (6). Although it is attractive to speculate that oxidative stress plays a major role in pathogenesis of BPPV, there are few validated blood markers of the antioxidant status of BPPV.

Current evidence suggests that serum uric acid (UA), bilirubin (BIL), albumin (ALB), and creatinine (CRE) are the main non-enzymatic antioxidants in human plasma, accounting for 85% of the total antioxidant capacity (7). UA is a naturally occurring product of purine metabolism and is known as a strong scavenger of peroxynitrite. UA can exert protective antioxidant effects, inhibit inflammatory cascades, reduce blood–brain barrier permeability, and protect central nervous tissue (8). BIL was previously considered as a fat-soluble metabolite with only slight cytotoxicity, but recent studies have found that BIL is a natural antioxidant with strong antioxidant activity and an endogenous scavenger of reactive oxygen species (ROS) (8). CRE is a metabolite of creatine phosphate, which exists in skeletal muscle and is one of the components of total antioxidant determination (9). ALB is the main antioxidant molecule in extracellular fluid and can remove ROS and reactive nitrogen species (RNS) produced by various reactions (10). The serum levels of these markers can be used to predict whether oxidative stress is involved in the pathology of BPPV.

ALB and CRE levels are lower in patients with BPPV as compared to healthy controls (HCs) (11, 12). However, in BPPV, the exact relationship between UA and BPPV remains controversial (13), while that between BIL and BPPV remains unknown. Overall, previous studies have failed to comprehensively investigate the significance of these four markers (UA, BIL, ALB, and CRE) of antioxidant status in BPPV.

Therefore, the aims of the present study were to (1) test the hypothesis that serum levels of UA, BIL, ALB, and CRE are low in patients with BPPV, and (2) determine if any of these markers are protective factors in BPPV.

MATERIALS AND METHODS

Participants

The study cohort consisted of 210 people, including 70 patients with idiopathic BPPV recruited from the Neurology Department and 140 sex- and age-matched HCs recruited from the Physical Examination Center at our hospital from January 1, 2015 to December 31, 2018.

Inclusion and Exclusion Criteria

The diagnosis of BPPV was based on a typical history of recurrent, brief attacks of positional vertigo and positioning tests, such as the Dix-Hallpike test or roll test (2). Only patients with new-onset idiopathic BPPV were include in this study. All patients with BPPV underwent canalith repositioning maneuvers of the affected semicircular canal. Moreover, for all BPPV patients, a thorough medical history was obtained and neurological testing was performed.

The exclusion criteria were as follows: (1) hospitalization for more than 48 h after vertigo; (2) secondary factors, such as a history of head trauma and vestibular neuritis; (3) pre-existing chronic instability at the onset of BPPV; (4) severe cardiovascular disease, central nervous system disease, parathyroid dysfunction, or thyroid disease; (5) severe renal and/or hepatic impairment; (6) hypertension and/or diabetes; and (7) current infection.

Measures

Serum levels of UA, ALB, CRE, and total BIL (TBIL) were measured using a Hitachi LST008 analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan) after 8–10 h of fasting during the first 48 h after the onset of BPPV. The concentrations of alanine transaminase (ALT), aspartate transaminase (AST), fasting blood-glucose (FBG), total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), and thyroid stimulating hormone (TSH) were measured by the same method.

Ethical Approval

The study protocol was approved by the local Ethics Review Board and conducted in accordance with the ethical standards of the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 24.0. (IBM Corporation, Armonk, NY, USA). All data are presented as the mean ± standard deviation (SD). To evaluate the significance of the difference between the groups, the independent-samples *t*-test was used for normally distributed data, while the Mann–Whitney *U* test was used for non-normally distributed data. Analysis of covariance was used to compare serum levels of UA, TBIL, ALB, and CRE between the BPPV and HC groups. Multiple stepwise logistic regression analysis was performed to identify predictive indicators of BPPV. The odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated. On-parameter receiver operating characteristic (ROC) analysis was conducted and the area under curve (AUC) was calculated using 95% CIs. Cut-off values were calculated for each factor. A probability (p) value of < 0.05 was considered statistically significant.

RESULTS

General Statistics

The clinical characteristics of the study participants are summarized in **Table 1**. As compared with the HC group, serum levels of UA ($p = 0.021$) and CRE ($p = 0.005$) were significant lower, while ALB and TBIL levels were very significantly lower ($p < 0.001$) in the BPPV group (**Table 1**).

Subgroup Analysis by Sex

The effects of sex on serum levels of UA, TBIL, ALB, and CRE between the BPPV and HC groups were determined (**Table 2**, **Figure 1**). As expected, the results showed highly significant

TABLE 1 | The clinical characteristics of the study samples.

Variables	BPPV (Mean ± SD)	Control (Mean ± SD)	*p*-Value
Sex (F/M)	70 (48/22)	140 (96/44)	– – – – – –
BMI (kg/m²)	23.64 ± 0.42	23.42 ± 0.28	0.826
Alcohol (F/M)	16 (2/14)	24 (1/23)	0.218
Smoking (F/M)	21 (1/20)	18 (3/15)	0.314
SBP (mmHg)	123.76 ± 1.50	125.54 ± 1.03	0.958
DBP (mmHg)	80.83 ± 1.05	80.39 ± 0.70	0.619
WBC (*10^9/L)	6.79 ± 0.20	6.76 ± 0.13	0.683
HGB (g/L)	133.79 ± 1.4	136.39 ± 1.13	0.204
PLT (*10^9/L)	231.43 ± 6.56	225.59 ± 4.15	0.313
CRE (μmol/L)	61.19 ± 1.81	67.01 ± 1.13	0.005**
ALT (U/L)	18.69 ± 1.09	19.26 ± 0.74	0.341
AST (U/L)	20.51 ± 0.61	21.14 ± 0.50	0.504
ALB (g/L)	43.07 ± 0.42	46.72 ± 0.22	0.000***
TSH (mIU/L)	1.84 ± 0.11	1.81 ± 0.07	0.934
TC (mmol/L)	5.05 ± 0.11	4.90 ± 0.06	0.592
TG (mmol/L)	1.45 ± 0.23	1.15 ± 0.05	0.577
HDL (mmol/L)	1.42 ± 0.03	1.46 ± 0.03	0.451
LDL (mmol/L)	3.02 ± 0.09	2.83 ± 0.06	0.134
UA (μmol/L)	303.00 ± 10.12	331.86 ± 7.73	0.021*
TBIL (μmol/L)	9.52 ± 0.47	11.90 ± 0.35	0.000***
FBG (mmol/L)	5.14 ± 0.05	5.10 ± 0.04	0.584

*BMI, body mass index, defined as weight in kilograms divided by the square of height in meters; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cells; HGB, hemoglobin; PLT, blood platelet; CRE, creatinine; ALT, alanine transaminase; AST, aspartate transaminase; ALB, albumin; TSH, thyroid stimulating hormone; TC, total cholesterol; TG, triglycerid; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UA, uric acid; TBIL, total bilirubin; FBG, fasting blood-glucose. Values are expressed as Mean ± SD. The differences were considered significant if p-value < 0.05. ***p-value < 0.001, **p-value < 0.01, *p-value < 0.05.*

differences in serum levels of UA, TBIL, and CRE between males and females in the HC group, but not ALB ($p = 0.819$). In contrast, there were no significant differences in the serum levels of UA, TBIL, ALB, and CRE between males and females in the BPPV group ($p = 0.276$, 0.078, 0.826, and 0.290, respectively). Thus, there was no sex-specific differences in the BPPV group, as in the HC group. Notably, there was no sex-specific difference in serum ALB between males and females in the BPPV and HC groups.

Sex-specific comparisons showed that there were no significant differences in serum levels of UA and CRE among males between the BPPV and HC groups ($p = 0.239$ and 0.392, respectively). On the other hand, with the exception of CRE ($p = 0.096$), there were highly significant differences in serum levels of UA, TBIL, and ALB among females between the BPPV and HC groups. In summary, there were no significant differences in serum CRE levels between males and females in the BPPV and HC groups, but highly significant differences in serum levels of TBIL ($p = 0.018$) and ALB ($p = 0.000$) among females between the BPPV and HC groups. The high significance between males and females in the BPPV group as compared to the HC group also explains why there was no significant difference between males and females in the BPPV group.

TABLE 2 | Serum levels of UA,TBIL, ALB, and CRE in the BPPV and HC groups (mean ± SD).

Patients	Male	Female	P^1	P^2	P^3
UA					
BPPV	371.82 ± 16.52	271.46 ± 9.80			0.276
HC	403.57 ± 15.33	299.00 ± 6.52	0.239	0.009**	0.000***
TBIL					
BPPV	10.73 ± 0.94	8.96 ± 0.53			0.078
HC	13.45 ± 0.71	11.19 ± 0.38	0.018*	0.000***	0.005**
ALB					
BPPV	44.07 ± 0.72	42.62 ± 0.51			0.826
HC	48.20 ± 0.37	46.04 ± 0.24	0.000***	0.000***	0.819
CRE					
BPPV	76.98 ± 2.70	53.95 ± 1.41			0.290
HC	82.29 ± 1.48	60.01 ± 0.79	0.392	0.096	0.000***

*P^1, male patients with BPPV vs. male HC; P^2, female patients with BPPV vs. female HC; P^3, male vs. female in each group. The differences were considered significant if p-value<0.05. ***p-value < 0.001, **p-value < 0.01, *p-value < 0.05.*

Multiple Stepwise Logistic Regression Analysis

Multiple stepwise logistic regression analysis unexpectedly revealed that a reduction in serum ALB, but not UA, TBIL, or CRE, was associated with BPPV ($p < 0.05$; OR = 0.688; 95% CI = 0.607–0.780) (**Table 3**).

ROC Analyses

ROC analyses were performed to assess the levels of ALB. The AUC for ALB was 0.787 (0.720 – 0.855). The cut-off value of ALB was 45.15 g/L with a sensitivity of 74.29% (62.97– 83.07%) and specificity of 73.57% (65.71– 80.18%) (**Figure 2**).

DISCUSSION

The results of the present study showed that serum levels of UA, BIL, ALB, and CRE were significantly lower in the BPPV group than the HC group. In addition, subgroup analysis based on sex confirmed these results for BIL and ALB. Moreover, ALB was associated with BPPV. To the best of our knowledge, this is the first report of the relationship between BIL and BPPV, and the first report of UA, BIL, ALB, and CRE as indicators of oxidative stress to evaluate the antioxidant status of BPPV.

BPPV is induced by the detachment of otoconia, which are composed of inorganic calcium carbonate crystals and proteins (14). Many studies have shown that otolith shedding is associated with calcium homeostasis in the inner ear. Evidence supports a role of oxidative stress in calcium homeostasis (15). Calcium metabolism is closely related to oxidative stress (16). The endoplasmic reticulum is the main organelle for calcium storage. Under oxidative stress conditions, the endoplasmic reticulum can increase the inflow of calcium, thus, triggering ROS production and accumulation in the mitochondria (17). Subsequently, in response to reperfusion injury, calcium

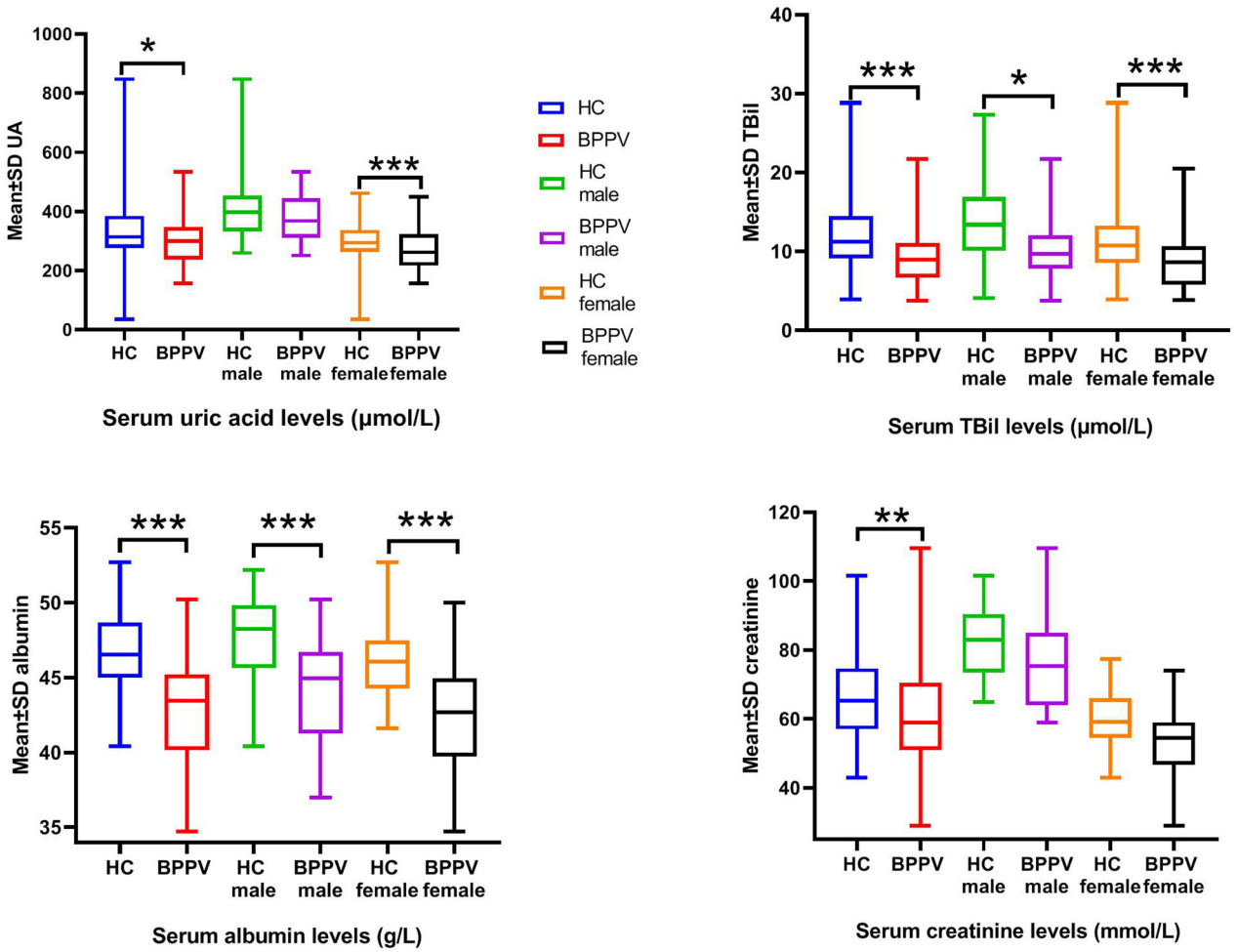

FIGURE 1 | Serum levels of UA, BIL, ALB, and CRE between males and females in the BPPV and HC groups. ***p-value < 0.001, ** p-value< 0.01, *p–value < 0.05.

ions flowing into the mitochondria causes rupture of the mitochondrial membrane and subsequent apoptosis (18). Tsai et al. found that malondialdehyde levels were higher in the BPPV group before the relocation of calcium. The higher level of antioxidant superoxide dismutase in the post-treatment group suggests that oxidative stress might play a role in the pathology of BPPV (15).

In this study, serum levels of UA, BIL, ALB, and CRE were lower in the BPPV group as compared to the HC group, suggesting an association between oxidative stress and BPPV. Epidemiological studies have shown that the prevalence of BPPV is relatively high in those aged 50–60 years and the ratio of female to male is 2–3:1 (14). As shown in **Figure 1**, all blood markers were lower in women than men by both inter-group and intra-group comparisons (although not all findings were statistically significant), indicating weaker antioxidant capacity in women, which could explain the higher incidence of BPPV in women. Therefore, further studies are warranted to elucidate the mechanism underlying changes in serum levels of UA, BIL, ALB, and CRE associated with BPPV.

UA and BPPV

UA is a naturally occurring product of purine metabolism and is known as a strong scavenger of peroxynitrite. In addition, UA acts as a protective antioxidant in neurodegenerative diseases, such as Parkinson's disease (19), Guillain–Barre syndrome (20), multiple sclerosis (21), and amyotrophic lateral sclerosis (22). However, there is no consensus whether UA is a protective or risk factor for BPPV. Some studies have reported that UA levels are reduced in patients with BPPV (12), while other have not replicated these findings (11). A meta-analysis reported that the relationship between UA and BPPV is complex, but may not be an independent risk factor for BPPV (13). The results of the present study indicated that UA levels were reduced in BPPV. However, there were significant differences in UA levels among females, but not males, between the BPPV and HC groups. The differences between the sexes may be caused by differences in the levels of protective estrogen in females as well as differences in dietary and lifestyle habits (23). Moreover, these differences may have something to do with the duality of UA, which is considered a natural antioxidant, but also has pro-oxidation properties,

TABLE 3 | A multiple stepwise logistic regression to identify independent factors of BPPV.

Variables	OR (95% CI)	*p*-Value
UA	1.000 (0.966–1.004)	0.970
TBIL	0.900 (0.818–0.991)	0.032 *
ALB	0.688 (0.607–0.780)	0.000 ***
CRE	1.000 (0.970–1.032)	0.978

*The differences were considered significant if p-value < 0.05. ***p-value < 0.001, **p-value < 0.01,*p-value < 0.05.*

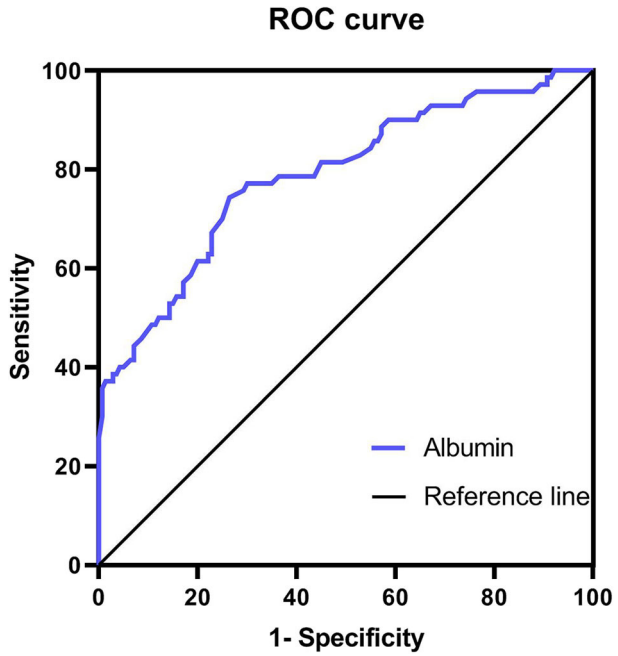

FIGURE 2 | ROC curve of albumin to identify BPPV.

leading to increased expression of ROS, lipid peroxidation, DNA damage, and the production of inflammatory cytokines (24).

Creatine and BPPV

CRE is a waste product produced by muscles from the breakdown of creatine and is known as an effective scavenger of free radicals (9). In this study, CRE levels were lower in the BPPV group that the HC group, which may be due to the depletion of free radicals. However, there were no significant difference in CRE levels among males and females between the BPPV groups, but not in HC groups. Actual CRE levels are easily affected by blood volume and physical condition (25). However, the lower CRE levels in the healthy females reflected lower antioxidant levels and a higher risk for BPPV.

BIL and BPPV

Some studies have shown that BIL is an effective antioxidant even at physiological concentrations by increasing antioxidant enzyme activities and decreasing ROS levels (26). Many studies have reported a negative association between BIL levels and a range of diseases associated with oxidative stress, such as diabetes (27), asthma (28), and inflammatory bowel disease (29). Yao et al. found that short-term preservation of BIL could prevent cell damage and maintain the viability and function of transplanted islets (30). The results of the present study also revealed lower BIL levels in the BPPV group with statistical differences between males and females.

ALB and BPPV

ALB is the major antioxidant molecule in extracellular fluid and can remove ROS and RNS. The antioxidant capacity of ALB is stronger than that of UA, BIL, ALB, and CRE (31). Redox modification changes the physiological properties of serum ALB, which can serve as a biomarker of oxidative stress (32). Actually, the oxidative state of ALB is reportedly modulated in metabolic syndrome (33), inflammation (34), and immunoglobulin A nephropathy (35). The results of the present study also revealed lower ALB levels in the BPPV group with statistical differences between males and females. Yuan et al. speculated that repeating dizziness and vomiting could lead to malnutrition and hypoproteinemia in patients with BPPV (12). We disagree with this view because relatively few patients with BPPV reported vomiting. Moreover, short-term vomiting or anorexia did not lead to a decrease in serum ALB. We believe that a low concentration of ALB represents a strong state of oxidative stress in BPPV. Furthermore, the serum ALB redox status in patients with vestibular neuritis was significantly lower than in HCs (36), as was the incidence of MD (37). Kim et al. studied the differences of protein profiles between patients with recent hearing loss and a HC group, and found that the concentrations of ALB-like proteins in the plasma and inner ear were higher in the HC group (38). In summary, ALB may be a protective factor for BPPV, although further studies are needed to clarify the underlying mechanism.

Is BPPV an Autoimmune Disease?

Here, serum levels of BIL and ALB were decreased in the BPPV group. Multiple stepwise logistic regression analysis revealed that serum concentrations of BIL (although not statistically significant) and ALB were related to BPPV. Of note, previous studies have shown that low serum BIL and ALB levels are associated with various autoimmune diseases, such as neuromyelitis optica (39), multiple sclerosis (40), myasthenia gravis (41), and anti-N-methyl-D-aspartate receptor encephalitis (42). Hence, to determine whether BPPV is an autoimmune disease, further studies are needed to reveal the association between serum levels of BIL and ALB, and the pathogenesis of BPPV.

As discussed in previous sections, the results of the present study revealed lower serum levels of UA, BIL, ALB, and CRE in the BPPV group, suggesting higher levels of oxidative stress in BPPV patients, although it is uncertain whether low antioxidant status led to or was the result of disease. Nonetheless, the low antioxidant status in BPPV patients could not reverse damage to the vestibular system due to free radical toxicity. As another possibility, serum levels of UA, BIL, ALB, and CRE were reduced in the BPPV group because of the removal of excessive free radicals. However, future studies are needed to elucidate the

pathological mechanisms underlying these associations in the inner ear.

Three were three major limitations to this study. First, this was a preliminary descriptive study, which lacked evidence of biological and pathological mechanisms. Second, only patients hospitalized for idiopathic BPPV were included in this study. Third, serum levels of UA, BIL, ALB, and CRE were not followed-up in acute and remission patients. Since data are scarce, the evidence to support the conclusion remains weak, thus further studies with larger populations are needed to define these relationships.

CONCLUSIONS

Serum levels of UA, BIL, ALB, and CRE were reduced in patients with BPPV. In addition, reduced ALB was independently associated with BPPV, although further studies are required to clarify the underlying mechanism. This finding may be attributed to an active oxidative process in BPPV patients with low antioxidant status.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine and conducted in accordance with the ethical standards of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

K-HX and L-LL: conceptualization. Q-QC and HL: data curation. C-YS, X-FH, and J-SH: software. B-XW, R-NL, and Y-KR: validation. K-HX and L-LL: writing original draft and writing review and editing. All authors contributed to the article and approved the submitted version.

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Effect of the Epley Maneuver and Brandt-Daroff Exercise on Benign Paroxysmal Positional Vertigo Involving the Posterior Semicircular Canal Cupulolithiasis: A Randomized Clinical Trial

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Objective: To investigate the therapeutic efficacies of the Epley maneuver and Brandt-Daroff (BD) exercise in patients with benign paroxysmal positional vertigo involving the posterior semicircular canal cupulolithiasis (PC-BPPV-cu).

Methods: We conducted a randomized clinical trial to evaluate the therapeutic effect of the Epley maneuver and BD exercise in patients with PC-BPPV-cu. Patients were randomly assigned to undergo the Epley maneuver ($n = 29$) or BD exercise ($n = 33$). The primary outcome was an immediate resolution of positional nystagmus within 1 h after a single treatment of each maneuver on the visit day. Secondary outcomes included the resolution of positional nystagmus at 1 week, the change of maximal slow phase velocity (mSPV) of positional nystagmus, and dizziness handicap inventory (DHI) immediately and at 1 week.

Results: Immediate resolution occurred in none of 29 patients in the Epley maneuver group and only 1 of 33 patients in the BD exercise group. The Epley maneuver and BD exercise had an equivalent effect at 1 week in treating PC-BPPV-cu in terms of resolving positional nystagmus (48 vs. 36%, $p = 0.436$) and the decrease of mSPV and DHI.

Conclusion: Neither the Epley maneuver nor BD exercise has an immediate therapeutic effect in treating PC-BPPV-cu. Clear classification of PC-BPPV should be required at the time of different pathology and different treatment response.

Keywords: vertigo, nystagmus, benign paroxysmal positional vertigo, cupulolithiasis, Epley maneuver, Brandt-Daroff exercise, posterior semicircular canal

INTRODUCTION

Cupulolithiasis of benign paroxysmal positional vertigo involving the posterior semicircular canal (PC-BPPV-cu) is a rare form of BPPV. Prof. Epley previously described nystagmus characteristics and his clinical experience of diagnostic posture (1). He suggested that half Hallpike maneuver can provoke persistent up and ipsitorsional nystagmus because the cupula of PC may be oriented along earth-horizontal axis, and thus the weighted cupula has maximal propensity to be deflected earthward (1). Based on his theory, Barany's society formulated the diagnostic criteria of PC-BPPV-cu on 2015 (2). PC-BPPV-cu generates upward and ipsitorsional nystagmus, but the duration of symptoms and positional nystagmus are longer (over 1 min) than experienced with canalolithiasis of PC-BPPV (PC-BPPV-ca) (1–4).

Since effective treatment of PC-BPPV-cu has not been validated, a recent clinical guideline did not recommend specific treatment options based on the subtypes of PC-BPPV (canalolithiasis or cupulolithiasis) (5, 6). Most clinics treating dizziness customarily perform diverse maneuvers for treating PC-BPPV-cu, such as the Epley maneuver, Brandt and Daroff (BD) exercise, vibratory stimulation, and head-shaking maneuver.

The BD exercise is a movement/habituation-based vestibular rehabilitation treatment and includes a sequence of rapid lateral head/trunk tilts repeated serially. This exercise could be adopted for treating cupulolithiais based on the assumption that the mechanical stimuli exerted on the cupula would help dislodge the debris from the cupula (7). However, there are no available data on the therapeutic efficacy in PC-BPPV-cu.

This study conducted a randomized clinical trial to determine the treatment efficacies of the Epley maneuver and BD exercise in patients with PC-BPPV-cu.

MATERIALS AND METHODS

Subjects

We recruited 62 patients with a diagnosis of PC-BPPV-cu at the dizziness clinics of two university hospitals between March 2018 and October 2019. All participants met the diagnostic criteria of PC-BPPV-cu (2). Exclusion criteria included central nervous system disorders that could explain the positional vertigo and nystagmus, transition from geotropic to apogeotropic form during or after therapeutic maneuvers, multiple canals' involvement, secondary BPPV, and poor cooperation for treatments. To exclude central pathologies, all patients received neuro-otologic examinations, including spontaneous and gaze-evoked nystagmus, saccades, smooth pursuit, head impulse tests, cerebellar function tests, and assessment of balance. Patients with abnormal neurological or neuro-otological signs were referred for brain MRIs.

Diagnostic Procedures

We performed half Dix-Hallpike maneuver and/or Dix-Hallpike maneuver to identify PC-BPPV-cu (2). The patients were also assessed with the supine head roll-test and the straight head hanging test to exclude BPPV involving horizontal or anterior canals. Nystagmus was recorded without visual fixation at a sampling rate of 120 Hz using a 3D video-oculography (SLMED, Seoul, Korea). Digitized vertical position data of the eye for maximal slow phase velocity were analyzed by the equipment software with video-oculography and verified manually.

Study Design and Randomization

We attempted to determine therapeutic efficacies immediately and at 1 week after the Epley maneuver compared with BD exercise by a randomized clinical trial. Based on data from a previous study (8), we estimated that the proportion of patients with immediate resolution in PC-BPPV would be 80% with the Epley maneuver and 40% with the BD exercise. By adopting 0.9 power to detect a significant difference ($p = 0.05$, two-sided) and a dropout rate of 20%, we calculated that 29 patients were required for each treatment arm.

The patients with PC-BPPV-cu were randomly assigned to the Epley maneuver ($n = 29$) and DB exercise ($n = 33$) groups (**Figure 1**) using a web-based program. All patients completed dizziness handicap inventory (DHI) on the first visit day. Trained physiotherapists performed the assigned treatment once. A non-study physician, blinded to the maneuver applied to each patient, determined the immediate efficacy within 1 h. The patients in the BD exercise group were instructed to perform the BD exercise at home three times a day for 1 week. At the end of 1 week, all patients completed a DHI and were re-assessed for positional nystagmus.

The primary outcome was the immediate resolution of positional nystagmus after a single application of each treatment. The secondary outcomes were the resolution of positional nystagmus after 1 week, the change of maximal slow phase velocity (mSPV) of positional nystagmus, and changes in the DHI immediately after treatment and at 1 week.

Applied Treatments

For the Epley maneuver in right PC-BPPV-cu, the head was turned 45° to the patient's right while sitting upright. Then, the patient was moved from the sitting position to the supine with the head hanging for 1 min or until the right-torsional up beating nystagmus was diminished. The head was turned 90° toward the unaffected left side twice, in a nearly face down position. The patient was then brought to the sitting up position. The patients with left PC-BPPV-cu underwent treatment in the opposite direction (9).

BD exercise was performed with a trained physiotherapist on the visit day. Patients were made to lie on their side rapidly, sit up, lie on the opposite side, and then sit up again. Each position was maintained for at least 30 s (7), and repeated serially 10 times. The patients were instructed to perform this exercise themselves at home three times daily for a week.

Statistical Analysis

Student, paired *t*-test, or Mann-Whitney U-test was used to compare the continuous variables, and Fisher's exact-test or χ^2-test was applied for the categorical variables. All statistical procedures were performed using SPSS statistical

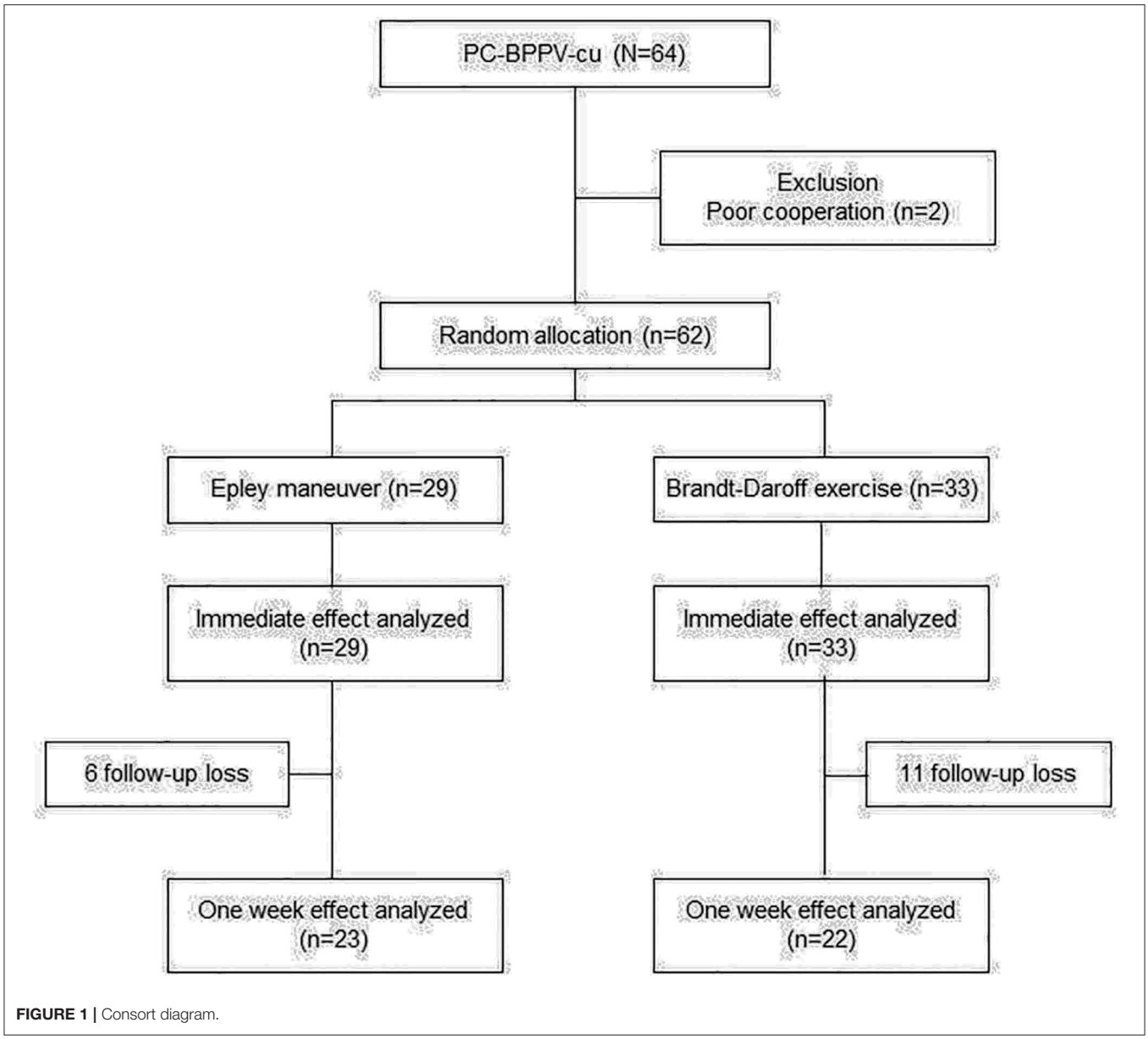

FIGURE 1 | Consort diagram.

software (version 23.0; SPSS, Chicago, IL, USA) and $p < 0.05$ was significant.

Standard Protocol Approvals, Registrations, and Patient Consents

The trial was registered at cris.nih.go.kr (KCT0002929). This study was performed under ethical principles consistent with the Declaration of Helsinki. The protocol and informed consent were reviewed and approved by the corresponding health authorities and ethics boards/institutional review boards for both participating study sites (1802-023-064 and 05-2018-076). Enrolled patients gave written informed consent before participation in the trial.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

RESULTS

Demographic Characteristics

Of the 64 patients with PC-BPPV-cu, 62 were included for analysis on the visit day. Two individuals were excluded because they could not receive treatment because of severe vomiting (**Figure 1**). The mean age was 65 years (SD = 10.6, range 31–88) and 46 (74%) were women. Clinical variables did not differ between groups with Epley maneuver ($n = 29$) and DB exercise ($n = 33$) (**Table 1**).

TABLE 1 | Comparison of clinical findings between Epley maneuver group and Brandt-Daroff exercise group.

	Epley maneuver ($n = 29$)	Brandt-Daroff exercise ($n = 33$)	p-value	Total ($n = 62$)
Age, year (mean ± SD)	65.8 ± 8.9	64.2 ± 12.0	0.540	65.0 ± 10.6
Sex, men/women	8/21	8/25	0.780	16/46
Direction, left/right	10/11	14/19	0.606	24/38
Duration of symptoms, days (mean ± SD)	10.9 ± 23.7	7.2 ± 10.3	0.439	8.9 ±17.8

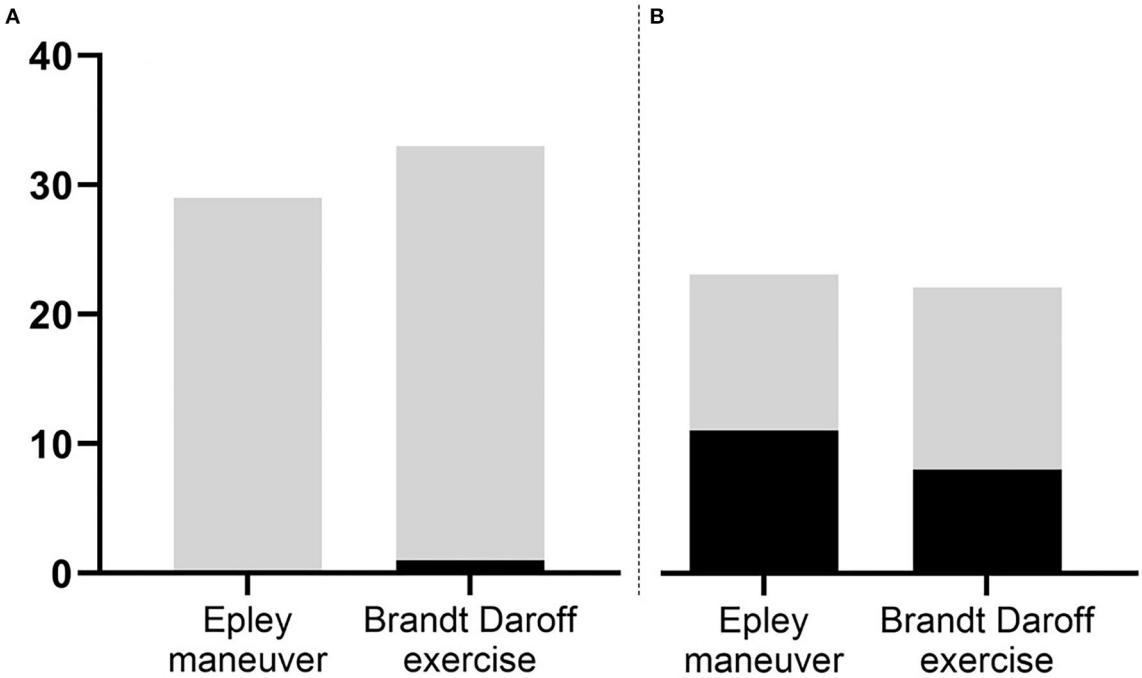

FIGURE 2 | The success rate of Epley maneuver and Brandt-Daroff exercise. **(A)** On the visit day, only one patient in Brandt-Daroff exercise group shows the resolution of positional nystagmus. **(B)** At 1 week, 48% in Epley maneuver group and 36% in Brand-Daroff exercise group show the resolution of positional nystagmus without difference between two groups ($p = 0.436$, χ^2-test). Vertical axis means the number of patients. The patients without nystagmus during Dix-Hallpike maneuver are revealed as black column, the gray column means contrary.

Immediate Efficacies

After the initial maneuver, immediate resolution occurred in none of the 29 patients (0%) in the Epley maneuver group and in only 1 of 33 patients (3%) in the BD exercise group (**Figure 2A**). The patient showed conversion to PC-BPPV-ca. Also, there was no significant decrease in the mSPV in either of the two groups (**Figure 3A**).

Response After 1 Week

After 1 week, 17 patients (17/62, 27%) were lost for follow-up, despite repeated attempts to reach them. Ultimately, the data of 45 patients were analyzed (23 with Epley maneuver and 22 with BD exercise). Clinical variables did not significantly differ between groups with Epley maneuver and DB exercise (**Supplementary Table 1**) and between initial and follow-up groups (data not shown). Epley maneuver and BD exercise had equivalent effect at 1 week in treating PC-BPPV-cu (48 vs. 36%, $p = 0.436$, χ^2-test, **Figure 2B**). Both DHI and mSPV also significantly decreased compared to those on the first visit day, but the change did not differ between the two maneuvers (**Figure 3**).

DISCUSSION

Neither Epley maneuver nor BD exercise resulted in an improvement in PC-BPPV-cu immediately after treatment. Also, the therapeutic efficacy did not differ between the groups with Epley maneuver and BD exercise after a week, although DHI and mSPV decreased in each group.

The incidence of PC-BPPV-cu is not established, but there is a consensus that it is rare form of PC-BPPV (2). In a previous study, eight of 111 PC-BPPV (7.2%) was cupulolithiasis type (3). The authors investigated that the vertical torsional nystagmus during Dix-Hallpike test had long time constant (>40 s) while the time constant of positional nystagmus in PC-BPPC-ca was short (<20 s) (3). Also, the sum of mSPV of positional nystagmus

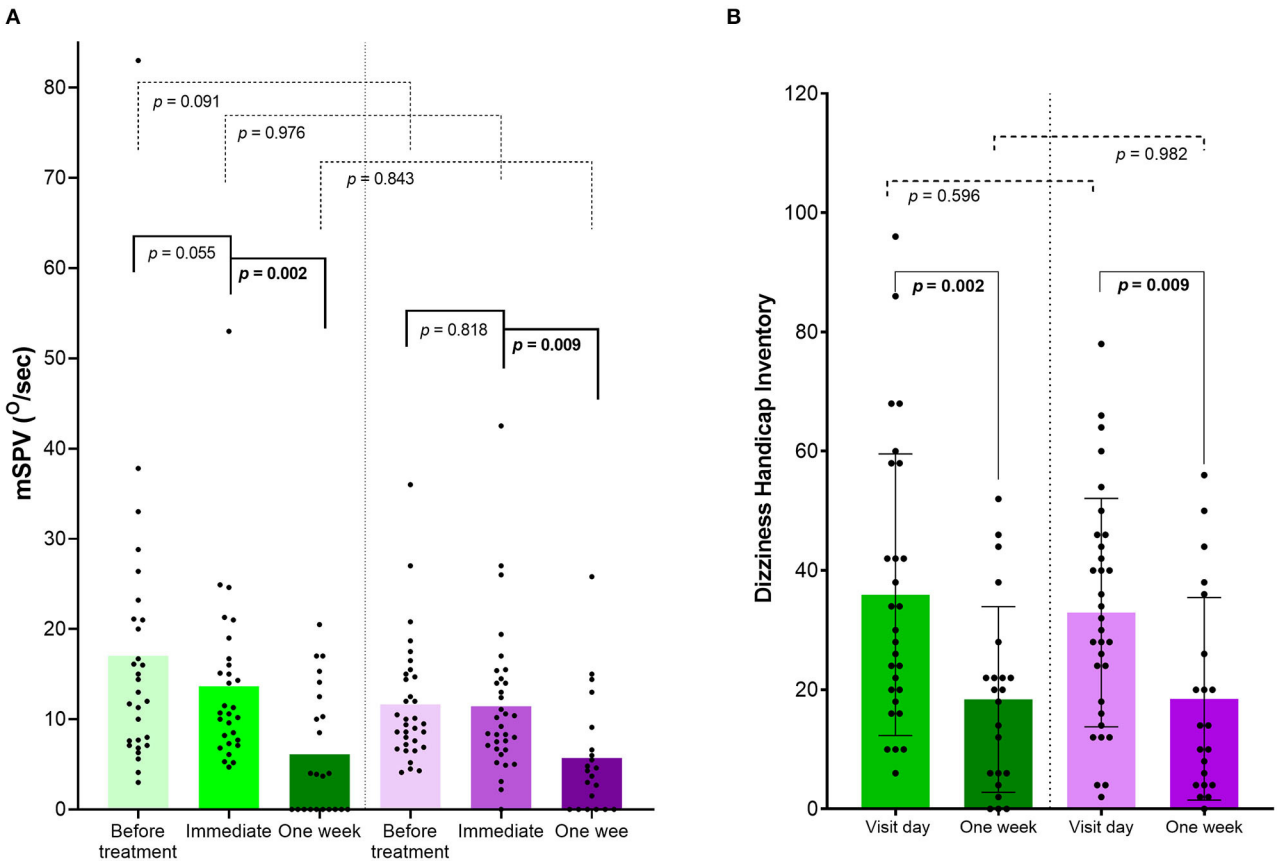

FIGURE 3 | The change of maximal slow phase velocity (mSPV) of positional nystagmus **(A)** and dizziness handicap inventory (DHI) **(B)** by application of Epley maneuver and Brandt-Daroff exercise immediately and at 1 week. The mSPV does not decrease by application of both Epley maneuver (green, 17.0 ± 15.4°/s vs. 13.6 ± 9.5°/s, $p = 0.055$) and Brandt-Daroff exercise (purple, 11.6 ± 6.8°/s vs. 11.4 ± 8.2°/s, $p = 0.818$) on the visit day, but decreases at 1 week (6.1 ± 7.0°/s, $p = 0.002$ and 5.7 ± 6.6°/s, $p = 0.009$). There is no significant difference between two maneuvers before ($p = 0.091$), immediately ($p = 0.976$), as well as at 1 week ($p = 0.843$). The DHI significantly decreases at 1 week in both Epley maneuver (green, 35.9 ± 23.6 vs. 18.4 ± 15.6, $p = 0.002$) and Brandt-Daroff exercise groups (purple, 32.9 ± 19.1 vs. 18.5 ± 17.0, $p = 0.009$). There is no difference between two maneuvers on the visit day ($p = 0.596$) and at 1 week ($p = 0.982$). mSPV, maximal slow phase velocity of positional nystagmus.

(about 12°/s, similar to our data) was significantly lesser than that of PC-BPPV-ca (about 42°/s) (4). They explained that the force pulling cupula of moving debris in canal is greater 15 times than attached otoconia on the cupula by Pascal's principle (4).

Although Epley and Semont maneuvers are proven to be highly effective in patients with PC-BPPV-ca, research on the treatment efficacy in PC-BPPV-cu has been extremely rare. Only one observational study described the treatment efficacy in 10 patients with PC-BPPV-cu (10). They applied one each of the Semont maneuver, Epley maneuver, or hybrid maneuver (modified Semont maneuver), but none showed the resolution of positional nystagmus at 1 week, suggesting that treatment of PC-BPPV-cu would be more difficult than expected (10).

Our study is the first clinical trial to compare the therapeutic efficacy in PC-BPPV-cu of the Epley maneuver and the BD exercise. Through a randomize clinical trial, we found that neither the Epley maneuver nor the BD exercise are immediately effective for treating PC-BPPV-cu. At 1 week, there was equivalent therapeutic effect between the two maneuvers in terms of resolving positional nystagmus and decrease of mSPV and DHI. However, since our study did not adopt a control (sham) group, we could not exclude bias for the spontaneous remission. Actually, the resolution rate at 1 week in our study is like the natural course of untreated PC-BPPV, which has a spontaneous remission of 30% within 1 week (11). Our results suggest that clear classification of PC-BPPV-cu and PC-BPPV-ca should be required at the time of different pathology and different treatment response.

Future studies with a randomized, sham-controlled design are needed to validate the efficacy of various maneuvers including the Semont maneuver, head-shaking, and vibratory stimulation for the treatment of PC-BPPV-cu. Semont maneuver would be effective for PC-BPPV-cu because the maneuver use high acceleration of the head (9). Conceptually, Epley is a maneuver to redirect free otoconia in the canal, which is unlikely to be helpful in resolving cupulolithiasis. For its part, the more

abrupt Semont maneuver is an unlocking maneuver for otoconia adhering to the cupola and, therefore, should be a priori more useful in cupulolithiasis. Since the addition of the pressure of the endolymph and the inertia of the heavy material in the posterior canal is theoretical base to Semont maneuver, it is not certain that Semont maneuver is more favorable to PC-BPPV-cu than–ca (12). Theoretically, the best position of PC-BPPV-cu for provocating positional nystagmus would be a Half Hallpike maneuver, because the cupula of PC may be oriented along an earth-horizontal axis during the maneuver, and thus the weighted cupula has a maximal propensity to be deflected earthward (1). Therefore, with this position maintained, application of oscillation for an extended period might settle the particles into the utricle, or the acceleration and deceleration of the head through this position may dislodge particles attached to the cupula.

Furthermore, the head-up posture during sleep for 3 months may be helpful to reduce the subjective symptoms and subjective visual vertical tilt in the intractable BPPV over 3 months, which was irrelevant to the involved semicircular canal (13). If the otolithic debris may float freely in the utricle, the head-up posture can prevent the debris to fall into the semicircular canal (14). Although it depends on the country's medical infrastructure and process, the head-up posture may be applied before the repeated maneuvers and re-visit to the hospital if the medical accessibility or the diagnosis to neurotologic specialists is not easy.

This study has several limitations. First, a relatively small number of patients was included. Second, the number of losses to follow-up was high after 1 week (27%). However, this was mitigated because clinical variables did not differ between the first and follow-up groups (**Supplementary Table 1**). Third, we did not execute a substitute CRM replacing the Epley or BD exercise, and a sham maneuver. Fourth, since the Brandt and Daroff exercises seek habituation, it is not logical to make an evaluation of their effectiveness and improvement of DHI immediately after the first session and even in a week. The perception of disability does not change immediately, even if the maneuver had been successful. It would have been appropriate to assess its effectiveness after at least 1 week.

In conclusion, neither the Epley maneuver nor the BD exercise improved PC-BPPV-cu immediately after treatment. A sham-controlled randomized study with a substitutional maneuver should be conducted to determine effectiveness for PC-BPPV-cu.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Anonymized data will be shared by request from any qualified investigator. Requests to access these datasets should be directed to Seo-Young Choi, csy035@hanmail.net.

ETHICS STATEMENT

The protocol and informed consent were reviewed and approved by the corresponding health authorities and ethics boards/institutional review boards for all participating study sites (1802-023-064 and 05-2018-076). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

S-YC conducted the experiments, analyzed and interpreted the data, and wrote the manuscript. JC, J-HC, and EO conducted the experiments, and analyzed and interpreted the data. K-DC conducted the design and conceptualization of the study, interpretation of the data, and revised the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.603541/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
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Two Symptoms Strongly Suggest Benign Paroxysmal Positional Vertigo in a Dizzy Patient

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Introduction: This prospective cohort study determined which questions in patient history are most likely to identify symptoms that are independently associated with a diagnosis of benign paroxysmal positional dizziness (BPPV) in patients presenting with dizziness, and to evaluate whether the patient's age and type of BPPV are of influence.

Methods: We included adult patients with dizziness referred to our dizziness center, Apeldoorn, the Netherlands, from December 2018 to November 2019. All patients completed a questionnaire, underwent vestibular testing and received a diagnosis. Symptoms strongly suggesting BPPV were tested with multivariable analysis to determine their independent associations with BPPV. Subgroup analysis was performed for patient age, and the type of BPPV.

Results: We included a total of 885 patients, 113 of whom (13%) were diagnosed with BPPV. The duration of dizziness spells <1 min (Q2) and dizziness provoked by rolling over in bed (Q4) were independently associated with the diagnosis BPPV. Q2 showed a sensitivity of 43%, and a specificity of 75%; Q4 scored 81% and 68%, respectively. Overall, the way patients perceived their dizziness (vertigo, light-headedness or instability) was not independently associated with the diagnosis BPPV. In younger patients, light-headedness and instability decreased the likelihood of BPPV compared to vertigo.

Conclusion: The most reliable predictors for BPPV in patient history are a short duration of the dizziness spell and provocation of dizziness by rolling over in bed. Unlike younger patients, elderly patients with BPPV do not only perceive the dizziness as vertigo, but also as a feeling of instability.

Keywords: BPPV, patient history, symptoms, diagnosis, dizziness, vertigo, predictive model

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the most common vestibular type of vertigo, with an estimated incidence of 64 cases per 100,000 people per year and a lifetime prevalence of 2.4% (1, 2). The typical presentation of BPPV consists of recurrent, brief attacks of vertigo generally provoked by changes in head position, such as looking up, bending over, lying down, or rolling over in bed (3–5). However, several alternative presentations are possible. For example, some patients

present with complaints of prolonged unsteadiness instead of the typical brief vertigo sensation. This is most common in elderly patients (6).

BPPV is diagnosed by provoking vertigo by positional testing and via observation of typical nystagmus (5). The gold standard for the diagnosis of posterior canal BPPV is the Dix-Hallpike maneuver, whereas horizontal canal BPPV is mostly diagnosed with the supine roll test (5). Besides diagnostic positional maneuvers, patient history is critical for the recognition of BPPV and for classifying the etiology (7, 8). The evaluation of a patient with dizziness can be difficult because of the broad etiology and wide array of questions and tests necessary to come to a diagnosis. It is even more difficult in the geriatric population as increased comorbidity may cause multiple, non-specific symptoms. This may lead to diagnostic delay or leave BPPV unrecognized, which in turn may cause patients to reduce their daily activities and increases the risk of falls (9, 10). Generally, BPPV is well-treatable with canalith repositioning procedures, and as such diagnostic delay could even lead to patients missing out on available treatment. In order to prevent this diagnostic delay and promote early recognition and treatment, it may be helpful to assess which symptoms regarding patient history are the most valuable ones for identifying BPPV in patients presenting with dizziness.

Previous research has identified several items that are useful during history taking of the patient with BPPV, such as the nature of dizziness (i.e., vertigo as opposed to light-headedness), the duration of attacks, and the presence and the frequency of associated symptoms (11–13). Also, the provocative head movement may differ depending on the affected canal. For example, dizziness evoked by looking up could possibly occur more often in patients with posterior canal BPPV than in patients with horizontal canal BPPV.

Another approach that is useful for the early detection of BPPV is the use of predictive models. The purpose of such a model is to predict whether a patient presenting with dizziness has BPPV based on the patient's answers to a set of questions. One of these models is the linear prediction (LP) model developed by Friedland et al., which has shown promising results in the prediction of BPPV (14, 15).

In order to facilitate the diagnosis of BPPV, our primary aim was to identify the questions that are the most valuable for history taking and to validate the predictive LP model of Friedland et al. (14). Secondly, we aimed to assess whether the diagnostic value of these symptoms differed between young and elderly patients and between patients with posterior canal BPPV and horizontal canal BPPV.

METHODS

Patients and Procedure

This prospective cohort study included all adult patients referred between December 2018 and November 2019 to the Apeldoorn Dizziness Center (ADC), the Netherlands. The ADC is a tertiary referral clinic for patients with dizziness.

All patients were requested to complete a study-specific questionnaire containing six questions about the nature and duration of their dizziness and the positions provoking dizziness (**Table 1**). This questionnaire, including informed consent form and study information sheet, was sent to patients' home addresses before their visit to the clinic. Patients were asked to select the best suitable option to describe the nature of their dizziness. For the "type of dizziness" item, they could only choose one of the available options. For the questions regarding the duration of dizziness and the positions provoking dizziness, they could only give a Yes or No answer.

TABLE 1 | Study-specific questionnaire.

Question	Response options
Q1—Specify the nature of the main type of dizziness experienced Choose only one option	- Vertigo - Light-headedness - Instability - Other
Q2—Is the duration of the dizziness spell <1 min?	Yes/No
Q3—Does lying down in bed provoke dizziness?	Yes/No
Q4—Does rolling over in bed provoke dizziness?	Yes/No
Q5—Does bending forward provoke dizziness?	Yes/No
Q6—Does looking up provoke dizziness?	Yes/No

The questionnaire was formed based on literature review of diagnostic criteria and questions found indicative of BPPV along with expert opinion (5, 11–13). Because of the goal to quickly and easily recognize BPPV, special interest was placed in concise questions with limited answer possibilities. Questions showing no relevant correlation to BPPV in previous literature were excluded. Questions 3–6 asking about the provocation of the dizziness also had the added goal of elucidating a potential correlation to the type of BPPV (posterior or horizontal).

All patients are subjected to our center's standard examinations for the workup for dizziness, which consist of a routine neuro-otologic examination including positional testing, otoscopy, the video head-impulse test and/or caloric testing, pure-tone audiometry, the hyperventilation provocation test, the postural hypotension test, and completion of the Hospital Anxiety and Depression Scale.

After taking patient history and performing the standard examinations, the ENT surgeon and the neurologist assessed whether the questionnaire and the diagnostic work-up was complete. Patients were excluded if either one was incomplete and the patient was not able or willing to complete the missing questions or tests. Then, they jointly formulated a diagnosis for each patient. The diagnosis of definite BPPV is based on the criteria of the "Consensus Document of the Committee for the Classification of Vestibular Disorders of the Bárány Society"

(5). As for the type of BPPV, a torsional-vertical nystagmus with vertigo following the Dix-Hallpike maneuver is classified as posterior canal BPPV, while a horizontal nystagmus with vertigo during the supine roll test is classified as horizontal canal BPPV.

If a patient experienced dizziness without a visible nystagmus, the diagnosis possible BPPV was established ($n = 6$). Patients who experienced BPPV-like symptoms in the past, but had negative provocation maneuvers were diagnosed as historical BPPV ($n = 82$). Both these patient groups were classified as "no BPPV."

Statistical Analysis

Continuous variables were described as mean and median, and categorical variables were described as numbers, and percentages.

We assessed the diagnostic value for each of the questions by calculating the odds ratio and its corresponding p-value using univariable logistic regression models. Next, the questions eliciting answers that were significantly associated with BPPV (i.e., $p < 0.05$) were entered into a multivariable logistic regression model. For the questions that strongly suggested the diagnosis of BPPV in this model, we calculated the sensitivity and specificity.

Furthermore, we repeated this part of the analysis in subgroups based on the patient's age and on the type of BPPV (horizontal, posterior). Based on the patient's age, we compared if the nature of the dizziness (Q1) differed between patients younger or older than 65 years. The age cut-off was set at 65 because this is a widely accepted cut-off value for seniority. We analyzed differences in provocation of the dizziness (Q3–Q6) by comparing two subgroups based on type of BPPV (horizontal, posterior).

For validation of the diagnostic LP model for BPPV of Friedland et al., we used our study-specific questionnaire data to create an LP value for each patient. The model of Friedland et al. was completed by substituting the variable with a "1" if it was present or a "0" if it was not present. "Lying Down or Rolling Over" was classified as "1" if a patient reported provocation of dizziness by lying down in bed or rolling over (Q3 or Q4). "Vertigo" was set as "1" if the nature of the dizziness was classified as vertigo (Q1).

$$\begin{aligned} \mathrm{LP} = -2.19 \; &+ \; 1.87 \times \big(\text{Lying Down or Rolling Over}\big) \\ &+ \; 0.92 \times \big(\text{Vertigo}\big) - 0.98 \\ &\times \; (\text{LOS}: \text{Minutes to Hours}) - 1.11 \\ &\times \; \big(\text{LOS}: \text{Days}\big) - 1.84 \times \big(\text{Vertigo}\big) \\ &\times \; \big(\text{LOS}: \text{Days to Weeks}\big) \end{aligned} \quad (1)$$

The LP value was then converted to an estimated probability:

$$\Pr\left(BPPV\right) = \frac{e^{LP}}{1 + e^{LP}} \quad (2)$$

In our study-specific questionnaire, we distinguished between duration of more or <1 min (Q2), and as such we did not have access to duration data to the same extent as Friedland et al. whose formula splits the length of duration (LOS) into separate entities (minutes to hours, days, days to weeks). Hence, we classified all LOS variables as "0" if our patients reported dizziness lasting shorter than 1 min. Dizziness lasting more than 1 min was categorized by chance as "LOS: Minutes to Hours," or "LOS: Days" in a 50:50 distribution, except for dizziness perceived as vertigo and lasting longer than 1 min, which was categorized as "LOS: Days to Weeks."

The cut-off value ≥0.2 was used as confirmation of BPPV, based on a previous study by Friedland et al. (14). Based on these LP values, a confusion matrix was produced, and the sensitivity and specificity of the model were calculated by means of a receiver operating characteristic (ROC) curve.

Ethical Considerations

The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments up to 2013 (16) and was approved by the Local Review Board of Gelre Hospital. Written informed consent for participation in the study was obtained from all participants.

RESULTS

A total of 885 patients were included in the study, 113 of whom (13%) were diagnosed with BPPV. The mean age of the population was 57 years (SD 16.8, min/max 18–92), and 568 (64%) were female (**Table 2**). The mean age of patients diagnosed with BPPV was significantly higher than the mean age of patients without BPPV [62 years (SD 16) vs. 57 years (SD 17), $p < 0.01$], and the proportion of female patients was significantly higher in the BPPV group [73% ($n = 82$) vs. 63% ($n = 486$), $p < 0.05$]. Out of 113 patients diagnosed with BPPV, 101 (89%) patients had posterior canal BPPV, 11 patients were diagnosed with horizontal canal BPPV, and one patient suffered from anterior canal BPPV. The patient with anterior canal BPPV was excluded from analysis because multinomial logistic regression cannot be applied to a group of one.

Uni- and Multivariable Analysis of Study-Specific Questionnaire

Univariable analysis showed a correlation with all questions and the diagnosis of BPPV, except for the way patients perceived their dizziness (vertigo or instability, Q1) (**Table 3**). While the presence of light-headedness rather than vertigo reduced the chance of BPPV being present [OR: 0.45 (95% CI 0.24– 0.87), $p = 0.02$], dizziness experienced either as instability or vertigo was not significantly associated with a BPPV diagnosis [OR: 0.67 (95% CI 0.40–1.1), $p = 0.10$]. A total of 91 (81%) patients with BPPV reported dizziness provoked by turning over in bed, compared to 243 (32%) patients without BPPV. This resulted in an odds ratio of 8.94 (95% CI 5.5–14.6, $p < 0.01$).

Multivariable analysis demonstrated that a duration of dizziness spells <1 min (Q2) [OR: 1.8 (95% CI 1.1 to 2.8), $p = 0.02$] and dizziness provoked by turning over in bed (Q4) [OR 6.0 (95% CI 3.2–11.0), $p < 0.01$] were independently associated with the diagnosis of BPPV (**Table 3**). The duration of the dizziness spell <1 min (Q2) had a sensitivity of 43% and a specificity of

TABLE 2 | Patient demographics.

		BPPV *n* (% in group)	No BPPV *n* (% in group)	Total *n* (% of total)	*p*-Value
Number		113 (13%)	772 (87%)	885	
Age	*Mean (years)*	61.9	56.7	57.4	<0.01
	Elderly (≥ 65 years)	55 (49%)	269 (35%)	324 (37%)	
Gender	*Female*	82 (77%)	486 (63%)	568 (64%)	<0.05
Type of BPPV	*Posterior*	101 (89%)	NA	NA	
	Horizontal	11 (10%)	NA	NA	
	Anterior	1 (1%)	NA	NA	

BPPV, benign paroxysmal positional vertigo; NA, not applicable.

TABLE 3 | Univariable and multivariable analysis for association between study-specific questions and diagnosis of BPPV (BPPV, $n = 113$; no BPPV, $n = 772$).

Question			Univariable analysis			Multivariable analysis	
	Missing	Answer	*n* (% of answer)	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Q1—Type of dizziness	61	*Vertigo*	50 (16%)	1.0	–	1.0	–
		Light-headedness	13 (8%)	0.45 (0.2–0.9)	0.02	0.70 (0.35–1.40)	0.32
		Instability	32 (11%)	0.67 (0.4–1.1)	0.10	1.2 (0.69–2.0)	0.54
		Unspecified	8 (12%)	0.71 (0.3–1.6)	0.40	1.06 (0.45–2.51)	0.90
Q2–Duration <1 min.	1	*No*	64 (10%)	1.0	–	1.0	–
		Yes	49 (20%)	2.26 (1.5–3.4)	<0.0001	1.77 (1.11–2.83)	0.02
Q3–Provoked by lying down in bed	2	*No*	50 (8%)	1.0	–	1.0	–
		Yes	63 (28%)	4.80 (3.2–7.2)	<0.0001	1.48 (0.87–2.50)	0.14
Q4–Provoked by turning over in bed	4	*No*	22 (4%)	1.0	–	1.0	–
		Yes	91 (27%)	8.94 (5.5–14.6)	<0.0001	6.01 (3.27–11.0)	<0.0001
Q5–Provoked by looking up	1	*No*	35 (9%)	1.0	–	1.0	–
		Yes	78 (16%)	1.94 (1.3–3.0)	0.002	1.064 (0.64–1.78)	0.81
Q6–Provoked by bending over	1	*No*	25 (7%)	1.0	–	1.0	–
		Yes	88 (17%)	2.85 (1.8–4.5)	<0.0001	1.26 (0.71–2.22)	0.43

OR, odds-ratio; CI, confidence interval.

75%. For dizziness provoked by turning over in bed (Q4), these percentages were 81 and 68%, respectively.

The way patients perceived their dizziness (vertigo, light-headedness, or instability) was not independently associated with the diagnosis BPPV.

Subgroup Analysis

We observed no significant differences in the manner of provocation (Q3–Q6) between the patients with posterior canal BPPV and the ones with horizontal canal BPPV.

In a subgroup analysis comparing the older to the younger patients, 324 (37%) patients were assigned to the elderly group (≥65 years). Of these patients, 55 (49%) were diagnosed with BPPV (**Table 2**). In the group of elderly patients, we did not find an association between the perceived type of dizziness and the occurrence of BPPV, while for the younger patients, BPPV was negatively associated with light-headedness and instability compared to vertigo [OR: 0.37 (95% CI 0.16–0.87), $p = 0.02$; OR: 0.36 (95% CI 0.15–0.84), $p = 0.02$] (**Table 4**).

Validation of LP Model

We validated the LP model for BPPV of Friedland et al. (14). Using the cut-off value of ≥0.2 for the LP value, the sensitivity was 83% and the specificity 66%. The ROC-curve showed that the AUC of this model was 0.76 (**Supplementary Figure 1**). Using the ROC-curve, we found that lowering the cut-off point to ≥0.15 changed the sensitivity to 66% and the specificity to 83%.

DISCUSSION

In this prospective cohort study, we determined the diagnostic value of several questions for the recognition of BPPV in patients with vestibular complaints. This would enable easy and fast assessment of patients presenting with dizziness, which can be valuable for otolaryngologists and neurologists, physicians working in emergency rooms, and general practitioners working in primary care. Early recognition of BPPV could reduce diagnostic delay and could prevent physicians from missing the diagnosis altogether, which puts the patient at an increased

TABLE 4 | Subgroup analysis for elderly and younger patients regarding perceived type of dizziness and diagnosis of BPPV.

	Missing	Perceived type of dizziness	*n* (% of answer)	OR (95% CI)	*p*-Value
Elderly (≥65 years)	30	*Vertigo*	16 (22%)	1.0	–
		Light-headedness	6 (14%)	0.60 (0.2–1.7)	0.34
		Instability	25 (16%)	0.68 (0.3–1.4)	0.27
		Other	3 (17%)	0.73 (0.2–2.8)	0.64
Younger	31	*Vertigo*	34 (14%)	1.0	–
		Light-headedness	7 (6%)	0.37 (0.2–0.9)	0.02
		Instability	7 (6%)	0.36 (0.2–0.8)	0.02
		Other	5 (10%)	0.68 (0.3–1.8)	0.45

OR, odds-ratio; CI, confidence interval.

risk of falling, impairment of daily activities, and missing out on treatment.

Two symptoms showed a strong and independent association with BPPV: the specific trigger of rolling over in bed, and a dizziness spell with a duration of <1 min. These results are in line with several previous studies, which also found that these symptoms had a positive association with BPPV (11, 13, 14, 17–21).

We found that whether patients perceived their dizziness as vertigo or instability was not a predictor of BPPV, whereas a perception of light-headedness clearly was a negative predictor for a diagnosis of BPPV. In subgroup analysis, both light-headedness and instability in younger patients were negatively associated with the diagnosis of BPPV ($p < 0.05$). This result is in accordance with results reported by Batuecas-Caletrio et al. and Piker et al. who showed that elderly patients with BPPV present less frequently with the classic vertigo sensation (6, 22). This could be explained by a decreased sensitivity of the otolithic organ due to otoconial degeneration (23, 24).

The question concerning the type of perceived dizziness had a substantially higher number of missing entries ($n = 61$, 7%) than the other study-specific questions ($n = 1$–4, 0.1–0.5%). Patients who did not answer this question either could not characterize their dizziness as one of the possible options or experienced multiple types of dizziness. The high number of missing entries shows that many patients find it difficult to describe the nature of their dizziness. This finding is consistent with the literature. Newman-Toker et al. found that patients were inconsistent and unreliable in their answers when having to pick a single type of dizziness (25). Seventy-nine percent of the patients picked more than one answer when given that option. In comparison, questions related to symptom duration and dizziness triggers were answered more consistently, and Newman-Toker et al. concluded that these questions would prove more useful for diagnosing BPPV (25). A possible explanation for the difficulty patients have in characterizing their dizziness is lack of familiarity with dizziness-related symptoms, as well as the fact that the duration of symptoms often is too short to assess the quality (26).

Combining the high rate of missing or inconsistent answers regarding the nature of the dizziness and our finding that there is no association between the type of dizziness and the presence of BPPV, we propose that the nature of dizziness should play a less prominent role in the diagnostic work-up of BPPV. Instead, the primary questions should be the ones focusing on triggers and on symptom duration. This change in priority will require a change in procedure and in education, as it has been shown previously that the majority of physicians endorse a main role for the nature of dizziness in determining of the etiology of dizziness (27).

We found no association between the type of head movement provoking dizziness and the affected semicircular canal of the vestibular organ. A possible explanation of this result could be the small number of patients diagnosed with horizontal canal BPPV in our study population ($n = 11$). To our knowledge, only one article has previously examined this possible association (28). The authors investigated whether the trigger for the dizziness could predict which semicircular canal is affected, but they did not find an association between the two phenomena. Further research is required to elucidate the apparent discrepancy between known pathophysiology and clinical practice.

Besides establishing which questions should be prioritized in the diagnosis of BPPV, we also validated the predictive model of Friedland et al. (14) with the data of our study-specific questionnaire. Using a cut-off of ≥0.2 for the LP value, we found that the model had a high sensitivity of 82% and a specificity of 66% with an AUC of 0.76. Our findings are almost identical to the cross-validation by Friedland et al. who found a sensitivity of 79% and specificity of 65%, with an AUC of 0.76 (14). Changing the cut-off point to 0.15 in our population changed the sensitivity to 66% and the specificity to 83%. This cut-off point could be more useful for ruling out the suspected diagnosis of BPPV, and it would prevent patients with a negative result from undergoing unnecessary diagnostic tests. Comparing the diagnostic power of the model to the two predictors with the strongest association with BPPV (Q2—duration of the spell <1 min, Q4—provoked by rolling over in bed), the model performs similarly to "provocation by rolling over in bed," but does not seem to add any diagnostic value over the use of single questions. However, the limitations of this result should be kept in mind, as we did not have all the data necessary for the length of spell variables (minutes to hours, days, days to weeks). The assumption that all vertiginous dizziness lasting

longer than 1 min counts as a positive interaction term ["1.84 × (Vertigo) × (LOS: Days to Hours)"] most likely results in an overestimation of this term. This overestimation results in a lower LP value and a structurally lower Pr(BPPV), resulting in fewer patients diagnosed with BPPV by means of this formula than is actually the case. It is therefore expected that our assumption results in an underestimation of the sensitivity found for the LP model.

A potential limitation of our study lies in the fact that our results are not suited to be extrapolated to first-line medical care as provided by emergency departments and general physicians. Because the data were gathered in a tertiary center, there is a risk of selection bias, and the patient population most likely has different characteristics than a non-preselected population. However, similar results have been found in studies set in a general medical department and in a secondary emergency hospital (11, 13).

Another limitation concerns the generalization of the two questions which were found to associate most strongly with a diagnosis of BPPV. Because these questions were part of a set of only six questions instead of a broader set, they might have erroneously been marked as correlated to BPPV. However, considering the findings compare favorably with previously published literature (11, 13, 14, 17–21), the influence of this limitation is most likely minor.

In conclusion, a strong, independent association exists between BPPV and the duration of a dizziness spell and the trigger situation of rolling over in bed. Interestingly, the nature of the dizziness was only of diagnostic importance in younger patients. We did not find an association between different types of provocative head movements and the affected semicircular canal. The predictive model of Friedland proved to perform well for confirming the suspected diagnosis of BPPV, but did not add diagnostic value compared to dizziness provocation by rolling over in bed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Review Board of Gelre Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TB: research idea. VD and BM: designed the study. VD: analyzed the data and wrote the manuscript. TB, BM, and TS: revised the manuscript. All authors contributed to the article and approved the submitted version. They confirm that questions related to the accuracy of the work were adequately discussed and resolved.

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SUPPLEMENTARY MATERIAL

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A Show of Ewald's Law: I Horizontal Semicircular Canal Benign Paroxysmal Positional Vertigo

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Objective: To evaluate horizontal semicircular canal (HSC) effects according to Ewald's law and nystagmus characteristics of horizontal semicircular canal benign paroxysmal positional vertigo (HSC-BPPV) in the supine roll test.

Methods: Patients with HSC-BPPV ($n = 72$) and healthy subjects ($n = 38$) were enrolled. Latency, duration, and intensity of nystagmus elicited by supine roll test were recorded using video nystagmography.

Results: In patients with HSC-BPPV, horizontal nystagmus could be elicited by right/left head position (positional nystagmus) and during head-turning (head-turning nystagmus), and nystagmus direction was the same as that of head turning. Mean intensity values of head-turning nystagmus in HSC-BPPV patients were (44.70 ± 18.24)°/s and (44.65 ± 19.27)°/s on the affected and unaffected sides, respectively, which was not a significant difference ($p = 0.980$), while those for positional nystagmus were (40.81 ± 25.56)°/s and (17.69 ± 9.31)°/s (ratio, 2.59 ± 1.98:1), respectively, representing a significant difference ($p < 0.0001$). There was no positional nystagmus in 49 HSC-BPPV patients after repositioning treatment, nor in the 38 healthy subjects. No significant difference in head-turning nystagmus was detected in HSC-BPPV patients with or without repositioning.

Conclusions: The direction and intensity of nystagmus elicited by supine roll test in patients with HSC-BPPV, was broadly consistent with the physiological nystagmus associated with a same HSC with single factor stimulus. Our findings suggest that HSC-BPPV can be a show of Ewald's law in human body.

Keywords: canalithiasis, horizontal semicircular canal, otolithic membrane, video nystagmography, Ewald's laws

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV), the most common peripheral vestibular disorder, is characteristic by recurrent attacks of brief positional vertigo (dizziness) and nystagmus elicited by a change in head position relative to gravity (1). The horizontal semicircular canal (HSC) is the second most affected canal, with HSC-BPPV accounting for 5–30% of all BPPV cases (2). In patients with HSC-BPPV, direction-changing positional nystagmus—horizontal, not vertical—can be elicited by specific diagnostic positional maneuvers, such as the supine roll test. In 1824, Marie–Jean–Pierre Flourens first found the relationship of eye movement and canals through damage to the pigeons' semicircular canals caused changes in their behavior (3). Since then, J. Richard Ewald conducted more elaborate experiments in 1892 (4). He observed the intensity and direction of nystagmus by inserting a small tube into the semicircular canal of the pigeon and applying positive and negative pressure. Flourens' and Ewald's Laws play an important role in our understanding of the physiology of human semicircular canals and the diagnosis of vestibular disorders. Both were derived from animal experiments, while a functional model of a single semicircular canal has not been established in human body.

At present, the diagnosis of HSC-BPPV was mainly based on the visual observation of nystagmus, and its excitatory or inhibitory effects have not been quantified. Caloric test is a classical method for research into the function of the HSC, however, it is difficult to stimulate the unilateral horizontal semicircular canal with a single factor (5). In HSC-BPPV, rolling of the otoconia from the posterior arm of the HC toward the ampulla in the affected side due to gravity drives the endolymph to the ampulla, while the otoconia rolls to the canal from the ampulla, driving the endolymph away from the ampulla (6, 7). Therefore, HSC-BPPV could reflect the direction and intensity of the nystagmus elicited by equal excitation and inhibition on a single horizontal semicircular canal, and clarify the gradient of those effects, which will be helpful in understanding the functional status of single horizontal semicircular canals.

In this study, we recorded and analyzed the latency time, direction, intensity, and duration of nystagmus in patients with HSC-BPPV during the supine roll test using 2-dimensional video nystagmography (2-D VNG). Further, we discussed the internal relationship between HSC-BPPV and Ewald's law, providing a basis for deeper understanding of the physiological characteristics of the human horizontal semicircular canal.

MATERIALS AND METHODS

Subjects

This was a prospective study involving assessment of 72 patients with vertigo, examined at the ENT Department of MY Hospital, Tianjin First Central Hospital between July 2018 and February 2019. Of 72 patients, 49 had accepted repositioning treatment and 23 had accepted other treatment. Healthy subjects (n = 38) were recruited as a control group. All subjects provided informed consent prior to their inclusion in the study. The study procedures have been approved by the Ethics Committee of the Tianjin First Central Hospital.

TABLE 1 | Demographic features of subjects in the HSC-BPPV and control groups.

Group feature	Control	HSC-BPPV	
		Before reposition	After reposition
Number	38	72	49
Age (years)*	52.7 ± 15.5	53.3 ± 14.8	53.6 ± 14.4
Sex (M:F)*	9:29	18:54	13:36

*HSC-BPPV, horizontal semicircular canal benign paroxysmal positional vertigo; M, male; F, female; *p > 0.05.*

Inclusion Criteria:

(1) Patients with a history of vertigo as a predominant symptom, or associated with other complaints, such as dizziness, vomiting, headache, hearing loss, etc.
(2) Patients diagnosed with geotropic HSC-BPPV, according to the *Clinical practice guideline: benign paroxysmal positional vertigo* (8).

Exclusion Criteria:

(1) Patients with apogeotropic HSC-BPPV, SSC-BPPV, PSC-BPPV, multiple-canal BPPV, cupulolithiasis, spontaneous, or other types of positional nystagmus.
(2) Patients with neurological deficits, including hemiplegia, quadriplegia, and stroke (cerebrovascular accident).

Methods

A detailed medical history, with a primary focus on the type of vertigo, and including the onset of symptoms, as well as their severity, duration, and associated factors, was obtained. Induction of nystagmus and corresponding parameters were observed and recorded using 2-D VNG (France Synapsys) during supine roll and Dix-Hallpike tests.

The supine roll test was performed to diagnose HSC-BPPV, and consisted of turning the head from the supine to either lateral position, when the patient was lying down in a supine position, with the head maintained at a 30 degree upward angle. The remaining steps of the exercise were the same as those for the supine roll test in *Clinical Practice Guideline* (9). The direction, latency time, duration time, and intensity of nystagmus were recorded in the supine position, left head position, and right head position, as well as during the process of head-turning. Latency time was the period from the end of a head turn (right/left head position) to the onset of continuous horizontal nystagmus. Duration was the period of continuous horizontal nystagmus from the onset to the end. The peak slow-phase velocity within 10 s from the onset of nystagmus was recorded as the intensity of nystagmus. Nystagmus direction and intensity were recorded in the supine and left/right head-turning positions during the supine roll test. Dix-Hallpike test was used as a preliminary method to analyze the characteristics of nystagmus and identify PSC-BPPV and multiple-canal BPPV, and its relevant data were

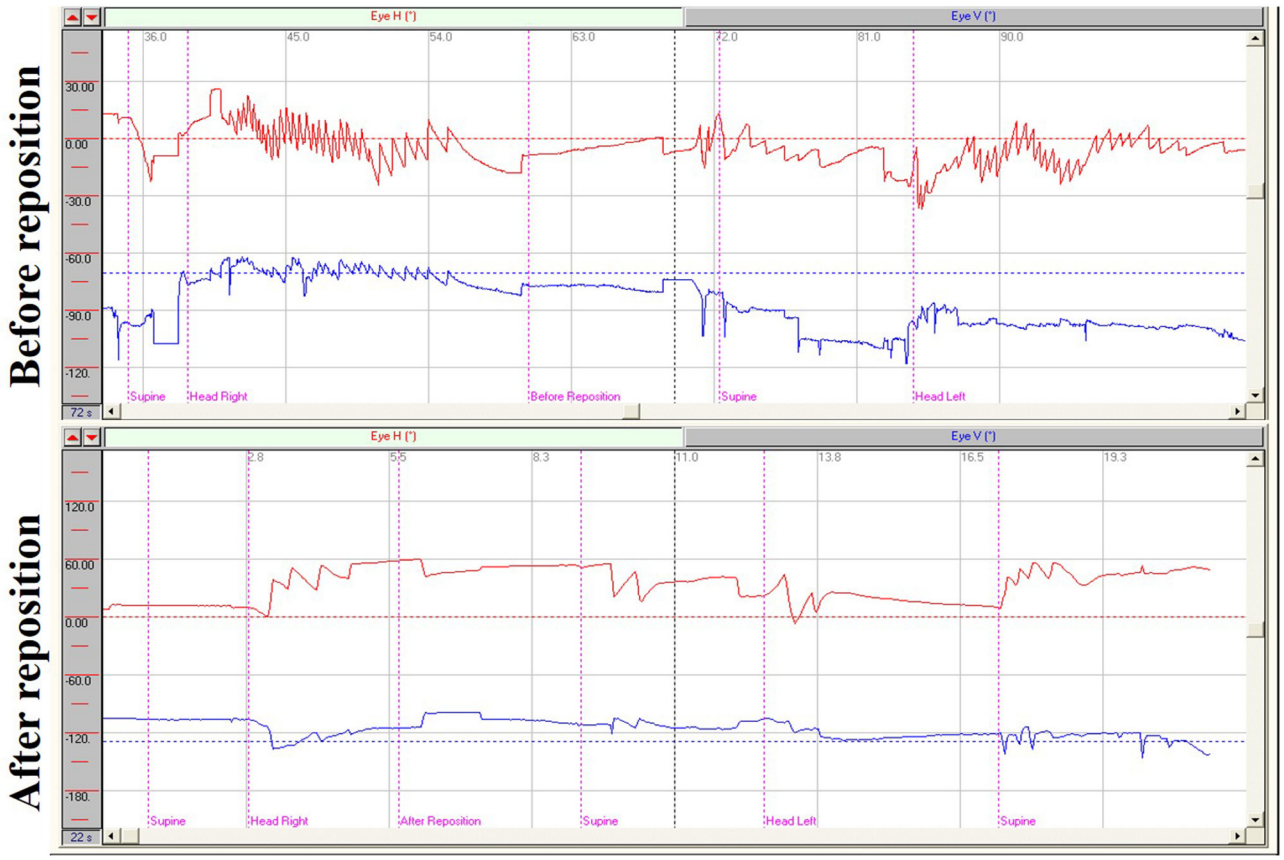

FIGURE 1 | Nystagmus measurements from supine roll tests of a patient with right HSC-BPPV before and after repositioning. **Before reposition**: Right horizontal positional nystagmus (72.5°/s), accompanied by weak vertical upward nystagmus, was elicited when the patient was moved from supine to head-right position and left horizontal positional nystagmus (35.7°/s) was elicited when the patient was moved from the supine to head-left position. Head-turning nystagmus was elicited in the same direction when the patient was moved from the head-right to supine position as from the supine to the head-left position, and vice versa. **After reposition:** Only head-turning nystagmus was detected on supine roll test of the patient with HSC-BPPV after CRP treatment.

not included in this data analysis. Based on the evidence on cupulolithiasis or canalithiasis in BPPV, multiple countries have established similar guidelines for the diagnosis and treatment of BPPV, with the canalith repositioning procedure (CRP) the primary treatment approach used (10).

Analysis

The parameters of horizontal nystagmus elicited by the supine roll test were compared within and between groups. IBM SPSS Statistics 22 (IBM SPSS, Turkey) was used for statistical analyses and GraphPad Prism 5 (GraphPad, San Diego, CA, USA) and R scripts were used to generate figures.

RESULTS

General Demographic Characteristics of Subjects

Patients with HSC-BPPV (18 men and 54 women) ranged in age from 21 to 81 years (mean 53.3 years). The control group comprised 38 healthy subjects (9 men and 29 women; mean age 52.8 years; age range 20–70 years). Demographic data for BPPV and control groups are summarized in **Table 1**. There were no significant differences in age or sex ratio between the two groups ($p > 0.05$). The supine roll test was performed on both sides for all patients with HSC-BPPV and controls, among which 49 cases with HSC-BPPV underwent successful repositioning using the barbecue maneuver.

General Characteristics of Nystagmus in Patients With HSC-BPPV on Supine Roll Test

In supine roll tests of patients with HSC-BPPV, horizontal nystagmus was elicited by placing the head in the right and left positions (positional nystagmus), as well as during the process of head-turning (head-turning nystagmus). In general, the direction of nystagmus was the same as that of head turning. Further, the intensity of head-turning nystagmus was weaker and that of positional nystagmus stronger. After a latency period, positional nystagmus elicited by the right/left position first rose to peak intensity, then weakened and gradually disappeared. Duration ranged from 6 to 81 s (mean 27.17 s) on the affected side,

and 6–74 s (mean 22.76 s) in the unaffected side. Positional nystagmus was caused by canalolithiasis and manifested as bilateral geotropic horizontal nystagmus, accompanied by a weak vertical upward nystagmus, which was more pronounced on the affected side, and disappeared following CRP treatment (**Figure 1**). Head-turning nystagmus was elicited by the process of head-turning from supine to the lateral position (head-left and head-right) and vice versa in the supine roll test, both before and after CRP treatment (**Figure 1**). Head-turning nystagmus was also detected in the healthy subjects, and characterized by horizontal nystagmus in the same direction as head turning during the supine roll test, consistent with the findings in patients with HSC-BPPV; however, no positional nystagmus was detected in healthy subjects.

Head-Turning Nystagmus on Supine Roll Test of Patients With HSC-BPPV and Healthy Subjects

The ranges of head-turning nystagmus intensity were 11.5–88.9°/s (mean 45.5°/s) and 11.6–98.5°/s (mean 43.8°/s) elicited by turning from the supine to head-right and head-left positions, respectively, in the 72 patients with HSC-BPPV. After CRP treatment, intensity ranged from 20.7 to 84.6°/s (mean 43.5°/s) and 20.8–86.3°/s (mean 45.1°/s) in 49 patients. We also analyzed head-turning nystagmus elicited by head-turning from supine to the affected and unaffected sides in patients with HSC-BPPV; no difference was detected between the two groups either before or after CRP treatment ($p = 0.987$ and $p = 0.488$, respectively). Intensity ranged from 21.9 to 100°/s (mean 51.3°/s) and 16.3–101.3°/s (mean 52.5°/s) in the 38 healthy subjects. In summary, there was no significant difference in head-turning nystagmus of HSC-BPPV patients, either before or after repositioning, or in healthy subjects ($p > 0.05$) (**Figure 2**).

Positional Nystagmus on Supine Roll Test of Patients With HSC-BPPV

The latency, duration, and intensity of positional nystagmus on supine roll test were recorded and analyzed for 72 patients with HSC-BPPV. On lying with the affected ear down, horizontal geotropic nystagmus was observed, with a mean onset latency of 1.78 ± 2.11 s (range, 0–10 s), and the mean duration of positional nystagmus was 27.17 ± 13.78 s (range, 6–81 s). Rolling patients onto the unaffected side resulted in markedly lower values for both latency and duration, at 1.06 ± 1.72 s (range, 0–10 s) and 22.76 ± 11.89 s (range, 6–74 s), respectively ($P < 0.05$). The characteristics of positional nystagmus in 72 patients with HSC-BPPV are presented in **Table 2**. Further, the intensity values of positional nystagmus on the affected and unaffected sides were 40.81 ± 25.56°/s (range, 3.5–131.6°/s) and 17.69 ± 9.31°/s (range, 2.1–41.6°/s), with a ratio of (2.59 ± 1.98):1, representing a significant difference between groups ($P < 0.0001$) (**Figure 3**).

Next, we compared head-turning and position nystagmus on the affected and unaffected sides in 72 patients with HSC-BPPV before CRP treatment. Positional nystagmus was markedly more intense on the affected side than that on the unaffected side ($p < 0.0001$); however, head-turning nystagmus intensity did not differ significantly between the two sides ($p = 0.987$). In particular, positional nystagmus was markedly less intense than head-turning nystagmus ($p < 0.0001$) when the patient was moved from the supine position to the unaffected side, while there was no difference between the two groups when patients were moved from supine to the affected side ($p = 0.294$) (**Table 3**).

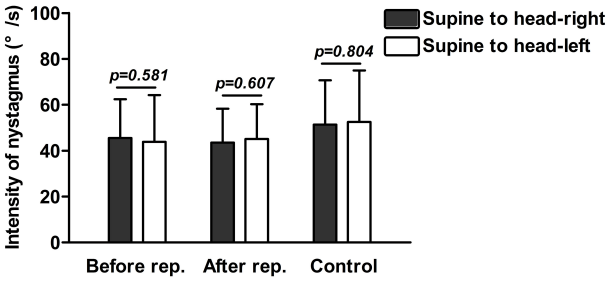

FIGURE 2 | Head-turning nystagmus on supine roll test of patients with HSC-BPPV with/without CRP treatment and healthy subjects. **Before rep.**: Head-turning nystagmus on supine roll test of patients with HSC-BPPV without CRP treatment. **After rep.:** Head-turning nystagmus on supine roll test of patients of HSC-BPPV with CRP treatment. **Control:** Head-turning nystagmus on supine roll test of healthy subjects.

TABLE 2 | Characteristics of positional nystagmus in 72 patients with HSC-BPPV.

Head position	Latency (s)	Duration (s)	Intensity (°/s)
Affected side	1.78 ± 2.11	27.17 ± 13.78	40.81 ± 25.56
Unaffected side	1.06 ± 1.72	22.76 ± 11.89	17.69 ± 9.31
t-value	2.238	2.055	7.209
p-value	0.027	0.042	0.000

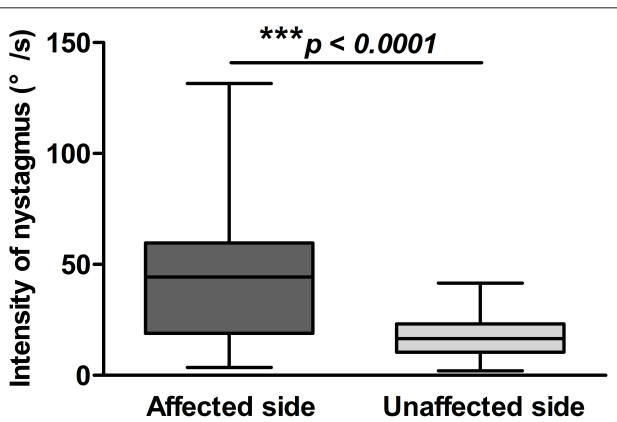

FIGURE 3 | Positional nystagmus on the affected and unaffected sides in 72 patients with HSC-BPPV. Positional nystagmus elicited on the affected and unaffected sides on supine roll test of patients with HSC-BPPV. The intensity values of positional nystagmus differed significantly between the affected and unaffected sides, with values of 40.81 ± 25.56°/s (range, 3.5–131.6°/s) and 17.69 ± 9.31°/s (range, 2.1–41.6°/s), respectively, and a ratio of (2.59 ± 1.98):1.

TABLE 3 | Comparisons of nystagmus on the affected and unaffected sides in 72 patients with HSC-BPPV.

	Head-turning nystagmus (°/s)	Positional nystagmus (°/s)	*t*-value	*p*-value
Affected side	44.70 ± 18.24	40.81 ± 25.56	1.053	0.294
Unaffected side	44.65 ± 19.27	17.69 ± 9.31	10.690	0.000
t-value	0.016	7.209		
p-value	0.987	0.000		

DISCUSSION

Benign paroxysmal positional vertigo is common, sometimes terrifying, but rarely portends serious disease. It is usually easily diagnosed and treated, and both the patient and the physician are immediately gratified. While much has been learned about the pathogenesis of BPPV in the past decades, many of its features remain mysterious (11). Previously, the physiological characteristics of BPPV were studied through biomechanical models (12, 13) and animal models (14). However, a functional model of a single semicircular canal has not been established in human body. According to Flourens' and Ewald's law, we know that the rotation plane of nystagmus is consistent with the plane of excited semicircular canal, but the excitatory or inhibitory effects have not been quantified.

Here, we focused on establishing a functional model of a single semicircular canal and chose HSC-BPPV for several reasons. In patients with HSC-BPPV, the horizontal nystagmus, rather than the torsional vertical nystagmus, can be elicited by a change in head position relative to gravity. HSC-BPPV was resulted from displacement of an otoconial mass within the endolymph of the HSC. Otoconia roll in opposite directions, due to gravity, when the head is turned to the affected and unaffected sides, stimulating the HSC of the affected side with the same factor bilaterally, producing a physiological stronger excitatory effect and weaker inhibitory effect, respectively. However, stimulation by the otoconia had yet to begin during the process of head-turning in the supine roll test, while physiological head-turning caused the endolymph to flow in the opposite direction of head-turning. Horizontal semicircular canals on both sides were stimulated simultaneously, eliciting horizontal nystagmus with the same direction as the head turning and no difference in intensity.

According to Ewald's law (15), rolling of the otoconia from the posterior arm of the HSC toward the ampulla in the affected side due to gravity drives the endolymph to the ampulla (as angular acceleration stimulation is applied to the semicircular canal alone) in the supine roll test, which excites the hair cells and elicits horizontal nystagmus, accompanied by weak vertical nystagmus. When the head is turned to the unaffected side, the otoconia rolls to the canal from the ampulla, driving the endolymph away from the ampulla (as angular deceleration stimulation is applied to the semicircular canal alone), inhibiting the hair cells in the affected side and eliciting a weaker horizontal nystagmus than the one triggered by the excitatory stimulus (16, 17). Further, the process of head-turning from the supine to the lateral position (head-left and head-right) and vice versa in the supine roll test is similar to that in the rotational test, which can apply angular acceleration and deceleration stimuli on bilateral horizontal semicircular canals, respectively, resulting in horizontal nystagmus in the same direction as head turning. A weak vertical nystagmus can be induced in the supine roll test because of the anatomic structure of the HSC in the inner ear. Della Santina et al. (18) reported that the mean horizontal semicircular canals plane tilted slightly up laterally 20° above Reid's horizontal planes, which was defined as a plane passing through the center of each bony external auditory canal (at the lateral entrance of the tympanic bone) and the cephalic edge of the inferiormost aspect of each infraorbital rim. According to Ewald's law, we know that the rotation plane of nystagmus is consistent with the plane of excited semicircular canal. Hence, geotropic horizontal nystagmus, accompanied by a weak vertical upward nystagmus, was caused by canalolithiasis. Based on the factors leading to BPPV (19) (i.e., otoconia loss, head displacement, and semicircular canal well) and the interaction between otoconia and endolymph in a semicircular canal, HSC-BPPV could be regard as a show of Ewald's law in human body theoretically.

At present, research into the function of the HSC is mainly conducted using caloric and rotational tests, because of the specific anatomical structure involved and the limitations of screening equipment. However, it is difficult to stimulate the unilateral horizontal semicircular canal with a single factor using either approach. Inhibitory or excitatory effects on the HSC can be caused by a single temperature (cold or warm) stimulus, and the dual effects of positive and negative stimuli cannot be determined simultaneously. Alternate warm and cold stimulation of both ears can reflect the dual effects of positive and negative stimuli; however, it is challenging to ensure that both effects are equal (5). Therefore, the caloric test can only predict that the bilateral horizontal semicircular canal should have an equal effect (nystagmus) in response to equal stimuli, but has not been standardized and is not quantitative. The lesion side, according to the relative difference in bilateral intensity of nystagmus, is evaluated first. The rotational test can be used to evaluate the function of the HSC by rotating around the vertical axis, which simulates physiological horizontal rotation stimuli; however, the horizontal semicircular canals on both sides receive inhibitory or excitatory stimuli simultaneously during this test. Therefore, this approach can only reflect comprehensive effects on both sides, despite only using a single stimulus on one side. That is, the rotation test cannot reveal physiological effects on a single horizontal semicircular canal receiving positive and negative stimuli. There have been ongoing efforts in the study of vestibular

medicine to establish a functional model of a single semicircular canal and assess its effects according to Ewald's laws, which can facilitate exploration of its physiological properties.

In this study, we analyzed the characteristics of nystagmus on supine roll test in 72 patients with HSC-BPPV, 49 of whom were treated with CRP, as well as 38 healthy subjects, and found that head-turning nystagmus was in the same direction as head turning in all groups and that its intensity did not differ significantly among groups. Positional nystagmus was also elicited in patients with HSC-BPPV, but not healthy subjects. Nystagmus features, including latency, duration, and intensity, differed significantly between the affected and unaffected sides. These results suggest that there are physiological and pathological differences in the nystagmus induced by the supine roll test, corresponding to head-turning and positional nystagmus. The head-turning nystagmus was elicited during head turning from supine to the lateral position and vice versa in both patients with HSC-BPPV with/without CRP treatment and healthy subjects. The positional nystagmus, elicited at the right/left position after a latency, resulting from the displacement of an otoconia by gravity, can also be regarded as physiological nystagmus. The intensity values of positional nystagmus elicited on the affected and unaffected sides of the head were 40.81 ± 25.56°/s and 17.69 ± 9.31°/s, respectively, with a ratio of (2.59 ± 1.98):1. Ichijo (20) reported that the intensity of nystagmus elicited on the affected and unaffected sides of the head varied markedly among 20 patients with HSC-BPPV, with a ratio of 5:2, which is broadly consistent with our findings. Further, we showed that there was no positional nystagmus on supine roll test of patients with HSC-BPPV treated with CRP, due to the absence of otoconia stimulus, while head-turning nystagmus was still elicited, and did not differ significantly from that observed in healthy subjects. Notably, although there was no significant difference, the intensity of head-turning nystagmus in patients with HSC-BPPV with or without CRP treatment was weaker than that in healthy subjects, possibly due to semicircular canal dysfunction in these patients. The lesion of semicircular canals has the same etiological factors with the utricle pathological change in BPPV, and the dysfunction mostly happens in low-frequency range of semicircular canal frequency band. The ectopic otoconia is not the main etiological factors for that (21). The ectopic otoconia would be returned back to utricle after CRP treatment, but the dysfunctional of the semicircular canals remained. Therefore, the intensity of nystagmus in patients with BPPV after CRP treatment was weaker than that in healthy subjects. Our findings suggest that supine roll testing of patients with HSC-BPPV can both reflect the direction and intensity of the nystagmus elicited by equal excitation and inhibition on a single horizontal semicircular canal, and clarify the gradient of those effects, which will be helpful in understanding the functional status of single horizontal semicircular canals.

CONCLUSION

HSC-BPPV is considered a clinical disease; however, the nystagmus, elicited by the displacement of otoconia and semicircular canals on supine roll test follows the laws of Flourens and Ewald. This is reflected in the direction and intensity of nystagmus elicited by a single horizontal semicircular canal, indicating that it has physiological properties. These finding suggest that HSC-BPPV can be a show of Ewald's law in human body, and used as a physiological stimulus model to understand deeply the characteristics of the human horizontal semicircular canal.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of the Tianjin First Central Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WW and TC: study design. TC, WW, SL, QL, CW, and XZ: acquired and analyzed the data. XZ, YB, WW, XH, and TC: drafted the manuscript. All authors data interpretation and critical revision of the manuscript.

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ORIGINAL RESEARCH
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Clinical and VNG Features in Anterior Canal BPPV—An Analysis of 13 Cases

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Objective: To define diagnostic VNG features in anterior canal BPPV during positional testing (Dix-Hallpike, supine head hanging, and McClure Pagnini tests).

Study Design: A retrospective study of patients diagnosed with anterior canal BPPV across four referral centers in New Delhi, Kochi, Bangalore, and Dubai.

Subjects and Methods: Clinical records of 13 patients with AC BPPV out of 1,350 cases, during a 3-years period, were reviewed and analyzed by four specialists.

Results: Four patients had positional down beating nystagmus with symptoms of vertigo during the bilateral DHP maneuver. Seven cases had positional down beating nystagmus only on one side of DHP. Typical down beating nystagmus was seen in 10 out of 13 cases during the straight head hanging maneuver. Down beating torsional nystagmus was seen in 6 out of 13 cases. Down beating with horizontal nystagmus was seen in three cases (in DHP and MCP mainly) while pure down beating nystagmus during SHH was only seen in four cases.

Conclusion: We conclude that anterior canal BPPV is a rare but definite entity. It may not be apparent on positional testing the first time, so repeated testing may be needed. The most consistent diagnostic maneuver is SHH though there were patients in which findings could only be elicited using DHP testing. We recommend a testing protocol that includes DHP testing on both sides and SHH. MCP testing may also evoke DBN with or without the torsional component. Reversal of nystagmus on reversal of testing position is unusual but can occur. The Yacovino maneuver is effective in resolving AC BPPV. We also propose a hypothesis that explains why DHP testing is sensitive to AC BPPV on either side, whereas MCP lateral position on one side is only sensitive to AC BPPV on one side. We have explained a possible role for the McClure Pagnini test in side determination and therapeutic implications.

Keywords: Anterior canal BPPV, VNG, VNG features, Dix Hallpike test, McClure Pagnini, Yacovino maneuver, Down beating Nystagmus, Benign paroxysmal positional vertigo

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INTRODUCTION

Benign positional paroxysmal vertigo (BPPV) is the most frequent vestibular disorder displaying a 10% incidence rate in the general population (1). Posterior-canal BPPV accounts for 80–90% of cases, while lateral-canal BPPV (LC-BPPV) occurs in 10–20% of patients. Anterior (superior) canal BPPV (AC BPPV) is very rare (1–2%) (2–4).

Posterior canal BPPV, and lateral canal BPPV are well-defined entities, and their diagnosis is based on the direction of the nystagmus elicited by head position change, which include up beating and torsional in posterior canal BPPV and horizontal in horizontal canal BPPV.

The diagnostic criteria for BPPV of the anterior semi-circular canal (AC BPPV) is less clearly defined. Even the existence of the AC BPPV has been questioned (2).

The presence of a downbeat nystagmus with or without a torsional component during positional testing is the only described feature of AC BPPV (5). There is a need to firmly establish the existence of, define the diagnostic criteria, and clarify the treatment for AC BPPV.

To this end, we undertook an analysis of 13 cases of AC BPPV with a view to identify reliable diagnostic criteria during positional tests like supine head hanging (SHH), Dix-Hallpike (DHP) and McClure Pagnini (MCP) tests for this rare form of BPPV.

MATERIALS AND METHODS

This study analyzed patients diagnosed with AC BPPV from among over 1,350 patients of vertigo, seen in four referral centers for vertigo and dizziness in New Delhi, Kochi, Bangalore, and Dubai, during a 3-years period from 2017 to 2020. The records, both clinical and VNG, were each reviewed by all four vertigo specialists equally, and only 13 cases of AC BPPV were confirmed.

The patients were tested as per protocol and treated in their respective centers, and consent for the use of the data for publication after suitable anonymization was obtained.

The patients' details and VNG findings were discussed jointly by the consultants via video conferencing at a meeting convened for this study.

All these patients had been referred for a neuro-vestibular opinion after excluding other medical and central causes, because of one or more of the following problems: vertigo, dizziness, or postural instability.

The clinical history was compatible with BPPV, i.e., describing brief episodes of rotational vertigo lasting for a few minutes, when turning in bed, lying down and looking up, bending forwards, or extending the head backwards.

The physical examination consisted of a basic clinical, neurological evaluation and otoneurological examination such as range of motion of eyes, Otoscopy, Romberg and Unterberger tests, and cranial nerve and cerebellar tests.

Videonystagmography was undertaken using the same device (Balance Eye ®) in all centers. Balance Eye is a binocular VNG system which is class 2A European CE certified. It has the provision for eye movement recording with vision allowed and denied. We evaluated oculomotor activities like saccades, smooth pursuit, gaze with and without fixation and responses to horizontal high frequency headshake, hyperventilation, lateral canal head impulse test, and positional tests.

To explain the movement of otoconial debris in the McClure Pagnini position, we used the three-dimensional (3D) study tool of the membranous labyrinth named BPPV viewer developed by Traboulsi and Teixido (6).

The diagnosis of BPPV was confirmed using the diagnostic criteria established by the (2). These include a history of recurrent transient positional dizziness/vertigo and an induced positional nystagmus by the Dix-Hallpike test (DHP), McClure Pagnini supine roll test (MCP) done bilaterally, and supine head hanging test (SHH) (5, 7, 8).

A diagnosis of AC BPPV was made if a short duration (less than a minute) of vertical down beating nystagmus (DBN) with or without a torsional component was observed during the DHP and/or SHH tests. We used the Barany society criteria (9) to record the type of torsional nystagmus. The nystagmus beats predominantly downward but with a small torsional component in which the upper pole of the eye beats toward the affected ear (9).

The AC BPPV was classified as Definite if the vertigo was resolved by a repositioning maneuver (Yacovino maneuver) (5) and Probable if it was refractory (5).

CASE REPORTS

Case 1

A 73-year-old female complained of vertigo of a spinning nature, 2 min in duration, and was present only when changing head posture and bending forward for 3 months. It was not associated with any other symptoms like headache, phonophobia, and photophobia. It was relieved after vomiting. Her medical and audiological examination was normal for her age.

VNG Examination

DBN was seen during the DHP on the right with extension, the DHP on the left was negative. Down beating nystagmus was seen on the right lateral MCP and supine head extension (90°) maneuver. She was treated with the Yacovino maneuver and her symptoms resolved instantly. We unfortunately lost this patient before follow-up.

Case 2

A 67-year-old lady had complaints of a "spinning" sensation with vomiting over the last 3 months with reduced hearing and aural fullness of the right ear. Over the last year she had occasionally experienced tinnitus in both ears, with the right being more affected than the left ear. She also had hypertension and cervical spondylosis. Audiological evaluation showed mild

Abbreviations: AC, anterior canal; BPPV, benign paroxysmal positional vertigo; DHP, Dix-Hallpike; DBN, down beating nystagmus; MCP, McClure Pagnini; SHH, supine head hanging; LC, lateral canal; PC, posterior canal; VNG, videonystagmography.

sensorineural hearing loss in the right ear and normal hearing with a sensorineural component at high frequencies in the left ear. Cervical VEMP was normal for both ears. The medical and neurological examination was normal.

VNG Findings

The saccades and smooth pursuit examination were normal. Down and right beating nystagmus was seen during the DHP on the left and right (left > right).

The Yacovino maneuver was done but the symptoms recurred after 5 days. We attempted the Yacovino maneuver again on a second visit, but she was not relieved of her symptoms. We performed the DHP maneuver and saw that DBN was more on the left than the right side on her third visit. We performed the Yacovino maneuver again with her head rotated to the right side by 30° to make the left anterior canal more vertical. She was relieved of vertigo sensation after that maneuver. The symptom-free follow-up period is now 3 months.

Case 3

A 43-year-old male came in with a history of spinning vertigo lasting for less than a minute starting 2 weeks prior. The vertigo was triggered by positional changes like sitting up from the supine position and while turning in bed. The vertigo was associated with nausea. He denied any history of head injury.

His clinical examination was normal. On positional testing the DHP test on the left side elicited the symptoms of vertigo and down beating torsional (upper pole of eye beating to left) nystagmus. On getting up, the patient had symptoms of vertigo without any apparent nystagmus on VNG. The MCP maneuver was negative on the right side. On the left side, the patient had symptoms of vertigo and down beating nystagmus. The SHH maneuver elicited vertigo and down beating torsional (upper pole of eye beating to left) nystagmus. The patient underwent the Yacovino maneuver with apparent success and his symptoms resolved and have not recurred over the last 6 months.

Case 4

A 65-year-old male presented with vertigo and neck pain starting 2 years prior. Vertigo episodes were brought on from getting up from bed and looking down. It lasted for a few seconds along with the sense of imbalance. Audiometric findings revealed bilateral moderate to severe high frequency sensorineural hearing loss.

VNG Findings

During the DHP test, a few down beats were seen with extension on the right, while the left was negative for vertigo and nystagmus. On the right lateral during MCP down and left beating nystagmus was seen, while returning to supine position displayed only down beats.

The Yacovino maneuver was done on follow-up and he recovered from vertigo attacks. He has been symptom-free for the past 2 months.

Case 5

A 56-year-old lady complained of vertigo especially when looking down and turning her head to either side 1 month prior. She also had left ear pain and tinnitus and had fallen once for which she was admitted. She was unable to do her daily chores of house cleaning and washing clothes. Her medical and neurological examination was normal, and apart from degenerative changes in the cervical spine, there were no comorbid conditions.

VNG Findings

Left and down beating nystagmus was seen on right during the DHP test, which reversed to right and down on making her sit, left, and DBN was seen on the right lateral of the MCP with reversal on getting up. Disappearance of symptoms after the Yacovino maneuver led to the diagnosis of AC BPPV. The patient has been symptom-free for 6 weeks now.

Case 6

A 55-year-old gentleman presented with a history of short episodes of spinning vertigo when lying down in bed and when turning over in bed for the last 4 months. The episodes were short, eventually he also felt dizziness while walking. Dizziness subsided within 10 days but after 3 months he again felt the same dizziness for which he came to our clinic.

VNG Findings

Down beats with associated vertigo were seen on right DHP maneuver. Short-lived down beats were also seen on the SHH maneuver. He recovered from vertigo after the Yacovino maneuver and has been symptom free for 2 months.

Case 7

A 43-year-old male came in with a history of spinning vertigo lasting for less than a minute during that day. The vertigo was triggered by positional changes like sitting up from the supine position. He denied any history of head injury. His clinical examination was normal.

VNG Findings

The DHP maneuver on the right side elicited the symptoms of vertigo and down beating nystagmus. The torsional component was not apparent. There was no reversal of nystagmus on sitting up. The DHP on the left side and MCP maneuver were negative. The SHH maneuver elicited vertigo and DBN. The nystagmus duration was only for a few seconds and for 4–5 beats. The torsional component was not apparent. The patient underwent the Yacovino maneuver and has been symptom-free for over a month now.

Case 8

A 36-year-old male came in with a history of spinning vertigo lasting for less than a minute after 1 week. The vertigo was triggered by positional changes like sitting up from the supine position. He had associated nausea and vomiting. He denied any history of head injury.

His clinical examination was normal. The DHP on both the sides was negative. The MCP maneuver on the right side was negative and on the left side it elicited torsional (upper pole beating to left) nystagmus. The SHH maneuver elicited vertigo and down beating torsional (upper pole beating to right) nystagmus. The patient underwent the Yacovino maneuver and has been symptom free for a period of 1 month.

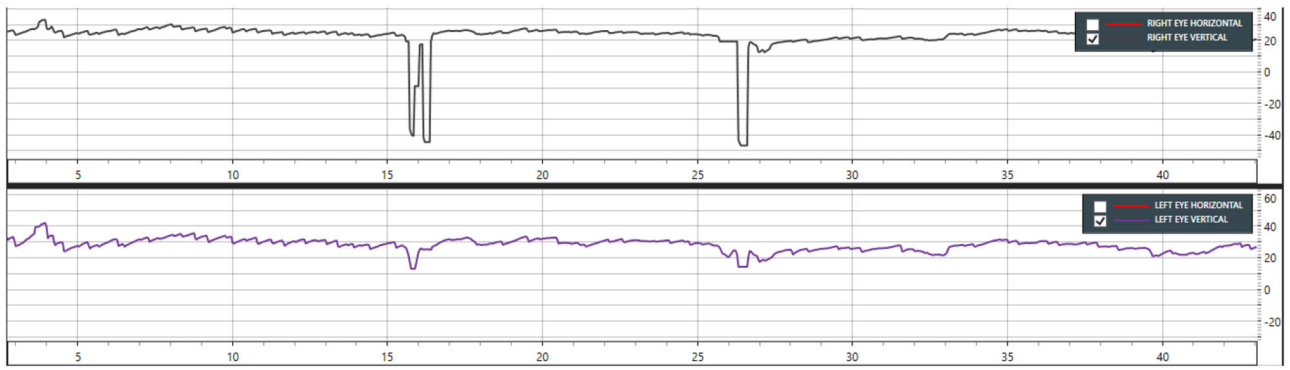

FIGURE 1 | Case 13—Dix-Hallpike left showing down beating nystagmus from 5 to 40 s (Only vertical movements are shown in this graph).

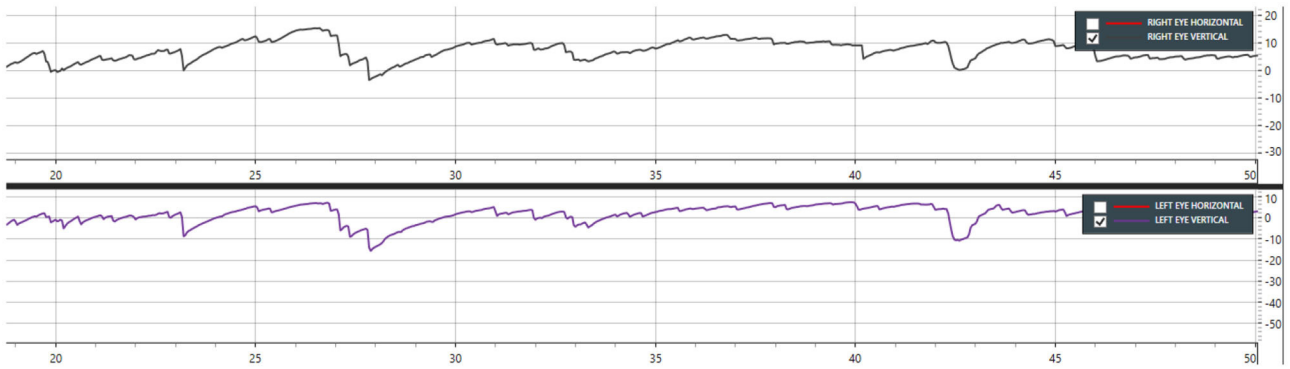

FIGURE 2 | Case 13—Dix-Hallpike right showing down beating nystagmus from 19 to 48 s (Only vertical movements are shown in this graph).

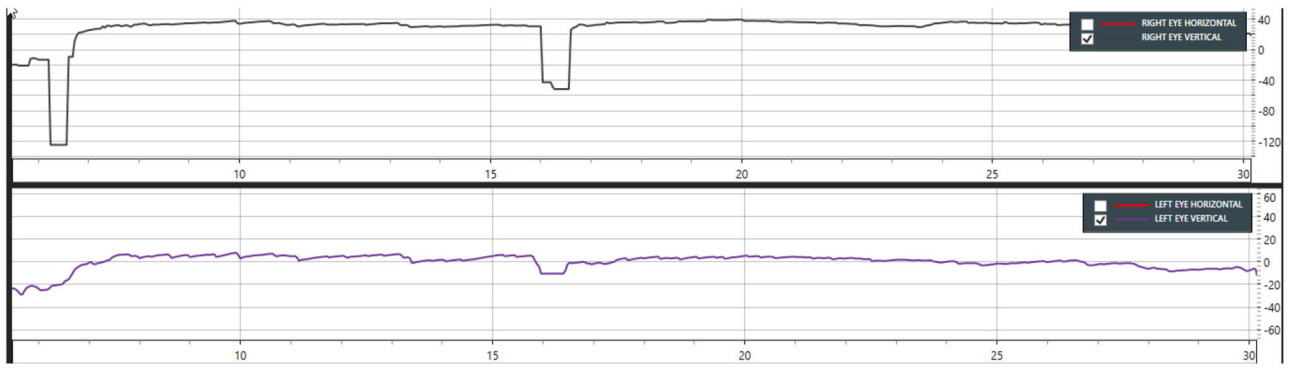

FIGURE 3 | Case 13—Supine head hanging showing down beating nystagmus from 5 to 25 s. Note that DBN is most prominent in the left eye (Only vertical movements are shown in this graph).

Case 9

A 36-year-old female came in with a history of spinning vertigo lasting for less than a minute starting 3 weeks earlier. The vertigo was triggered by positional changes like bending down and moving her head while walking. She had associated nausea and denied any history of head injury.

Her clinical examination was normal. The DHP on both sides was negative but while getting up from the right side the patient had sitting up vertigo without any nystagmus. The MCP maneuver on the right and left side was negative. The first SHH maneuver was negative (probably due to voluntary convergence) but on sitting up the patient had vertigo with up beating nystagmus for 3 s. The second SHH maneuver showed

down beating torsional (upper pole beating to left) nystagmus. The patient underwent the Yacovino maneuver and has been symptom free for over 1 month now.

Case 10

A 50-year-old female came in with a history of spinning vertigo lasting for less than a minute starting over 6 weeks prior. The vertigo was triggered by positional changes like turning to left in the supine position. She had associated nausea and vomiting during a few episodes.

Her clinical examination was normal. She underwent positional testing. The findings were as follows: the DHP test on both sides was positive and showed DBN without a torsional component. The MCP maneuver on the right side was negative and on the left side it elicited torsional (upper pole beating to left) nystagmus. The SHH maneuver elicited vertigo and down beating torsional (upper pole beating to left) nystagmus. The patient underwent the Yacovino maneuver but the symptoms recurred again after 15 days. She recovered after a third Yacovino maneuver. She has been asymptomatic since then.

Case 11

A 46-year-old doctor came to our clinic with a history of spinning vertigo lasting for a few seconds for the last 5 days. The vertigo was triggered by positional changes like turning to either side in the supine position. It was also triggered by looking up and down. Neurological and other examinations were normal.

She underwent positional testing with the help of VNG. The findings were as follows: the DHP test on both sides was positive and showed DBN without a torsional component. On the right side, the DHP showed down and right beating nystagmus. The SHH maneuver elicited vertigo and down beating torsional (upper pole beating to left) nystagmus. The patient underwent the Yacovino maneuver but it failed. She recovered after a fourth Yacovino maneuver. She has been asymptomatic since then (**Supplementary Videos 1**, **2**).

Case 12

A 52-year-old lady came in with a history of spinning vertigo lasting for less than a minute which began that day. The vertigo was triggered by getting up from the supine position. She had associated nausea and vomiting. She denied any history of head injury.

On positional testing, the DHP test on the right side elicited vertigo with DBN. On getting up from the right side, the patient had sitting up vertigo without any nystagmus. DHP on the left side was negative for symptoms and nystagmus, but the patient had sitting up vertigo without any apparent nystagmus. The SHH maneuver elicited vertigo and down beating torsional (upper pole beating to right) nystagmus. The patient underwent the Yacovino maneuver which resolved the symptoms.

Case 13

A 70-year-old gentleman came to our clinic with spinning vertigo which began 2 weeks prior. Duration was for a few seconds and it was associated with position change and looking up and down. He had a known case of hypertension and was taking regular medication.

TABLE 1 | Age, sex, history, and duration of vertigo in 13 patients.

No.	Sex	Age	Clinical history	Head trauma	Time course	Sensorineural hearing loss (SNHL)
1	F	73	Vertigo	No	3 months	No
2	F	67	HT	No	90 days	Mild SNHL R
3	M	43	Vertigo	No	14 days	No
4	M	65	Neck pain, vertigo	No	2 years	B/L mod SNHL
5	F	56	Ear fullness, tinnitus, and vertigo	No	30 days	Yes
6	M	55	Vertigo	No	120 days	No
7	M	43	Vertigo	No	1 day	No
8	M	36	Vertigo	No	7 days	No
9	F	36	Vertigo	No	21 days	No
10	F	50	Vertigo	No	6 weeks	No
11	F	46	Vertigo	No	5 days	No
12	F	52	Vertigo	No	1 day	No
13	M	70	Vertigo	No	14 days	No

VNG Findings

DHP on both sides showed DBN. No nystagmus was seen on the MCP test. Down beating nystagmus was also seen during the SHH maneuver with extension. There was no reversal in any positional test. The patient underwent the Yacovino maneuver twice which resolved his symptoms (**Figures 1**–**3**).

Summary of all cases and findings are given in **Tables 1**, **2**.

DISCUSSION

The anterior semicircular canal is one of two semicircular canals in the sagittal plane, whose anatomical orientation is 41° to the sagittal plane while the posterior canal is oriented 56° to the sagittal plane. These canals converge at the crus commune, which leads to the utricle (10). Terms like superior canal and anterior canal are used interchangeably in literature. In this article we will use the term anterior canal (11).

Anterior canal BPPV (AC BPPV) is the rarest form of BPPV, with reported incidence of 1–2%, (4, 5, 12–14) although some authors have reported higher incidences in their series (10, 11). There is no consensus on the diagnosis and treatment, and the existence of AC BPPV as a separate entity has been questioned (15). In our study we noted an incidence of <1% (13 cases out of 1,350 cases of vertigo, pooled data from four specialized vertigo clinics).

Involvement of the anterior canal is suggested when a down beat nystagmus with a small torsional component appears on positional tests. The torsional component, if it is present, is usually in the direction of the involved ear as judged by the movement of the upper pole of the eye (12).

TABLE 2 | Findings in DHP, MCP, and SHH maneuvers with direction and type of nystagmus.

	DHP right	DHP left	MCP right lateral	MCP left lateral	SHH/ Yacovino	Reversal
1	Down	–	Down	–	Down	No
2	Down + H(Rt)	Down + H(Rt)	Not done	Not done	–	No
3	–	Down + T(Left)	–	Down	Down + T(Left)	No
4	Down	–	Down + H(Left)	–	Not done	No
5	Down + H(Left)	–	Down + H(Left)	–	–	Yes
6	Down	–	Not done	Not done	Down	No
7	Down	–	–	–	Down	No
8	–	–	–	T(left)	Down and T (Right)	No
9	–	–	–	–	Down + T(Left)	Yes
10	Down	Down	–	Torsional (Left)	Down +T(Left)	No
11	Down + T(Rt)	Down	Not done	Not done	Down + T(Right)	No
12	Down	–	Not done	Not done	Down + T(Right)	No
13	Down	Down	–	–	Down	No

H(rt) and H(lf) indicates Horizontal right and left beating nystagmus. T(lf) and L(rt) indicates Torsional nystagmus with upper pole of eye beating to left and right side.

Note that DBN is also seen in cases of the apogeotropic variety of PC BPPV. DBN also occurs in central positional nystagmus associated with various brainstem and cerebellar lesions (16, 17), and this needs to be differentiated. In our study, central positional nystagmus was ruled out clinically and radiologically prior to evaluation in the vertigo and balance clinics in all cases.

There are two features that make determining the side of AC BPPV difficult. The first is that the torsional component may be very subtle and easy to miss. Second is that the nystagmus elicited is similar during DHP testing (down beating) on both sides even when the unilateral canal is involved, therefore the lateralization is hard to confirm (18–22).

According to the Barany Society criteria of 2015, the nystagmus of BPPV of the anterior canal can be elicited by any or all the positional tests, such as DHP tests unilaterally or even bilaterally and the SHH test (2) (**Table 1**).

Particles in the anterior canal can be free floating (canalolithiasis) or they might be attached to the cupula (cupulolithiasis) (23). Canalolithiasis of the anterior canal has a latency of up to 10 s and a maximum duration of 1 min. While cupulolithiasis of the anterior canal can present as persistent down beating nystagmus (more than 1 min) with or without torsional nystagmus (23).

Dix-Hallpike Test (DHP)

The DHP test is traditionally considered as a test for BPPV of the ipsilateral posterior canal. However as the test aligns a canal pair, i.e., ipsilateral posterior canal and contralateral anterior canal along the gravity plane, it is actually a test of a pair of canals rather than an individual canal.

Note that during natural head movements, the same movement is stimulatory to one canal and inhibitory to the other canal in the pair. During DHP testing, the gravity-induced debris movement is stimulatory to the anterior canal when debris is present in the anterior canal and stimulatory to the posterior canal when debris is present in the posterior canal. Therefore, the elicited nystagmus is that of excitation of the involved canal.

Down Beating Nystagmus

In our study, seven patients (1, 3, 4, 5, 6, 7, and 12) had positional DBN during the unilateral DHP test, while four patients out of 13 cases (cases 2, 10, 11, and 13) had positional DBN with symptoms of vertigo on the bilateral DHP test.

Casani et al. in their series of 18 cases noted positional DBN unilaterally with the DHP maneuver only in six cases and bilaterally in four patients (21).

Lopez-Escamez et al. found that DBN was seen during right DHP in five out of 14 cases, while during left DHP in only three cases. Three cases had positional DBN during both the left and right DHP test (22).

Similar findings are seen with Yang et al., where positional DBN was seen in 26 patients out of 40 during the DHP test (including both unilateral and bilateral), bilateral DHP was positive in 17 patients out of 40 (24).

Bertholon et al. reported that out of 12 patients, the nystagmus was triggered by the DHP test bilaterally in nine patients (75%) and unilaterally in one. In two patients with a typical history of positional vertigo but had a negative DHP test, the straight head-hanging maneuver was performed and was found to be effective.

The nystagmus of anterior canal BPPV is elicited in bilateral DHP testing even though only one side of the canal is involved (Eggers et al. and Barany's criteria) (19). It is believed that during a contralateral DHP maneuver, the affected canal is aligned with the gravity plane causing movement of the otolithic debris, whereas during an ipsilateral DHP test, the canal is oriented orthogonal to the gravity plane making it immune to gravity-induced debris movement. However, the fact that the anterior semicircular canal makes an angle of 40° with the para-sagittal plane and DHP testing involves turning the head by 45° results in the canal not being perfectly orthogonal to the gravity plane when performing the contralateral DHP test. This leads to movement of otolithic debris under the influence of gravity and explains the nystagmus.

Torsional Nystagmus

In our study, torsional nystagmus was seen in four cases (2, 3, 5, and 11) during the DHP test.

According to Eggers et al., positional DBN of anterior canal BPPV is best seen in the SHH test (19). But the torsional component is usually better seen with DHP positioning and less frequently seen with a SHH test (4, 18, 21, 25).

Casani et al. noted that there was a torsional component of the nystagmus in six out of 18 cases, it was noted in five cases in unilateral DHP and in one case, they found it on bilateral DHP (21).

All 14 patients had positional DBN on different positional tests including DHP according to Lopez et al. (22). However, no torsional nystagmus was reported in their study (22).

According to Ewald et al. and von Brevern et al., the torsional component might or might not be seen in AC BPPV (2, 5, 13, 26), possibly because of the anterior canal's anatomical orientation which is closer to the sagittal plane (about 41°) compared to that of the posterior canal (56°) (16). However, the invariable demonstration of a torsional component during provocative testing of superior canal dehiscence syndrome (SCDS) argues against the anterior canal's anatomical orientation as an explanation for the lack of torsional component in BPPV.

Furthermore, the provocative test of SCDS is done in the upright position and positional testing moves the head to varying degrees of extension from the supine position. This gravity-related position difference during the observation of provoked nystagmus between the two conditions combined with the observation that the torsional component varies between DHP and SHH tests gives credence to our hypothesis that the difference in torsion is related to the difference in degree of otolithic influences on semicircular canal responses.

In our study, in two cases (8 and 9) no nystagmus was seen during the DHP test, of them nystagmus was seen during the SHH and MCP tests (case 8). We hypothesize that the degree of otolithic stimulation is the determinant factor in eliciting torsional nystagmus. The debris moving in the plane of the same canal causes different degrees of torsional nystagmus depending on the testing maneuver employed (DHP and SHH), and possibly reflects varying degrees of otolith semicircular interactions depending on head orientation with respect to gravity.

Supine Head Hanging Test

In our study, 12 out of 13 patients underwent the SHH with extension maneuver and pure down beats were seen in four cases (cases 1, 6, 7, and 13), while down beating torsional nystagmus was seen in six cases in the SHH test.

Down Beating Nystagmus in SHH

Three cases out of 14 had positional DBN on the SHH test according to Lopez et al. (22). According to Yang et al., during the SHH test, a DBN was observed in 33 (82.5%) patients (24).

Torsional Nystagmus in SHH

In our study, down beating torsional nystagmus was seen in six out of 12 patients in the SHH test. Casani et al. noted that torsional nystagmus was seen in six out of 18 patients (21). Yang et al. noted that DBN with a torsional component was observed in seven patients out of 40 (24). Bertholon et al. reported that out of 12 patients, the DHP test was negative in two patients but the straight head-hanging (SHH) maneuver was positive. In six patients, torsional nystagmus was present during the positional tests (16).

In our study, we also found that SHH was more sensitive than the DHP test. It was positive in 10 cases out of 12. In two other cases (cases two and five), down beating nystagmus was only elicited during DHP tests.

McClure Pagnini Test

The role of the MCP test in AC BPPV has not been clarified, but the presence of a horizontal component with DBN has been mentioned in a few studies (24, 27).

Imbaud et al. (27) in their series of 20 patients with AC BPPV saw horizontal torsional nystagmus beating toward the uppermost ear in the lateral supine position with reversal on standing.

In our study, down beating torsional nystagmus was seen in four cases in the DHP and MCP tests, also in some cases it was associated with a mild horizontal component with down beats. However, in a few positions of DHP and MCP, pure down beating nystagmus was also seen (cases 1, 4, 6, 7, 10, 12, and 13).

The vertical canal plane orientation is traditionally described as a tilt away from the para-sagittal plane toward the coronal plane. However, it is also known that the vertical canals are also tilted toward the horizontal plane. This results in the projection vector of rotations around the vertical canals influencing the projection vectors of rotations around horizontal canals resulting in the observed horizontal component of nystagmus.

In our study, an MCP test was done in nine cases. We found that the nystagmus was similar in directional properties to that seen in the DHP tests, though of a lesser intensity. In few cases, nystagmus was consistently unidirectional in DHP and MCP, if nystagmus was elicited on the right DHP then nystagmus was only seen on the right lateral of MCP. In case 3, the nystagmus was only seen in a left sided examination (left DHP and left lateral of MCP). While in cases 1, 4, and 5, nystagmus was only seen on the right side (right DHP and right lateral of MCP).

In case 10, down beating nystagmus was elicited on both DHP (right and left) but MCP was only positive on the left lateral, which was exactly same as the direction of torsional nystagmus and toward the side of canal involved.

We propose that the direction of nystagmus on MCP may indicate the side of involvement. But on DHP tests on the right or an MCP in the right lateral position, the otoconial debris from the left anterior canal can be expected to move toward the common crus. However, no such movement of otoconial debris is expected in the right anterior canal as it is already in the most dependent position (**Figure 4**).

There can be three possibilities in the right lateral position of McClure Pagnini:

First, when the particles are at/near to the ampulla of the left (uppermost ear) anterior canal, no/minimal movement is seen in the right lateral position (part 1 of **Supplementary Video 3**). Second, when the particles are slightly away or distal from the

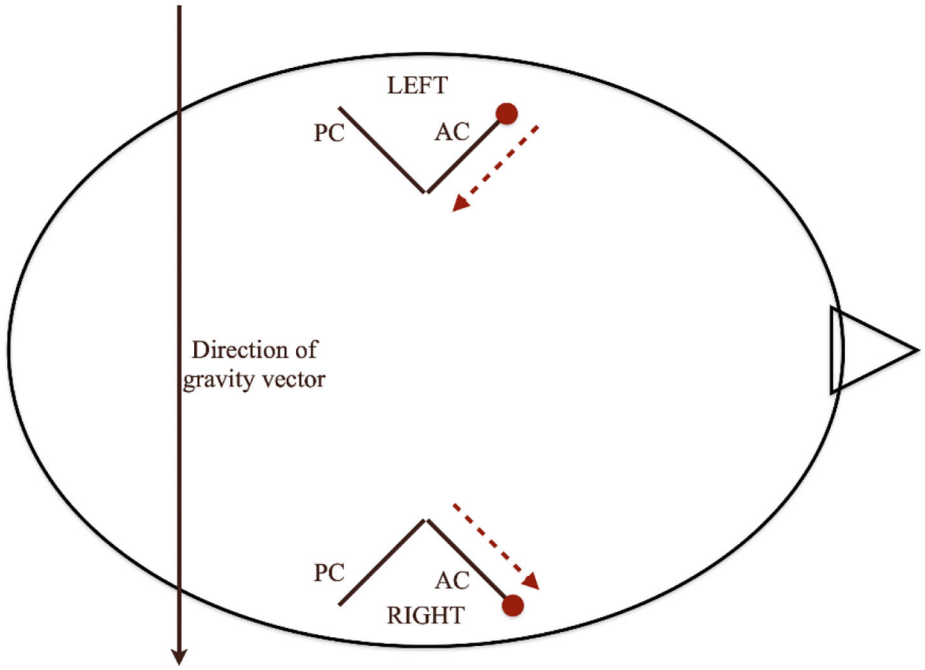

FIGURE 4 | Movement of otoconia in MCP test. The direction of nystagmus during MCP may indicate the side of involvement. But during the DHP test on the right side or an MCP test in the right lateral position, the otoconial debris from the left anterior canal can be expected to move toward the common crus. However, no such movement of otoconial debris is expected in the right anterior canal as it is already in the most dependent position.

ampulla (which might be due to DHP or SHH), we can see that the particles are moving toward the common crus (part 2 of **Supplementary Video 3**). Third, when the particles are in the right (undermost ear) anterior canal, in the right lateral position there is minimal or no movement of otoliths (part 3 of **Supplementary Video 3**). Therefore, the presence of nystagmus evoked in the lateral position of MCP suggests a distal location of the debris in the anterior canal of the uppermost ear.

This consideration can help us in the following ways. If we know the side of canal, we can tilt the head by 30° and make the Yacovino maneuver more effective. It will definitely bring down the number of Yacovino maneuvers performed in each patient. If we know that the left anterior canal is involved then we can ask the patient to sleep in the right lateral position for two days, which will help the particles go toward the common crus and eventually toward the utricle. We see the possibility of ourselves or other workers in trying the prolonged lateral decubitus position combined with the Yacovino maneuver for at least a subset of patients with positional down beating nystagmus.

Reversal of Nystagmus

In our study, two subjects (case five and nine) had a reversal of nystagmus on getting up, which is an unusual but not new finding. Imbaud et al. suggested that reversal is seen in cases of AC BPPV after making the patient sit up from a supine position (27). Some authors contest this and argue that reversal of nystagmus is not seen in cases of AC BPPV (18, 19).

Treatment

We performed the Yacovino maneuver in every patient and the definitive diagnosis of AC BPPV was made only after successful resolution of vertigo by the Yacovino maneuver.

If the side of involvement is known, the modified Yacovino maneuver is performed with the head turned 30° away from the affected side. The patient sits up at the end while maintaining 30° of head rotation.

If the side of involvement is not known, the Yacovino maneuver is completed but is not dependent on the side of the canal (5, 21, 24). It treats AC BPPV irrespective of the side of canal involved.

Surgical management has also been described by Naples et al., with plugging of anterior semicircular canal which is to be reserved for refractory cases (28).

CONCLUSION

We conclude that anterior canal BPPV is a rare but definite entity. It may not be apparent on positional testing the first time, so repeated testing may be needed with more than one maneuver. The most consistent diagnostic maneuver is SHH though there were patients in whom findings could only be elicited during DHP testing.

We recommend a testing protocol that includes DHP testing on both sides and SHH. MCP testing may also evoke vertigo and DBN with or without a torsional component. The utility of this finding in determining the side involved deserves further

exploration. Reversal of nystagmus during the reversal of testing position is unusual but can occur. The Yacovino maneuver is effective in resolving AC BPPV though some patients require up to four repetitions, requiring multiple visits.

We proposed a hypothesis that explains why DHP testing is sensitive to AC BPPV on either side, whereas an MCP lateral position on one side is only sensitive to one-sided AC BPPV.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SD, PP, and AR conducted the experiments, analyzed and interpreted the data, and wrote the manuscript. VP, AB, and PN conducted the experiments and analyzed and interpreted the data. RN conducted the design and conceptualization of the study, interpretation of the data, and revised the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.618269/full#supplementary-material

Supplementary Video 1 | Case 11—Dix-Hallpike left showing down beating nystagmus.

Supplementary Video 2 | Case 11—Dix-Hallpike right showing down beating torsional (upper pole beating to right side) nystagmus.

Supplementary Video 3 | Explanation of three types of debris movement in right lateral position of McClure Pagnini. First, when the particles are at/near to the ampulla of the left (uppermost ear) anterior canal, no/minimal movement is seen in right lateral position (part 1 of this video). Second, when the particles are slightly away or distal from the ampulla (which might be due to DHP or SHH), we can see that the particles are moving toward the common crus (part 2 of this video). Third, when the particles are in the right (undermost ear) anterior canal in the right lateral position, there is minimal or no movement of otoliths (part 3 of this video).

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BPPV Simulation: A Powerful Tool to Understand and Optimize the Diagnostics and Treatment of all Possible Variants of BPPV

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BPPV is a mechanical disorder caused by the displacement of otolith debris into the semicircular canals. The treatment involves different repositioning maneuvers to bring the debris back into the utricle. This study aims to show how dynamic simulation models based on fluid dynamics and MRI, can help to visualize and understand the movement of the debris within the canals during head movement in 3D as a function of time. The user can define the rotation angle and plane at each step of the maneuver and then the model visualizes the canal and the otoconial movement in 3D. The simulation developed also allows alteration of various parameters like the rotational head acceleration, the duration of each step of the maneuver, the initial position of the otoconial debris in the canal, the size and the number of the particles and fluid dynamics of endolymph. The clod movement is visualized in such a way that it allows a better understanding of the impact and efficacy of various liberation maneuvers and why certain maneuvers might fail when not applied properly in the clinic. The model allows simulation of multi-canal BPPV. In this paper we demonstrate the power of the model applied on the maneuvers of Semont and Yacovino when executed in different ways. The model aims to provide a visual explanation for the need of specific maneuvers for each type of BPPV. The simulator presented here can be used to test the efficacy of existing maneuvers and help in the development of new maneuvers to treat different BPPV variants.

Keywords: simulation, 3D, BPPV, maneuver, semont, yacovino, otolith, rotation angle

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INTRODUCTION

Benign Paroxysmal Positional Vertigo (BPPV) is amongst the most common causes of vertigo. It is a mechanical disorder of the inner ear caused by the displacement of calcium carbonate particles from the utricle into the semicircular canals. The precise mechanism and cause behind the detachment of otoconia form the utricular membrane and the migration into the canals is still unknown (1, 2).

Normally the canals are only sensitive to angular acceleration and do not sense linear accelerations because the specific mass of the cupula and endolymphe are virtual the same, close to 1.0. In BPPV patients, the presence in the canal of heavy otolith debris with a specific mass close to 2.7 makes the canal sensitive to the head orientation relative to the gravity vector. A change of

head position relative to the gravity vector therefore leads to a movement of free floating heavy debris (canalolithiasis) and induces an endolymphatic flow and an associated cupula deflection leading to nystagmus. A change of head position relative to the gravity vector also induces a cupula deflection when the debris is attached to the cupula (cupulolithiasis). A patient with BPPV, either Canalolithiasis or cupulolithiasis, will, therefore, experience rotatory vertigo by head tilts because the cupula deflection is now interpreted by the brain as an angular acceleration (1–7).

Stimulation of the canals by the movement of the otoliths in it, free-floating in the canals or attached to the cupula, generates a specific eye movement called nystagmus. The direction of the nystagmus is aligned with the orientation of the canals affected. Each type of BPPV is diagnosed by observing the patterns of nystagmus induced during positioning maneuvers that have been designed to move only the involved canal in the direction of maximal gravity (2). This nystagmus direction allows us to identify which canal is affected and where the debris is located in the canal. The different otolith positions in the canals generate different characteristic nystagmus patterns.

The treatment of BPPV is based on the detection of these characteristic nystagmus patterns to decide the appropriate maneuver required to reposition the otolith debris back into the utricle. The precise debris movements in the canals have been studied and clarified by physics using various models based on the fluid dynamics of BPPV (3–9). These studies form the basis for our current understanding of the latency, direction, reversal, and fatiguability of the nystagmus as a function of time, the size and number of otoconial particles.

Repositioning procedures for BPPV depend primarily on gravity and inertia. For a successful repositioning maneuver, correct orientation, and angulation of the semicircular canals during the maneuver play a crucial role. During construction of explanations of different BPPV nystagmus patterns, movements of moving urticular otoconial debris in the three-dimensional structure of the vestibular labyrinth should be considered (10).

Our endeavor in this article is to present a simulation to visualize the movement of the head, labyrinth, and otoconial debris in the 3-dimensional space for practical clinical use (**Figure 1**). It simulates the movement of the otoconial particles in the canals as a function of time and angulation during diagnostic and liberation maneuvers. In our opinion, these simulations make it possible not only to better understand but also to optimize the various diagnostic and liberation maneuvers.

Basically, two models are required to design a BPPV simulation: (1) the physics behind the debris movements and (2) the simulation algorithm based on these debris movements as a function of canal orientation relative to the gravity vector to visualize the clod movement in 3D as a function of time. For a detailed description of the physics model (1) we refer to for example the publications by Bosseli and many others (3–6). The limitations of practical application of these models lay in the limitation of exact and individual data of parameters *in vivo* involved. In reality, much is still unknown about BPPV, what is the size and variation in size of the clods, how are they distributed within a canal, are they more or less attached to the membranous

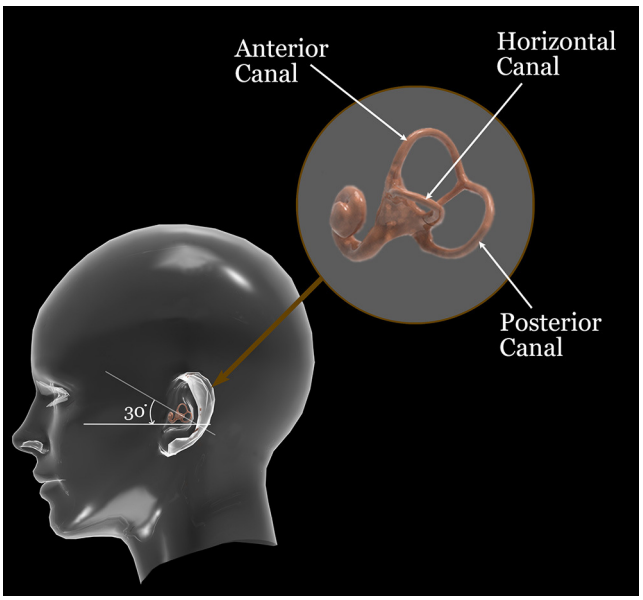

FIGURE 1 | Orientation of the three semicircular canals.

labyrinth or cupula? It is very likely that these issues will vary among patients and by that limits an exact application of the models (fluid dynamics) at current. Nevertheless, the physics models based on the fluid dynamics of BPPV (3–9) form the basis for our current understanding of the latency, direction, reversal, and fatiguability of the nystagmus as a function of time. The ideal would be to optimally visualize the otolith movement in any individual patient real time. However, at present, it is still not possible to visualize the debris by MRI or CT and there are as said too many unknown variables for extrapolation of the fundamental models to the clinical reality.

In most publications about liberation maneuvers (11–16), therefore 2D pictures are shown of the canal with the clod in different phases of the maneuvers, without any hard supporting evidence, simply because it is not available: only indirect evidence exists based on the observation of nystagmus. These papers are very useful and made to help clinicians to understand the sequence of otolith movements occurring during each step of the maneuvers. But 2D visualization is limited, and therefore we choose to add dynamics to it and to be able to change the projection angle, to see what is assumed to happen as can be seen from different angles at any moment. In this way our simulations will show that changing angulations can affect the outcome of otolith movement, why waiting between steps is required to ensure the clod moves to the starting position and how there may be a failure of a repositioning maneuver. These dynamic simulations can serve as a tool to develop modifications of existing maneuvers and also new maneuvers.

METHODS

The 3D morphology of the inner ear used is as realistic as possible and based on reconstructed MRI images of the temporal bone.

DICOM files of MRI images were used to extract the 3D inner ear. The three semi-circular canals and their orientation planes were determined. Angles were taken to quantify the spatial orientation of labyrinthine structures in relation to each other and in relation to aspects of the cranium. Our results agreed with those reported in other studies (3, 5, 17–20). In our simulation model, a thin tube was inserted at the center of each canal. A crystal resembling otoconial debris was put inside these canals while considering the particle drag (friction caused by the fluid on the object immersed in it) and the gravity acting on the crystal. A crystal size of 0.7 mm was taken to represent the otoconia and the diameter of tube of 1.5 mm has been used in the simulations. A fluid linear drag of 35N and fluid angular drag of 0.05N was applied. These parameters helped to study the otoconial movement during the maneuver. The simulation was created on Unity 3D Game engine software. The software allowed us to place the particle in more than one canal at the same time. A humanoid was animated within Autodesk Maya with precise angles for each step of different maneuvers. The head was linked to the semi-circular canals such that when the head moves, the associated canals are stimulated. As the humanoid animates into various positions, the crystal within its inner ear moves because of gravity.

Our goal was to study the effect of gravity on these particles, causing them to move toward the lowest dependent position when the head is moved at different angles while performing the maneuver. Different simulations were developed to understand these alterations in detail. This paper describes the simulation for different variations of the Semont and Yacovino maneuver.

MANEUVERS

Various maneuvers have been described for treatment of different BPPV variants. For PC-BPPV, the maneuvers described by Epley (11) and Semont et al. (12) are most commonly used. The Epley's maneuver uses the effect of gravity on the otolith particle to move it toward the utricle while Semont's maneuver works on the principal of acceleration and gravity (21–24). This paper describes the simulation of Semont's maneuver along with variations for posterior canal. The treatment for AV-BPPV by simulation of Yacovino maneuver and its variations is also described.

Variations of Semont's Maneuver

Semont's maneuver is used to treat posterior canal Canalolithiasis and Cupulolithiasis (Refer to **Table 1**). Here, we have considered four variants to understand which one of them can deliver the best results. The first simulation is of the classic Semont's liberatory maneuver for right posterior BPPV. The steps followed are described below:

1. The patient is made to sit on the bed with legs hanging down.
2. The patient's head is turned to the healthy left side by 45°.
3. The patient is then moved to the right side-lying position at an angle of 90° with the head pointing upwards.
4. The patient is now rapidly taken to the opposite side-lying position by swinging the body by 180°.
5. Finally, the patient is brought upright, and after that, the head is turned to the neutral position.

TABLE 1 | Types of BPPV and therapeutic maneuvers (PC–BPPV, Posterior canal BPPV; HC–BPPV, Horizontal canal BPPV; AC–BPPV, Anterior canal BPPV; QLR, Quick liberatory rotation); FPP, Forced Prolonged Positioning (11–16, 25).

Type of BPPV		Therapeutic Maneuver
PC–BPPV	Long arm canalithiasis	Epley/Semont
	Short arm canalithiasis	Brisk epley/Brisk semont/Side lying position with vibrator
	Non-ampullary end canalithiasis	Yacovino/QLR
	Canal side cupulolithiasis	Semont
	Utricular side cupulolithiasis	QLR from opposite side
HC–BPPV	Canalithiasis	Barbecue/Gufoni/FPP
	Cupulolithiasis	Barbecue/Modified gufoni/Zuma/FPP
AC–BPPV	Canalithiasis/Cupulolithiasis	Yacovino

At step 3, the debris can be seen moving away from the ampulla toward the lowest point of the canal due to gravity acting on it. In step 4, the rapid acceleration leads to a centrifugal force that keeps the clot attached to the membranous labyrinth, bringing the clod in the optimal position so that the clot will fall down driven by gravity and due to the deceleration (inertia of mass) also is launched toward the common crus and onwards to the utricle.

So, the simulator proves that the technique is useful for treating this type of BPPV, but it is important to swing the patient rapidly from the right to the left side (Simulation 1).

Simulation 1–Semont's Maneuver (click to view).

If this acceleration is too low during step 3, the particle may fail to move away from the ampulla. Simulation 2 shows that when step 2 is not done with sufficient high acceleration, the clot falls back into the ampullary arm. This simulation emphasizes the need for rapid acceleration in step 4 and how a slow movement can result in failure of the maneuver.

Simulation 2–Semont's Maneuver with slow acceleration (click to view).

Obrist et al. (26) described the Semont's Plus maneuver. In this modification, when the patient is brought to the side-lying position in Step 2, the head angulation is increased from 90 to 120 degrees. This brings the posterior canal to a position where gravity can act more effectively on the particle (Simulation 3). This makes the modified maneuver more efficient than the classic Semont's liberatory maneuver. It was also seen that the maneuver works well-even if the speed of the maneuver is decreased, unlike the previous variant.

Simulation 3–Semont's Plus maneuver (click to view).

The fourth variant shows what happens when the angulation is reduced on bringing the patient to the side-lying position. This is done by placing a pillow under the head (Simulation 4). This decreases the head angulation causing the otoconial particle to fall back into the canal. This emphasizes that correct head

angulation is very important for the maneuver to reposition the particle back into the utricle.

Simulation 4–Semont's maneuver with reduced head angulation (click to view).

Variations of Yacovino Maneuver

Yacovino maneuver is used to treat BPPV involving anterior semicircular canal, or when the debris is present in the common crus of the posterior semicircular canal. The maneuver consists of 4 steps:

1. The patient is asked to sit with the head facing forward.
2. The patient's head is brought to the head hanging position, 30° below the horizontal.
3. The patient's head is brought quickly forward to the "chin to chest" position while still in the supine position.
4. The patient is brought back to the sitting position.

Simulation 5 explains how the maneuver works for anterior canal BPPV at each step.

In Step 2, when the patient is brought to the head hanging position, the otoconial debris begins to move in the direction away from the ampulla.

Step 3–Gravity facilitates the particle to move toward the common crus.

Step 4–Particle falls back into the utricle.

This maneuver is widely accepted, but when we tried the maneuver in the simulator, we found that it has a high chance of canal switch with the particle entering into the posterior canal while treating the anterior canal BPPV (27).

Simulation 5–Yacovino maneuver (click to view).

In a variant of the described Yacovino maneuver, the patient is brought from the head hanging position to the sitting and kept there for 20 s. Finally, the neck is flexed forward after 20 s (Simulation 6). This demonstrates a better way of repositioning the particle back into the utricle than the classic Yacovino maneuver with a lesser chance of particle entering into the posterior canal.

Simulation 6–Yacovino maneuver with head brought straight up (click to view).

In the third simulation, when the patient is brought to the sitting position from the deep head hanging one, the neck is bent immediately (Simulation 7). We can see that due to this, the particle fails to move toward the common crus and instead falls back toward the ampulla.

Simulation 7–Failed Yacovino Maneuver (click to view).

RESULTS

The model allows a clear visualization of the semicircular canals and movement of otolith debris to the dependent portion of the canal during the maneuvers. The simulation model attempts to show the movement of the particle in a continuous way in three dimensions during the maneuver for better understanding. The whole simulation was created with an aim to understand the dynamics of the otoconial debris with respect to the position of the head.

DISCUSSION

The simulator is able to change the camera angulation that makes the three-dimensional spatial movement of the head, semicircular canals, and the otoconial debris easier to understand. The user can define the angulation at each step of the maneuver and have a three-dimensional visualization of the canal and the otoconial movement. The simulation developed allows alteration of various parameters like the angulation of the head, the initial position of the otoconial debris in the canal, size and the number of these particles, fluid dynamics of endolymph, and the time of each step of the maneuver. The simulator helps to understand the otoconial movement with respect to the movement of the head. This helps us to understand the optimum plane and angulation required to get the best results. It also helps to understand why the maneuver is ineffective when these planes and angles are not achieved. The mechanism of action of different maneuvers for each type of BPPV could be evaluated. Multi-canal BPPV occurs when there are clots in more than one canal. This can be studied well-using this simulator. Canal switch may be seen during or after BPPV repositioning. Using this simulator, one can understand the different mechanics of the fluid and the canal and thereby can avoid canal switch. In addition, this can also be used as a tool to devise and test the efficacy of new maneuvers.

CONCLUSION

A simulator based on the reconstructed human MRI images works as a guidance system during the maneuvers of BPPV. It helps to understand and observe what actually happens when the head moves. It provides a better understanding of what happens on incorrect angulations while performing the maneuver, which can complicate the treatment (e.g., Canal switch) (27). It can be used as a learning and a teaching tool for medical students and practitioners to understand the behavior of the particle present in the canal in relation to head movement. The high-quality 3D visualization of the canal linked to head movement helps to understand the importance of each step of the therapeutic maneuver. It also highlights the important head movements that bring the canals at an angle at which the gravity can act on the particle and remove it from the canal. Correct head angulation is the key to a successful maneuver. Thus, it can provide a thorough explanation for the maneuvers done incorrectly and eliminate the incorrect and unnecessary steps of the maneuver. Multi-canal BPPV is a complicated variant of BPPV as it affects more than one canal of the same or different ears. It is difficult to understand which canal needs to be treated first and what direction the particle moves when one of the affected canals is being treated. For example, if the otoconial debris is present in both the posterior and horizontal canal of the same side, Epley's maneuver will obviously remove the particle from the posterior canal. However, the simulator will also show what happens to the particle present in the horizontal canal due to the maneuver being performed. It can also provide a visual explanation for the need of specific maneuvers for each type of BPPV and why Gufoni maneuver can treat BPPV of the horizontal canal but

not the posterior canal BPPV. Due to the recognition of variants of BPPV, more new therapeutic maneuvers have been tried for treatment. The simulator can test and compare the efficacy of these maneuvers.

Currently, the major limitation of this simulator is that it does not entirely represent the population as the orientation of the semicircular canals vary from patient to patient. Our study is based on the orientation obtained from the reconstructed MRI images. We are fully aware that the natural variations in the orientation and morphology have a substantial impact on the validity of the extrapolation to the individual patient. Like various publication describing repositioning maneuvers for BPPV (15, 16, 21, 22), these simulations do not represent the physics of the otoconia. The ideal would be to optimally visualize the otolith movement of each patient, however at present, there are many unknown variables. In this study, the time taken for the particle to move at each step of the maneuver has been accelerated to make it more user-friendly.

However, we experienced that simulators are an effective way to understand all the types of BPPV and their therapeutic maneuvers. Other publications describe the initial and final position of the otolith at each step by two dimensional illustrations. The simulation model attempts to show the movement of the particle in a continuous way in three dimensions for better understanding. This tool provides insights that can lead to a more accurate diagnosis and treatment of BPPV.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

AB conceptualized the labyrinth simulation in 3D to understand the movement of the otolith clot during head movement in BPPV patients. She has written the manuscript of the publication. HK has given essential inputs to improve the simulation model in various stages of its development, notably in clot movement and visualization, and optimized the text. RB with his technological background and deep understanding of fluid dynamics and labyrinthe disorders. RB has developed the software simulation of BPPV. He has worked on demonstrating the effect of changing head positions and angulations on otolith clot movement in different canalolith repositioning maneuvers in 3 dimensions. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.632286/full#supplementary-material

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BRIEF RESEARCH REPORT
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BPPV: Comparison of the SémontPLUS With the Sémont Maneuver: A Prospective Randomized Trial

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Objective: To compare the efficacy of the Sémont maneuver (SM) with the new "SémontPLUS maneuver" (SM+) in patients with posterior canal BPPV canalolithiasis (pcBPPVcan).

Methods and Patients: In a prospective trinational (Germany, Italy, and Belgium) randomized trial, patients with pcBPPVcan were randomly assigned to SM or SM+; SM+ means overextension of the head by 60+° below earth horizontal line during the movement of the patient toward the affected side. The first maneuver was done by the physician, and the subsequent maneuvers by the patients 9 times/day on their own. Each morning the patient documented whether vertigo could be induced. The primary endpoints were: "How long (in days) does it take until no attacks can be induced?" and "What is the efficacy of a single SM/SM+?"

Results: In the 194 patients analyzed (96 SM, 98 SM+), it took 2 days (median, range 1–21 days, mean 3.6 days) for recovery with SM and 1 day (median, range 1-8 days, mean 1.8 days) with SM+ ($p = 0.001$, Mann-Whitney U-test). There was no difference in the second primary endpoint (chi²-test, $p = 0.39$).

Interpretation: This prospective trial shows that SM+ is more effective than SM when repeated therapeutic maneuvers are performed but not when a single maneuver is performed. It also supports the hypothesis of the biophysical model: overextension of the head during step 2 brings the clot of otoconia beyond the vertex of the canal, which increases the effectivity.

Classification of Evidence: This study provides Class I evidence that SM+ is superior to SM for multiple treatment maneuvers of pcBPPVcan.

Keywords: BPPV [2,182], Sémont maneuver [143], Epley maneuver [477], vertigo [18,284], dizziness [35,838]

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is a very frequent cause of vertigo, with a reported prevalence of 10-140 per 100,000 and a lifetime prevalence of 2.4% (1, 2). In about 85-95% of patients, the posterior canal is affected [pc-BPPV, for reference, see (3)] with a canalolithiasis (can) as the underlying pathomechanism (4, 5). The treatment of choice is liberatory or repositioning maneuvers to remove the otoconia from the affected canal (6). The Sémont maneuver (SM) was published in 1988 (7), and the Epley maneuver in 1992 (8); both are effective (9–11).

Based on our biophysical model of BPPV (12), we hypothesized that the new "SémontPLUS maneuver" (SM+) is more effective than SM because this model shows that the more the affected canal is tilted toward the affected side during the movement of the head toward the affected side, the further the otoconia move toward the exit of the posterior canal (13). This also predicts that more otoconia should then move beyond the vertex of the canal when the patient is subsequently moved toward the unaffected side (**Figure 1**, **Supplementary Video 1**). It should thus increase the effectivity of the maneuver.

In this prospective randomized trinational study, the first primary endpoint was "How long (in days) does it take until no attacks of spinning vertigo can be induced?" In this way, the effects of repeated maneuvers (three in the morning, three at noon, and three in the evening) were evaluated, with the first and second maneuvers done by the physician and the subsequent maneuvers performed by the patient—after careful instruction—as self-treatment maneuvers. This treatment regime was chosen because it reflects real world clinical practice. Further, this approach of evaluating not only the effects of a single maneuver is supported by a recent study evaluating the optimal reassessment time for treatment response in pc-BPPV (14). Finally, since symptoms typically occur and reoccur in BPPV in the morning—because otoconia may form a clot overnight, which has a higher impact on endolymphatic flow than single crystals (13, 15)—the first maneuver in the morning of each day was chosen as the first primary endpoint.

Many studies show that a single maneuver is not able to cure the majority of patients with BPPV with a wide range of reported success rates of a single SM in the literature, e.g., 37.5% (16) or 79.3% (17). Therefore, a second question was examined in this study: "Is a single SM+ more effective than a single SM?"

METHODS AND MATERIALS

Study Population and Procedures

Patients were screened and recruited in three academic centers in three countries (Germany: Department of Neurology and German Center for Vertigo and Balance Disorders, Ludwig Maximilians University Hospital, Munich; Belgium: Department of ENT, AZ Sint-Jan Brugge, Brugge; Italy: Department of ENT, University of Siena, Siena) from June 2018 to April 2020.

Inclusion criteria were the following: eligible patients were aged > 18 years and had confirmed pcBPPVcan according to the diagnostic criteria of the International Classification Committee of Vestibular Disorders (ICVD) (1). This means that a patient's history included attacks of spinning vertigo triggered by changes in head or body positions. The duration of attacks was <1 min, accompanied by nausea, vomiting, and/or oscillopsia. The clinical findings were that when positioned to the affected ear, a patient experienced vertical-torsional nystagmus beating toward the forehead with a crescendo-decrescendo time-course lasting less than a minute.

The exclusion criteria were the following: the patient not being able to give consent; subject not wanting any treatment for BPPV; the unwillingness or inability of the patient to perform self-treatment at home.

Study Procedures and Study Treatment

(1) Patients presented in one of the three clinics with vertigo or dizziness in the course of routine care. (2) A standard patient history was taken. Patients underwent a routine physical neurological, neuro-otological, and neuro-ophthalmological examination, including diagnostic maneuvers for BPPV. Standardized non-invasive laboratory testing with the video-head impulse test and caloric testing was performed. (3) The diagnosis of pcBPPVcan was made using the current diagnostic criteria (1). (4) The patient was informed about the study. (5) The patient gave his/her written consent. (6) Randomization (1:1) to each of the treatment groups, one-by-one in consecutive order. This was documented on a randomization list kept at each participating site, containing the number, SM or SM+, name, and date of birth of the patient. (7) SM or the SM+ (**Figure 1** and **Supplementary Video 1** of SM+) was carried out once. The angle of the head was measured using an AppStore App ("Kompass") installed on iPhones, which can also be used as an inclinometer, so that standardized examination conditions were guaranteed. The Sémont maneuver means horizontal, i.e., 0°; SM+ means 60° beyond earth horizontal; each of the three positions (with the head turned toward the unaffected side) was maintained for 60 s: (1) movement of the patient's body toward the affected side; (2) movement of the body toward the unaffected side; (3) sitting upright. Fifteen to sixty minutes after the first therapeutic maneuver, a second diagnostic maneuver was performed to check the effect of the first maneuver, i.e., whether positional vertigo and/or positional nystagmus can be induced. Depending on randomization to SM or SM+, the patient independently carried out SM or SM+ three times in the morning, three times at noon, and three times in the evening as instructed. The patient noted how many days after the start of the SM or SM+ maneuver it took for him/her to no longer experience positional vertigo. The time point was the first maneuver in the morning of the day on which the patient was not able to induce positional spinning vertigo. This was documented by the patient using a standardized evaluation sheet. On the day of inclusion, patients received a written form with a standardized questionnaire and an envelope that they had to send back to the center.

FIGURE 1 | Sémont maneuver (SM, two left columns) and Sémont PLUS maneuver (SM+, two right columns with overextension of the head by 60+° toward the affected side) for the treatment of pcBPPVcan. First and third column: maneuver performed by a physician (M.S.). Second column: movement of the clot of otoconia within the left posterior canal, based on a biomechanical model of BPPV (13). **(A)** upright position; **(B)** Position of the clot after a 90° movement of the patient to the left: clot does not reach the lowest point; **(C,D)** The clot can therefore fall back into the direction of the ampulla, leading to an unsuccessful maneuver. Third column: **(A+)** upright position. **(B+)** movement of the body by 150° toward the affected side moves the otoconia farther in the direction in which they should move. **(C+)** Since the clot is beyond the vertex, the movement of body by 240° moves the clot in the direction **(D+)** of the vestibulum.

Endpoints

Two primary endpoints were chosen to evaluate two questions: (1) the long-term effect of SM vs. SM+, i.e., the "real world recovery" for the patient and (2) the short-term effect of a single SM vs. SM+ because of the wide range of reported efficacy of single treatment maneuvers in the literature (see **Introduction**).

The first primary endpoint is How long (in days) it takes until no attacks of spinning vertigo can be induced "in the morning" by the maneuvers. Day 0 was the day of the examination and the first liberatory maneuver in the hospital, day 1 the next morning. For a maneuver to be rated as successful, the patient should not be able to induce positional vertigo in three consecutive maneuvers.

The second primary endpoint is the success rate of a single liberatory maneuver, i.e., either SM or SM+, on the occurrence of vertigo and/or positional nystagmus, tested after the first SM or SM+ ("yes" or "no"). If neither spinning vertigo nor nystagmus was induced in the diagnostic maneuver, the liberatory maneuver was rated as primarily successful. If vertigo and/or nystagmus were detected, it was rated as primarily unsuccessful.

Randomization

Patients who met the eligibility criteria for enrollment were randomized in a 1:1 ratio to receive either SM or SM+.

Statistical Analysis

Statistical analysis and graphic design were performed using R version 3.5.2 (the R Foundation for Statistical Computing, www.r-project.org). Since days to recovery were not normally distributed, non-parametric testing using the Mann-Whitney *U*-test was performed. To compare treatment success after the first maneuver, a chi-square test was applied. Differences were considered significant if $p < 0.05$.

Sample Size Calculation

To detect an improvement of the success rate (first primary endpoint) from 0.50 to 0.70 with a power of 0.80 on a significance level (one-sided testing) of $p = 0.05$, at least 93 analyzable patients are required in each group, resulting in a total number of at least 186 analyzable patients.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was performed in accordance with the Helsinki II Declaration. The study protocol, including the patient information and consent form, was approved by the local ethics committee of each participating institution (Leading ethics committee: Ethics committee of the Medical Faculty of the Ludwig Maximilians University, Munich, Germany; reference number: 17-477, and subsequently by the Ethics committee of AZ ST JAN, Brugge Oostende, Belgium, AV Ethics committee OG 065, BUN: 8049201835209 Int. Nr.2247, which required modifications of the protocol; date of final approval: May 17th, 2018). All participants gave written informed consent.

DATA AVAILABILITY POLICY

Upon request, further data including the study protocol will be shared with other investigators for the purpose of replicating procedures and results. Unidentified participant data may not be shared for legal or ethical reasons. Data cannot be shared publicly because participants did not explicitly consent to the sharing of their data as per the European Union's General Data Protection Regulation and the corresponding German privacy laws. Data are available through the Research Ethics Board of Ludwig Maximilians University, Munich, Germany, for researchers who meet the criteria for access to confidential data.

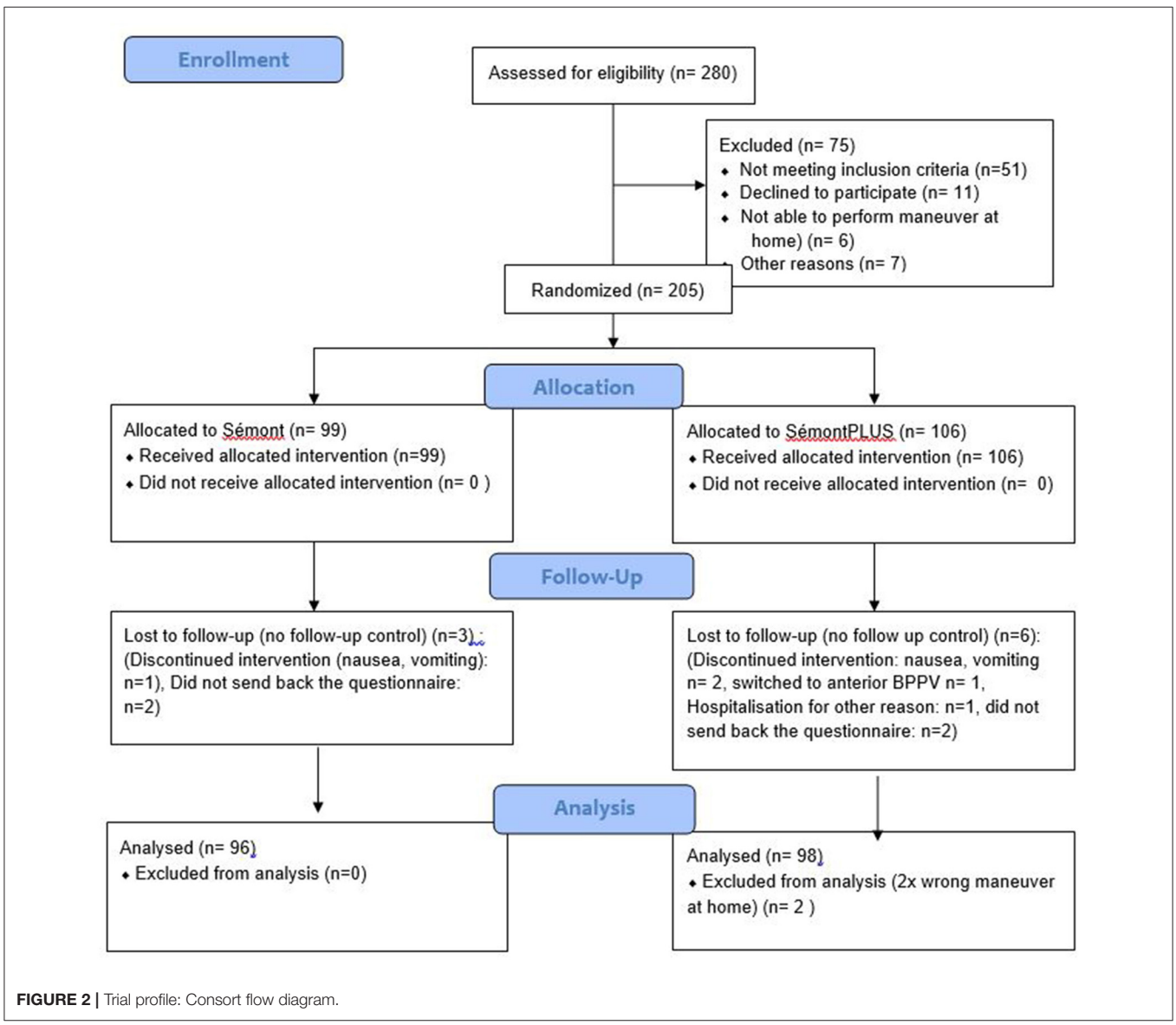

FIGURE 2 | Trial profile: Consort flow diagram.

TABLE 1 | Patient Characteristics.

	Allocated to the Sémont maneuver	Allocated to the Sémont Plus maneuver
Mean age (± SD), range	64 ± 13 years, 19–87 years	63 ± 13 years, 19–90 years
Sex: male/female	36/60	40/58
Affected side R/L	62/34	62/36
Etiology: idiopathic/other/missing data	79/15/2	85/12/1
First episode of BPPV/Recurrent BPPV/Missing data	54/40/2	60/37/1
Mean duration of symptoms before inclusion in the study:		
Median (in days)	7	5
Range (in days)	1–7200	1–5470
Missing data	11	6

RESULTS

Study Population

In the three centers, a total of 280 patients were assessed for eligibility (**Figure 2**; CONSORT flow diagram); 75 were excluded (51 did not meet the inclusion criteria, 11 declined to participate, 6 were not able to perform the maneuvers at home, and 7 were excluded for other reasons), so that 205 patients with pcBPPVcan were randomized. Ninety-nine were allocated to the SM and 106 to the SM+ group. Three patients were lost to follow-up in the SM group, and six patients were lost in the SM+ group. A total of 194 patients were finally analyzed: 96 patients in the SM group and 98 in the SM+ group. The mean age of the patients in the SM group (60 females) was 64 years (range 19–87 years); in the SM+ group (58 females) it was 63 years (range 19–90 years). In the SM group, 62 of 96 and in the SM+ group 62 of 98 had right pc-BPPV (**Table 1**).

Outcomes

The first primary endpoint is how long (in days) it takes until no attacks of spinning vertigo can be induced "in the morning" by the maneuvers. In the SM group, it took 2 days for recovery (median, range 1–21 days, mean 3.6 days). In the SM+ group, it took 1 day (median, range 1–8 days, mean 1.8 days) for recovery ($p = 0.001$, Mann-Whitney U-test) (**Figure 3**).

The second primary endpoint is the success rate of a single liberatory maneuver, i.e., either SM or SM+, on the occurrence of positional spinning vertigo and/or positional nystagmus, tested after the first SM or SM+ maneuver ("yes" or "no").

In the SM group, 46 out of 95 patients −48% (95% CI: 38–59%)—had neither positional vertigo nor positional nystagmus after the first maneuver. In the SM+ group, 54 out of 97 patients-−56% (95% CI: 45–66%)—were free of symptoms after the first maneuver. There was no statistical difference for the second primary endpoint (effect of a single maneuver) (chi-square test, $p = 0.39$).

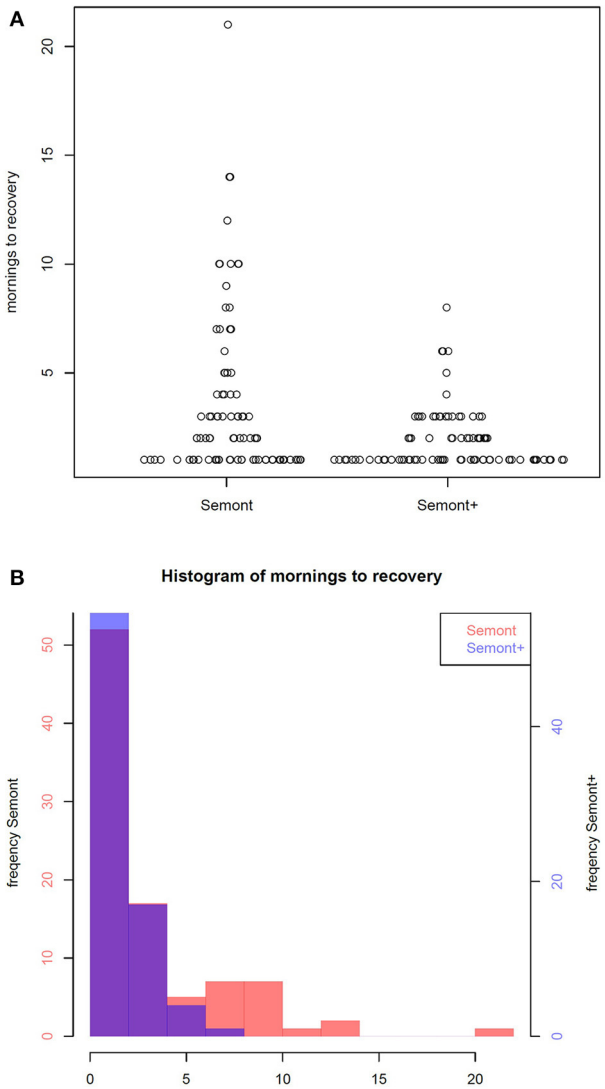

FIGURE 3 | Comparison of the Sémont with the SémontPLUS maneuver. **(A)** Scatter plot of the time to recover for the Sémont (left) and the SémontPLUS maneuver (right) in days. **(B)** Histogram of time to recover for the Sémont (red) and the SémontPLUS maneuver, purple, which is due to the overlay of red (SM) and blue (SM+), in days.

DISCUSSION

The major findings of this randomized prospective trinational study are as follows:

First, in the performance of multiple liberatory maneuvers for the treatment of pcBPPVcan SM+ significantly reduces the time until patients are free of attacks of vertigo by about 50%. These findings are in agreement with and support prior results

from biophysical studies on BPPV (13): the farther the head is turned toward the unaffected side during the movement of the body toward the unaffected side, the higher the efficacy of the liberatory maneuver. This was already suggested earlier with an overextension by 15° (6) and is now proven by this trial.

Second, the immediate success rate of a *single* maneuver was low, and there was no difference between the success rate of a single SM (48%) and a single SM+ (56%). This finding is in line with previous studies showing that a single maneuver is not sufficient for a successful treatment of pc-BPPV (16, 17). Therefore, the study was designed to evaluate the efficacy of multiple maneuvers, thereby also reflecting real world procedures for the treatment of BPPV in clinical practice: the combination of the first maneuver by the therapist in the office and subsequent self-maneuvers by the patient at home after receiving detailed instructions on how to perform the maneuvers, which was also developed, used, and recommended in other studies (18–21). At least for the Epley maneuver, the efficacy of the self-maneuver was shown to be higher than that of the Epley maneuver alone (22).

In a previous study, three SM per day with self-treatment were performed and after 1 week 58% of patients were cured (18). In our study with nine SM maneuvers per day, 57% were cured after only 2 days; after 1 week of nine SM per day 86% were free of symptoms. This comparison shows that the number of maneuvers per day also seems to be relevant. Therefore, we would suggest nine instead of three per day.

Finally, since SM+ is more difficult to perform than SM, it is possible that the study might have underestimated the efficacy of SM+. On the other hand, SM+ may not be suitable for all patients because it requires more skills than the regular SM. Therefore, the choice of maneuver to be used should be made on an individual basis.

In an on-going study with a similar design, the effects of SM+ are compared with the Epley maneuver (Project number 20-072). Furthermore, based on our findings, the efficacy of the diagnostic Sémont maneuver will be compared with the *diagnostic SémontPLUS maneuver* (dSM+) with an overextension by 60°, which should theoretically be more effective as well.

LIMITATIONS

This study has several limitations: first, one of the endpoints was based on a self-reported outcome by the patient and not by re-examination of the patient by a physician. However, patients received detailed instructions and used a standardized questionnaire. Furthermore, since symptoms typically first occur and re-occur in the early morning and then improve during daytime, a reevaluation in the hospital may also give false normal findings because patients might have already transiently recovered before reaching the hospital. Finally, treatment of the patient with benign PPV on a ward until recovery or recurrent daily visits to document the treatment effects is not practical and again does not reflect real world procedures. Second, in this study only the effects of a single therapeutic maneuver in combination with recurrent self-maneuvers by the patients were evaluated. Therefore, we cannot make a statement about the efficacy of repeated maneuvers performed by physicians or physiotherapists. Third, we did not specifically evaluate the side effects of both maneuvers or the impact of the maneuvers on quality of life or functioning.

CONCLUSION

This prospective randomized trial provides Class I evidence that SM+ is more effective than SM for the treatment of pcBPPVcan when repeated therapeutic self-maneuvers are performed but not when a single maneuver is performed. This is in line with the findings of the biophysical model: overextension of the head during step 2 of SM+ brings the clot of otoconia beyond the vertex of the canal, which increases the efficacy. Therefore, for clinical practice SM+ can be recommended for most patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Leading ethics committee: Ethics committee of the Medical Faculty of the Ludwig Maximilians University, Munich, Germany; reference number: 17-477 and subsequently by the Ethics committee of AZ ST JAN, Brugge Oostende, Belgium, AV Ethics committee OG 065, BUN: 8049201835209 Int. Nr.2247, which required modifications of the protocol; date of final approval: May 17th, 2018. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MS: idea for the study, conception, writing of the protocol, recruitment and examination of the patients, interpretation of the data, and drafting the manuscript. NG: interpretation of the data and drafting the manuscript. A-SV, SV, LS, and MM: recruitment and examination of the patients, interpretation of the data, and drafting the manuscript. OB: writing of the protocol, statistical design, sample size calculation, statistical analysis, interpretation of the data, and drafting the manuscript. AH: recruitment of patients, statistical analysis, interpretation of data, and drafting the manuscript. DO: idea for the study, conception, interpretation of data, and drafting the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.652573/full#supplementary-material

Supplementary Video 1 | SémontPLUS maneuver for right posterior canal BPPV. The overextension (with the right arm extended) is essential. Each position should be maintained for 60 s so that the otoconia can reach the lowest point relative to gravity.

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Conflict of Interest: MS has received speaker's honoraria from Abbott, Actelion, Auris Medical, Biogen, Eisai, Grünenthal, GSK, Henning Pharma, Interacoustics, MSD, Otometrics, Pierre-Fabre, TEVA, UCB, and Viatris. MS is a shareholder of IntraBio. MS is the distributor of M-glasses and the Positional vertigo App. MS acts as a consultant for Abbott, Actelion, AurisMedical, Heel, IntraBio, and Sensorion. NG received honoraria from IntraBio outside of this study. OB was employed by Relia Tec GmbH.

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