NEUROEPIDEMIOLOGY IN RESOURCE-LIMITED AREAS

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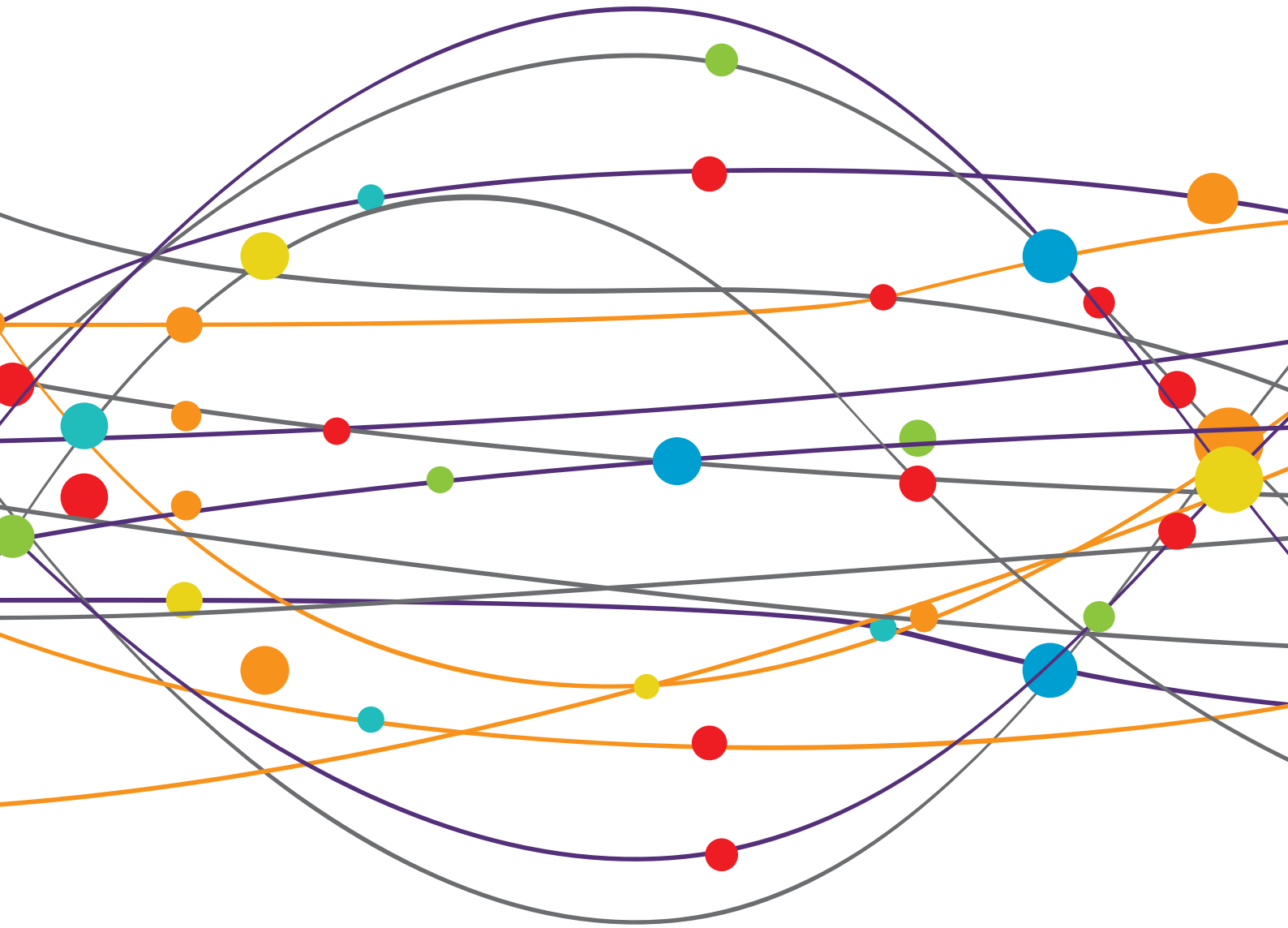

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NEUROEPIDEMIOLOGY IN RESOURCE-LIMITED AREAS

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Neuroepidemiology is a branch of epidemiology involving the study of neurological disease distribution and determinants of frequency in human populations. Neuroepidemiology has been perceived for a long time as a science of incidence, prevalence, risk factors, natural history and prognosis of neurological disorders. However, the other integral part of neuroepidemiology is experimental neuroepidemiology, which is research based on clinical trials of effectiveness or efficacy of various interventions in neurological disorders.

Neuroepidemiological researches have been conducted since 1960's, with the development of epidemiological methodology and advance of the clinical neurology. Most improvement of neuroepidemiology was in western countries, largely in US and European countries. This study field has been developed quite late in resource-limited areas, where 60% of world's populations are living in.

Disease burden of neurological disorders, such as stroke, epilepsy, migraine, neurodegenerated diseases (AD, PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), are extremely heavy in low and middle income countries (LAMICs), especially with the increasing aging population in these regions. Because of their progressive and disabling nature, these neurological disorders have major adverse personal, social, and economic consequences. Prevention and early detection are critical, because there are no cures and the clinical diagnosis typically occurs after substantial and often irreversible neuronal loss.

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Cross-Cultural Revision and Psychometric Properties of the Chinese Version of the Autism Spectrum Rating Scale (2–5 Years)

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Background: No sufficient biomarkers are available for early identification of autism in the general population. Currently, the diagnosis of ASD depends on behavioral assessments. A useful screening tool can help to detect early autistic symptoms and provide children an early opportunity for ASD-related interventions. This research aimed to assess cross-cultural adaptation and psychometric properties of the autism spectrum rating scale (ASRS) under the Chinese cultural environment.

Methods: Participants were recruited from 17 kindergartens and 5 special education schools across five cities (Shanghai, Guangzhou, Changsha, Chengdu, and Harbin) in China. A total of 2,181 kindergarten children and 207 ASD cases participated in this study. Mplus 7.03 was utilized to conduct exploratory factor analysis, followed by adaptive modifications to construct the revised Chinese version of the ASRS (RC_ASRS).

Results: The result showed that 62 items comprised a two-factor structure; Factor 1 (social communication, SC) included 21 items, and Factor 2 (unusual behavior, UB) included 41 items. Cronbach's alpha ranged from 0.87 to 0.91 within the RC_ASRS. The total score and the SC and UB scores were significantly higher in ASD cases than in kindergarten samples (Cohen's d ranged from 0.82 to 2.72). The total RC_ASRS score showed an area under the curve (AUC) of 0.95 (95% CI: 0.93–0.97). With a total score cut-off $\geq$ 60, the RC_ASRS is an excellent tool to identify ASD cases from Chinese kindergarten children (sensitivity = 88.6%, specificity = 84.5%).

Conclusions: The RC_ASRS has excellent psychometric properties and is a reliable, useful tool for early ASD screening among Chinese children.

Keywords: ASD, ASRS, early screening, cross culture, psychometric properties

INTRODUCTION

Autism spectrum disorder (ASD) is a cluster of neurodevelopmental disorders that develop in early childhood and are characterized by impaired social interactions and repeated stereotypic behaviors (1). ASD is a public health problem worldwide due to its significantly increased prevalence. Furthermore, ASD severely impacts the quality of life and places a substantial economic burden on individuals, families and society (2, 3). Currently, behavioral intervention is the primary treatment (4). Early intervention improves the prognosis of ASD (5–7). However, most children with ASD receive their first diagnosis when they enter the diverse school environment, which might be later than the optimal intervention age. Therefore, early identification and intervention are urgently needed for this population (8).

Currently, the diagnosis of ASD depends on behavioral assessment, because sufficient biomarkers are not available for the early identification of autism conditions in the general population. Experts have developed scales by combining both qualitative and quantitative methods based on the core symptoms of autism to help improve identification of ASD. These scales include the Checklist for Autism in Toddlers-23 (CHAT-23), the Social Responsiveness Scale (SRS), the Social Communication Questionnaire (SCQ), the Autism Behavior Checklist (ABC), the Childhood Autism Spectrum Test (CAST), and the Autism Spectrum Rating Scale (ASRS) (9–14). Although many tools are available, current ASD screening primarily focuses on children older than 5 years of age, whereas tools targeting children 2–5 years of age are lacking.

The ASRS was developed by Dr. Goldstein and Naglieri in 2009 and is available in two versions for young children 2–5 and 6–18 years of age (https://www.mhs.com). The ASRS shows excellent reliability and validity for ASD evaluation in the English-speaking population in the U.S. In our previous study (14), a systematic analysis of the Chinese version of the ASRS among 6-to-18-year-old children was conducted using community-based ASD cases. Notably, the appropriate revised Chinese version of the ASRS (6–18 years) had excellent psychometric properties and achieved a sensitivity of 94.2% and a specificity of 82.0% for ASD screening in Chinese children (15). Based on our previous results, this study focused on introducing the ASRS early screening version (2–5 years) and used exploratory factor analysis to evaluate its psychometric properties in the Chinese cultural background.

METHODS

Samples

The samples included two subsets from five cities collected from January 2016 to October 2016.

Children were recruited from 5 cites in China (Shanghai, Guangzhou, Changsha, Chengdu, and Harbin) from the enrolled members of a national epidemiological study of ASD in China, which was supported by the National Health and Family Planning Commission of the People's Republic of China (201302002). A total of 2,181 children from the general population aged 2–5 years were enrolled in this study from 17 kindergartens, and 207 clinically diagnosed ASD cases aged 2–5 years were recruited from special education schools across the five study sites to analyze the reliability and validity of the Chinese version of the ASRS. All recruited ASD cases met the DSM-5 diagnostic criteria, and the clinical diagnoses of ASD were confirmed by a pediatric psychiatrist at the research institutions (Children's Hospital of Fudan University, The Third Affiliated Hospital of Sun Yat-Sen University, West China Hospital of Sichuan University, Chengdu Women and Children's Hospital, The Second Xiangya Hospital of central South University, and the Harbin Medical University), which are authorized ASD diagnostic centers in China. Caregivers of all recruited children and ASD cases were invited to complete the Chinese version of the ASRS following a standard protocol.

Chinese Version of the ASRS

Our team adopted standard translation and back-translation procedures to develop the Chinese version of the ASRS with permission from the Multi-Health System (https://www.mhs.com). We recruited a few parents of ASD cases aged 2–5 years from the outpatient clinic of Children's Hospital of Fudan University to complete the Chinese version of the ASRS. All participants believed that the context of the Chinese version of the ASRS was understandable.

The 70-item pool of the ASRS was established based on the core symptoms of autism. Each item's response was measured using a 5-point Likert scale ("0" indicating never and "4" indicating very frequently) to quantify autistic symptoms. The ASRS includes three scales (the ASRS, DSM-5, and treatment scales) with different items forming the 70-item pool based on the specific purpose. The ASRS scales include two subscales comprising 62 of the 70 total items used for screening: Social/Communication (39 items, SC) and Unusual Behaviors (23 items, UB). The two subscales were combined into a single composite score (the total score), which was used for ASD screening among U.S. children. This study mainly focused on the ASRS scales with an exploratory factor analysis.

The DSM-5 scales consist of 35 of the 70 items according to the consensus ASD expert group and play an auxiliary role in the diagnosis of ASD. The treatment scales include the following 8 subscales: Peer Socialization (9 items, PS), Adult Socialization (5 items, AS), Social/Emotional Reciprocity (12items, SER), Atypical Language (6 items, AL), Stereotypy (6 items, ST), Behavioral Rigidity (8 items, BR), Sensory Sensitivity (6 items, SS), and Attention/Self-Regulation (10 items, ASR). The items in each subscale are selected from the 70-item pool by the consensus ASD expert group. These scales can be used to monitor the behavior intervention response for children with ASD.

The raw scores of each scale (ASRS, DSM-5, and treatment scales) were converted to standardized scores to facilitate interpretation of the results and comparisons with previous studies.

Procedure

The caregivers were invited to provide consent and complete the Chinese version of the ASRS under guidance of screening

booklets. Contact information, including the telephone numbers and e-mail addresses of the research team, were provided to help with questionnaire collection. This study was approved by the Children's Hospital of Fudan University Ethics Board ([2012] No. 185).

Statistical Analyses

The statistical package Mplus 7.03 (Muthén & Muthén, Los Angeles, CA, USA) was employed to perform the data analysis. An exploratory factor analysis (EFA) was used to examine the latent model structures. The model estimation was completed using robust weighted least squares means and variance adjustment (WLSMV) (16). The factor structure was estimated with the Chi-square goodness-of-fit test, root mean square error of approximation (RMSEA), comparative fit index (CFI), Tucker-Lewis index (TLI), and standardized root mean square residual (SMSR)(17). The number of factors retained in the model was determined by the scree test (18). Factors with loadings >0.3 or differences in cross-loadings >0.1 were retained, whereas all other items were removed from the model.

Item reliability was analyzed using Cronbach's alpha. We compared the mean scores of the ASRS between the ASD cases and the kindergarten children by using Student's *t*-test to measure the discriminant validity and calculated Cohen's *d* value to test between-group differences (effect size). The area under the curve (AUC) and 95% confidence intervals (95% CIs) were calculated to evaluate the overall performance of the questionnaire. The sensitivity and specificity values for the discrimination of children with ASD from the general population in the study samples were assessed based on the recommended cut-off total score of 60. All tests were two-tailed, and a *P*-value of 0.05 was retained as the level of statistical significance.

RESULTS

Sample Demographic Characteristics

In total, 2,181 ASRS questionnaires from 17 kindergartens and 207 from 5 special education school were collected. A total of 430 (19.7%) questionnaires from kindergartens and 40 (19.3%) questionnaires for ASD cases were not included in the final analysis due to a missing item or basic information (e.g., name and date of birth). Finally, a total of 1,751 questionnaires from the kindergartens and 167 from the ASD cases were included in the factor analysis. The mean age of the kindergarten children was 4.0 ± 0.8 years, and the male to female ratio was close to 1.08:1. In contrast, the mean age of the ASD children was 3.3 ± 1.1 years, and the male to female ratio was 6.95 to 1 (**Table 1**). The mean ages and sex ratios were significantly different between the two groups ($P < 0.001$).

TABLE 1 | Basic information for the samples.

Characteristics	Category	Kindergarteners (n = 1,751) Mean (SD) or n(%)	ASD cases (n = 167) Mean (SD) or n(%)	*P*-value
Age	Mean	4.0 (0.8)	3.3 (1.1)	*<0.001*
Gender	Male	910 (52.0)	146 (87.4)	*<0.001*
	Female	841 (48.0)	21 (12.6)	
Rater	Father	505 (28.8)	43 (25.7)	0.636
	Mother	755 (43.1)	71 (42.5)	
	Others	20 (1.1)	3 (1.8)	
	Missing	471 (27.0)	50 (30.0)	
Rater's education	Middle school	125 (7.1)	34 (20.4)	*<0.001*
	Vocational	669 (38.2)	67 (40.1)	
	Bachelor's	656 (37.5)	52 (31.1)	
	Master's	283 (16.2)	12 (7.2)	
	Missing	18 (1.0)	2 (1.2)	
Father's occupation	Farmer	291 (16.6)	40 (24.0)	0.135
	Worker	448 (25.6)	46 (27.5)	
	Manager	217 (12.4)	16 (9.6)	
	Technician	314 (17.9)	24 (14.4)	
	Other	451 (25.8)	41 (24.5)	
	Missing	30 (1.7)	0 (0.0)	
Mother's occupation	Farmer	252 (14.4)	37 (22.2)	0.002
	Worker	501 (28.6)	34 (20.4)	
	Manager	171 (9.8)	9 (5.4)	
	Technician	187 (10.7)	13 (7.8)	
	Other	609 (34.8)	70 (41.9)	
	Missing	31 (1.7)	4 (2.3)	

Italic values mean that the difference between the two groups was significant.

Exploratory Factor Analysis

The scree test was performed to determine the number of factors for inclusion in the Chinese version of the ASRS. Although a break was apparent in the slopes of the plotted eigenvalues, the shape of the curve suggested that 2 factors were appropriate for the current samples, as shown in **Figure 1**. According to the core domain of ASD, the chosen two-factor structure may be suitable for the Chinese version of the ASRS with the following model fit factors: RMSEA = 0.059, CFI = 0.81, TLI = 0.80, and SRMR = 0.06.

Eight of the 70 items were excluded due to factor loadings <0.3 or cross-loading differences <0.1; the loadings of all items are shown in Table S1. The 62 items comprised two factors, and the total numbers and factor names were similar to those of the unrevised Chinese version of the ASRS (C_ASRS). However, the number and context of each factor in the revised Chinese version of the ASRS (RC_ASRS) significantly differed from those of the C_ASRS (Factor 1: 21 vs. 39 items, Factor 2: 41 vs. 23). Factor 1 (social communication, SC) now included 21 items (1, 3, 4, 5, 13, 14, 16, 19, 21, 25, 28, 29, 35, 38, 40, 50, 52, 54, 56, 57, and 61), whereas factor 2 (unusual behavior, UB) included 41 items (2, 6, 9, 10, 12, 15, 17, 20, 22, 23, 24, 26, 27, 30, 31, 32, 33, 34, 37, 41, 42, 43, 44, 45, 46, 47, 48, 51, 53, 55, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, and 69).

The RC_ASRS Scores in Kindergarten Children

The total scores were 50.27 ± 10.59 vs. 50.45 ± 10.19 based on the fathers' and mothers' ratings, respectively. No significant

differences ($P = 0.785$) were observed. The average total scores were 50.72 ± 10.02 vs. 49.56 ± 10.26 for boys and girls, respectively. Boys had slightly higher scores on all subscales (**Table 2**). All subscale scores had slight differences across sites (All $P < 0.001$, see Table S2).

Item Reliability

Cronbach's alpha was used to measure the item reliability for the RC_ASRS (19); the values were 0.91 for all 62 items of the RC-ASRS, 0.87 for SC, and 0.91 for UB. The item reliability results revealed that the item structure of the RC_ASRS was robust and reasonable. The RC_ASRS was associated with a slightly higher Cronbach's alpha than the C_ASRS among Chinese kindergarten children, especially for the UB and total scores, as shown in **Table 3**.

TABLE 2 | Gender differences in the RC_ASRS scores of kindergarteners.

ASRS scale	Boys ($n = 910$)	Girls ($n = 841$)	*t*-value	*P*-value
SC	50.62 ± 10.14	49.44 ± 10.00	2.439	0.015
UB	50.57 ± 10.09	49.85 ± 10.65	1.444	0.149
Total score	50.72 ± 10.02	49.56 ± 10.26	2.396	0.017

SC, Social/Communication; UB, Unusual behaviors.

Discriminant Validity

To test the discriminant ability of the RC_ASRS and C_ASRS, we compared the mean scores between kindergarten children and ASD cases (**Table 4**). The total, SC, and UB scores of the RC_ASRS were significantly higher for the ASD cases than for the kindergarten children (Cohen's d ranged from 0.82 to 2.72). In contrast, the UB scores of the C_ASRS were significantly higher for the kindergarten children than for the ASD cases (the Cohen's *d*-value was <0.00).

ROC Analysis

The RC_ASRS had a total score AUC of 0.95 (95% CI: 0.93–0.97) vs. 0.85 (95% CI: 0.82–0.88) for the C_ASRS. The results indicated that the discriminant validity of the RC_ARSR for ASD screening in kindergarten children was significantly higher than that of the C_ASRS (**Figure 2**). The same analysis conducted by comparing differences among sexes showed equal performance

TABLE 3 | Analysis of item reliability for the RC_ASRS and C_ASRS.

Factors	RC_ASRS	Cronbach's alpha	C_ASRS	Cronbach's alpha
SC	21	0.87	39	0.89
UB	41	0.91	23	0.80
Total score	62	0.91	62	0.89

RC_ASRS, revised Chinese version of the ASRS; C_ASRS, unrevised Chinese version of the ASRS; SC, Social/Communication; UB, Unusual behaviors.

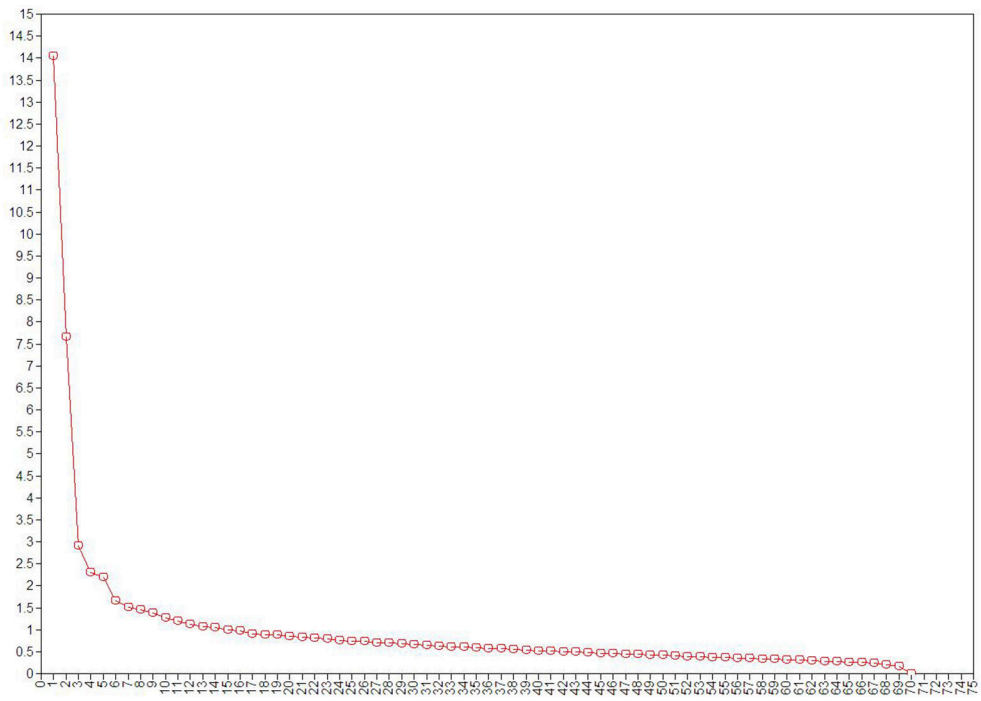

FIGURE 1 | Scree plot. We selected the number of factors for retention via the scree test where components with eigenvalues before the "break" of a scree plot were retained.

TABLE 4 | Discriminant validity of the RC_ ASRS.

	ASRS scale	Kindergarteners (n = 1,751)	ASD cases (n = 167)	t	P-value	Cohen's d
RC_ ASRS	SC	50.05 ± 10.09	80.79 ± 12.34	*-31.21*	*<0.001*	2.72
	UB	50.23 ± 10.37	58.59 ± 10.13	*-9.99*	*<0.001*	0.82
	Total score	50.17 ± 10.15	74.20 ± 11.01	*-29.00*	*<0.001*	2.27
C_ ASRS	SC	50.06 ± 10.12	83.27 ± 11.95	*-34.74*	*<0.001*	3.00
	UB	50.00 ± 10.51	41.34 ± 12.56	*8.625*	*<0.001*	−0.75
	Total score	50.03 ± 10.35	65.30 ± 11.35	*-18.05*	*<0.001*	1.41

RC_ASRS, revised Chinese version of the ASRS; C_ASRS, unrevised Chinese version of the ASRS; SC, Social/Communication; UB, Unusual behaviors. Italic values mean that the difference between the two groups was significant.

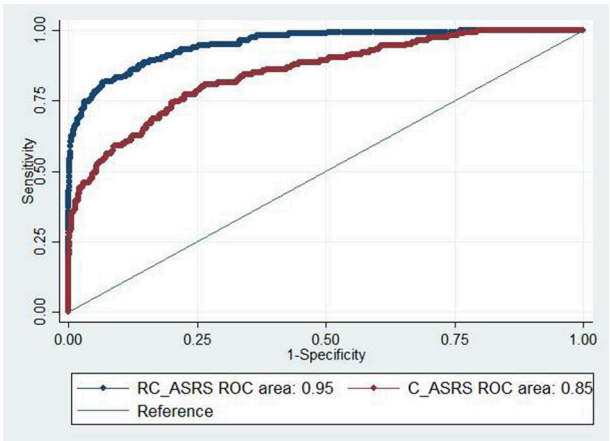

FIGURE 2 | Receiver operating characteristic (ROC) curves for the total scores for the RC_ASRS and C_ASRS.

among the boys and girls (AUC = 0.95; 95% CI: 0.93–0.97 vs. AUC = 0.94; 95% CI: 0.90–0.99) for the ASRS. A higher AUC was obtained for the mother raters than for the father raters (AUC = 0.97; 95% CI: 0.96–0.99 vs. AUC = 0.95; 95% CI: 0.92–0.98), although the differences was not significant.

A total score cut-off ≥60 for the RC_ASRS achieved the maximum Youden index (sensitivity, 88.6%; specificity, 84.5%). However, the same cut-off for the C_ASRS achieved comparable specificity but a poorer performance in sensitivity (sensitivity, 65.9%; specificity, 84.8%). The screening ability of the ASRS is slightly better among U.S. children than among Chinese children with the same cut-off (sensitivity, 88.6 vs. 89.8%; specificity, 84.5 vs. 90.3%) (https://www.mhs.com).

DISCUSSION

Autism assessment instruments are widely used for basic and clinical research on ASD. Most ASD scales developed to date are based on data obtained from the children of English-speaking populations, whereas few scales are based on data obtained from Chinese-speaking children. A previous study revealed that different cultural contexts could impact the performance of the scales (10). The ASRS is a relatively new ASD assessment tool with excellent reliability and validity in English-speaking children in the U.S. (https://www.mhs.com). In our previous study, we reported that the psychometric properties of the revised Chinese version of the ASRS (6–18 years) were better than the directly translated version tested in Chinese children. However, analysis of the factor structure and psychometric properties of the early version of the ASRS (2–5 years) remained unexplored. Our study addressed this problem and suggested that the RC_ASRS had excellent psychometric properties and was reliable and useful for ASD screening among Chinese children.

Factor analysis is a well-established method to determine the latent structures of questionnaires (20). This analysis was used to investigate the factor structure of the Chinese version of the ASRS in this study. To our knowledge, ASD symptoms are involved in two domains according to the DSM-5 manual. Ultimately, based on the shape of the scree plot, two factors were appropriate for the current sample. All model fit values were <0.9, which fell short of the optimal value in this study. Generally, the optimal value of the model was determined based on a theoretical model. The model fit rarely meets certain criteria, especially those composed of categorical variables (21). Thus, the inadequate model fit reached using the standard judgment criteria may have been due to the inclusion of categorical variables and the nonnormal distribution of the current data.

The factor name and the number of total items in the RC_ASRS were based on the EFA results, which were similar to the factor name and total items of the C_ASRS. One difference was the change in the item number and content of each factor. Several aspects might explain these changes; for example, items moved from the SC factor to the UB factor, and some items were added to the RC_ASRS from the item pool compared with the C_ASRS. Items should be removed or added with caution because unreasonable changes may affect the performance of a questionnaire. However, this difference may be reasonable, because diverse cultural aspects may have affected participants' understanding of some items. Some items belong to SC in the C_ASRS, such as item 15 ("Have trouble talking to other children"), item 17 ("Appear disorganized"), and item 22 ("Uses language that is immature for his or her age"). In contrast, these items were added to UB of the RC_ASRS. Previous reports have demonstrated the

necessity of modifying questionnaires based on different cultures or backgrounds (22, 23).

To test the psychometric properties of the RC_ASRS, we conducted item reliability and discriminant validity analyses. The item reliability was slightly better for the RC_ASRS than for the C_ASRS. The item reliability data indicated that the factor components were robust. In this study, the C_ASRS screening subscales (e.g., UB) showed that the score was significantly higher among the general child population than among children with ASD, which demonstrated that the C_ASRS had poor discriminative validity. However, all subscale scores of the RC_ASRS were significantly higher among the children with ASD than among the kindergarten children, which demonstrated that the RC_ASRS had an excellent identification ability for autistic symptoms among children from the general population compared with the C_ASRS. As indicated by the high AUC values, the RC_ASRS showed a better ASD screening performance. Using the same cut-off, the RC_ASRS had much higher sensitivity (88.6 vs. 65.9%) and equal specificity values (84.5 vs. 84.8%) than did the C_ASRS. All of these data showed that the RC_ASRS was more suitable for ASD screening among Chinese children than the C_ASRS.

Limitations

The samples were recruited across five cities in this study. Differences in language and economic levels exist in the current sample. The specific effect of each variable was not tested. The results should be interpreted with caution. First, EFA is a preliminary test, and the results must be confirmed with other samples. Second, due to missing data, all of the collected questionnaires were not included in the final analysis, but the study sample was sufficiently large, and the vast majority (80.0%) of questionnaires were included; thus, the deletion of missing data is unlikely to have affected the EFA results. The criteria for model fit and factor loading may also have affected the factor structure.

CONCLUSIONS

In conclusion, 62 items comprised the two-factor structure of the RC_ASRS, which showed excellent item reliability and discriminate validity with higher sensitivity and specificity. The RC_ASRS has suitable psychometric properties; therefore, it is useful for early screening for autism among Chinese children.

AUTHOR CONTRIBUTIONS

HZ and CL wrote the manuscript. HZ, CL, XL, LW, YH, LZ, and XZ collected the data. HZ and WY completed the data analysis. WY, Y-HJ and YW revised the manuscript. XL, LW, YH, LZ, XZ, XX, WY, and YW conducted and designed the study.

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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.2018.00460/full#supplementary-material

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The Epidemiological Characteristics of Stroke in Hunan Province, China

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Previous studies have shown that Hunan Province has a high incidence of stroke and a high proportion of intracerebral hemorrhage (ICH). Considering the changes over the past three decades, little is known about the current epidemiological characteristics of stroke in Hunan Province. In 2013, a cross-sectional study was conducted at seven national disease surveillance points (DSPs) in Hunan Province. A multistage cluster sampling method was used to select a representative sample. A total of 21,156 participants aged 20 years and older were examined. Among the 21,156 participants, the number of prevalent strokes, incident strokes and deaths was 307, 87, and 36, respectively. The 2010 China census-standardized prevalence, incidence and mortality were 1191.0 per 100,000 people [95% confidence interval (CI) 1044.8–1337.2], 333.6 per 100,000 person-years (95% CI 255.7–411.5) and 129.7 per 100,000 person-years (95% CI 81.1–178.3), respectively. Ischemic stroke (IS), ICH, subarachnoid hemorrhage (SAH), and stroke of undetermined type (UND) constituted 50.6, 41.4, 5.7, and 2.3% of all incident stroke cases, respectively. Tianxin, Liuyang, Wuling, and Hongjiang have high proportions of ICH (61.5, 58.3, 60, and 50%, respectively). Hypertension is the most common risk factor for prevalent stroke (71.34%), followed by smoking (30.62%) and alcohol use (25.73%). In conclusion, Hunan Province has an extremely heavy stroke burden. The high proportion of ICH is not limited to the Changsha community; it represents an important issue for all of Hunan Province.

Keywords: prevalence, incidence, morality, stroke, epidemiology, Hunan province

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INTRODUCTION

Cerebrovascular disease and ischemic heart disease were the leading causes of years of life lost (YLLs) for both sexes in 123 countries in 2016 (1). The Global Disease Burden Report 2015 (2) estimated that from 1990 to 2015, stroke accounted for 47.3% of total disability-adjusted life-years (DALYs) and 67.3% of deaths caused by all neurological disorders. Countries with low to mid-range scores on the socio-demographic index (SDI) have increased stroke rates, and these rates have the lowest values in the countries with the highest SDI scores.

A report by Yang et al. showed that stroke was the leading cause of death in China in 2010 (3). A number of stroke epidemiological studies have been conducted in China since the 1980s. A large stroke epidemiological survey started in 1986 (4), including 5.79 million population samples from 29 provinces and cities in China, and showed that the incidence of stroke in China was 115.9 per 100,000 person-years, and the prevalence of stroke was 259.86 per 100,000 people in China.

The geographic distribution of the incidence of stroke in China displayed a north-south gradient, which was characterized by a significantly higher incidence of stroke in northern China than in southern China (5, 6). However, Hunan Province was an exception. Hunan Province is located in South Central China, with a total area of 211,800 square kilometers, and the total population of Hunan Province is 65.68 million. Although this province is located in southern China, the incidence of stroke in Hunan was 141.2 per 100,000 person-years, and the mortality rate reached 86.2 per 100,000 person-years. Another survey that reported 10 consecutive years of stroke incidence monitoring in Beijing, Shanghai and Changsha (the capital of Hunan Province) between 1991 and 2000 showed that the incidence of stroke in Changsha was 150 per 100,000 person-years, which ranked first among the three cities (7). In addition, intracerebral hemorrhage (ICH) accounted from 50.3 to 55.4% of all strokes in Hunan, although it is extremely rare worldwide (8, 9).

Since the beginning of the twenty-first century, there have been some unfavorable changes in the lives of Chinese residents: unhealthy diet structures and lifestyle habits, inevitable aging of the population, urbanization, and other behavioral and social factors (3). Disease patterns have also changed accordingly. On the other hand, previous epidemiological data were mainly from the urban communities in Changsha and did not cover the rural regions. Whether the high proportion of ICH is a phenomenon unique to Changsha or a common characteristic in Hunan Province remains unknown. It is necessary to carry out a new round of epidemiological surveys to further elucidate the stroke burden and the subtypes of stroke in Hunan Province.

MATERIALS AND METHODS

Study Participants and Design

The method of this study is consistent with the national epidemiological survey of stroke (10). Our survey was conducted at seven monitoring sites (three urban and four rural regions) (**Figure 1**), based on the national disease surveillance points (DSPs) system. The survey districts in large, medium, and small cities were defined as urban regions, and other survey districts were defined as rural regions. The sample size of Hunan Province was calculated by a multistage stratified cluster sampling method that accounted for national representation in terms of socio-economic status, geographical distribution, educational level, medical care, and lifestyles. A town/district proportional to the population size of the survey district was selected. In each town/district, cluster sampling was used to select no <4,500 residents (calculated as an average of three persons per household multiplied by ∼1,500 households), and at least 85% of those individuals were expected to complete the entire survey process (∼3,800 residents from 1,300 households). The actual sample size was at least 26,600 residents for all age groups.

The face-to-face questionnaire surveys were performed door-to-door by Center for Disease Control (CDC) investigators who had been well trained. The study participants were people who had lived in that community (township or street) for at least 6 months. The investigators collected the following information: basic information about each family member (family households are the basic survey units, and all resident populations are included, including non-family members who have lived with the family for at least 6 months, such as nannies, drivers, or other lodged populations), the symptoms and medical history of each individual, and family members who died from stroke or prevalent stroke cases between September 1, 2012, and August 31, 2013. The point in time for determining prevalence was defined as 24:00 August 31, 2013. The incidence of stroke was defined as the rate of first-ever stroke cases that occurred during the year prior to the prevalence point (between 00:00 September 1, 2012, and 24:00 August 31, 2013). All deaths that occurred from 00:00 September 1, 2012, to 24:00 August 31, 2013, were recorded to determine later if stroke was the possible cause of death with a validated verbal autopsy technique (11, 12).

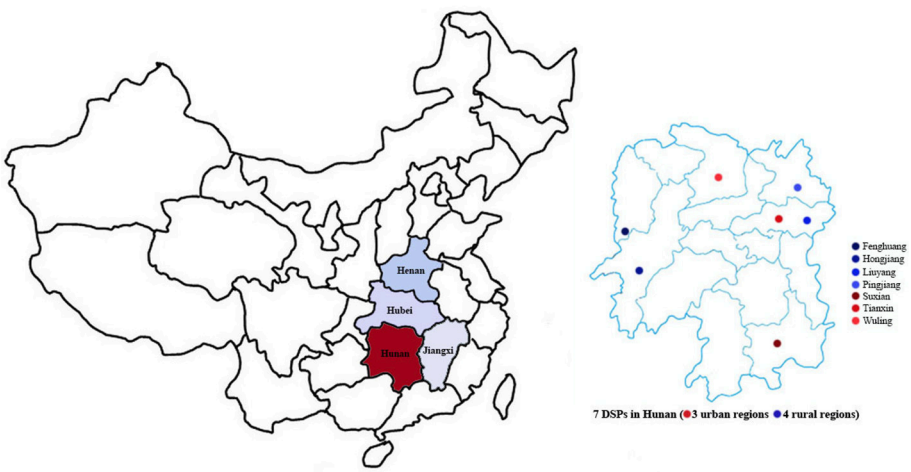

FIGURE 1 | Central China (including Hunan, Jiangxi, Hubei, and Henan) and 7 DSPs in Hunan Province (3 urban regions and 4 rural regions).

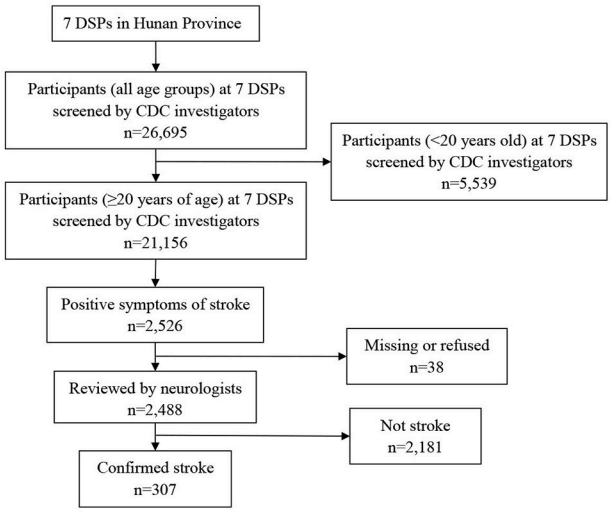

FIGURE 2 | Flowchart of stroke case evaluation.

In the second stage, two neurologists interviewed 2,526 participants with suspected stroke/transient ischemic attack (TIA, including all definite and possible cases) and completed the case confirmation forms. There were 38 patients who declined the interview or follow-up. First-ever stroke cases occurring between September 1, 2012, and August 31, 2013, were identified as incident strokes. All living subjects with confirmed stroke before August 31, 2013, were identified as prevalent stroke cases. People who died from stroke from September 1, 2012, to August 31, 2013, were used to calculate the mortality rate of stroke. All case reviews were supported by medical records, image data, official statistics, and death certificates (for fatal events). When appropriate, some study participants were requested to undergo a brain neuroimaging examination (for example, to exclude brain disorders mimicking stroke, such as hypertensive encephalopathy, infection, toxic/metabolic encephalopathy, Wernicke encephalopathy, epileptic seizure, mitochondrial encephalopathy, and transient global amnesia) and/or another neurological examination (lumbar puncture or electroencephalogram) (**Figure 2**).

Diagnostic Criteria

The diagnostic criteria for stroke were based on the World Health Organization (WHO) criteria (13): rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than that of vascular origin. The exclusion criteria were other nervous system abnormalities induced by trauma, metabolic disorders, tumors, or central nervous system infections. The pathological type of stroke was classified into four major categories: (1) subarachnoid hemorrhage (SAH) (lumbar puncture was the only diagnostic method for SAH); (2) ICH; (3) ischemic stroke (IS); and (4) undetermined type (UND). Stroke cases for which no brain imaging was performed within the first week of stroke onset or for which the results of imaging or autopsy could not be obtained for further confirmation by two neurologists were classified as UND.

TABLE 1 | Characteristics of the 21,156 participants (≥20 years) in 2013.

Characteristics	Overall	Men	Women	*p*
Participants, *n* (%)	21,156 (100.0)	10,566 (49.9)	10,590 (50.1)	
Residence, *n* (%)				<0.001
Urban	9,009 (42.6)	4,347 (41.1)	4,662 (44.0)	
Rural	12,147 (57.4)	6,219 (58.9)	5,928 (56.0)	
Age groups, *n* (%)				<0.001
20–29	4,470 (21.1)	2,072 (19.6)	2,398 (22.6)	
30–39	3,556 (16.8)	1,822 (17.2)	1,734 (16.4)	
40–49	4,819 (22.8)	2,493 (23.6)	2,326 (22.0)	
50–59	3,292 (15.6)	1,700 (16.1)	1,592 (15.0)	
60–69	2,816 (13.3)	1,423 (13.5)	1,393 (13.2)	
70–79	1,590 (7.5)	783 (7.4)	807 (7.6)	
≥80	613 (2.9)	273 (2.6)	340 (3.2)	
Education, *n* (%)				<0.001
Primary school or lower	7,829 (37.0)	3,646 (34.5)	4,183 (39.5)	
Middle school	11,776 (55.7)	6,136 (58.1)	5,640 (53.3)	
College and higher	1,146 (5.4)	581 (5.5)	565 (5.3)	
Missing	405 (1.9)	203 (1.9)	202 (1.9)	
Marital status, *n* (%)				<0.001
Married	16,788 (79.4)	8,322 (78.8)	8,466 (79.9)	
Single	2,409 (11.4)	1,452 (13.7)	957 (9.0)	
Widowed	1,549 (7.3)	578 (5.5)	971 (9.2)	
Missing	410 (1.9)	214 (2.0)	196 (1.9)	
Occupation, *n* (%)				<0.001
Student	292 (1.4)	111 (1.1)	181 (1.7)	
Worker	217 (1.0)	145 (1.4)	72 (0.7)	
Farmer	14,281 (67.5)	7,394 (70.0)	6,887 (65.0)	
Employee	1,307 (6.2)	777 (7.4)	530 (5.0)	
Entrepreneur	2,793 (13.2)	1,537 (14.5)	1,256 (11.9)	
Retired or unemployed	1,727 (8.2)	312 (3.0)	1,415 (13.4)	
Missing	539 (2.5)	290 (2.6)	249 (2.3)	

The term "workers" refers to individuals who work at factories. "Employees" refers to national public servants, professional technicians, office clerks, business managers, and active servicemen. "Entrepreneurs" refers to individual operators and freelancers.

Data Collection

The research staff reviewed all questionnaires that were sent to the Beijing Neurosurgical Institute prior to the end of 2013. Then, all questionnaires were entered into a database with a standard procedure. All research staff received standardized training and were formally certified before data collection. The quality and completeness of the questionnaires from each investigation site were verified and monitored by a professional quality controller to ensure compliance with the standardized study protocol. A strict double-entry system was used for quality control during the data collection and cleanup process. The Clinical Research Organization surveyed and monitored the entire survey process to ensure the consistency of data collection among all study sites. The study was approved by the ethical review committees of Beijing Tiantan Hospital and Xiangya Hospital.

TABLE 2 | Prevalence (with 95% CIs) of stroke per 100,000 Hunan adults by sex in 2013.

Age group (years)	Men			Women			Total		
	No. of strokes	Prevalence	95% CI	No. of strokes	Prevalence	95% CI	No. of strokes	Prevalence	95% CI
20–29	1	48.3	0–142.8	0	0	0–0	1	22.4	0–66.2
30–39	2	109.8	0–261.8	1	57.7	0–170.7	3	84.4	0–180.0
40–49	8	320.9	98.9–542.9	9	386.9	134.6–639.2	17	352.8	185.4–520.2
50–59	38	2,235.3	1,532.6–2,938.0	30	1,884.4	1,216.5–2,552.4	68	2,065.6	1,579.7–2,551.5
60–69	54	3,794.8	2,802.0–4,787.6	44	3,158.7	2,240.2–4,077.1	98	3,480.1	2,803.2–4,157.0
70–79	37	4,725.4	3,239.2–6,211.6	41	5,080.5	3,565.4–6,595.7	78	4,905.7	3,844.0–5,967.3
≥80	16	5,860.8	3,074.4–8,647.2	26	7,647.1	4,822.2–10,471.9	42	6,851.6	4,851.7–8,851.4
Total	156	1,476.4	1,246.5–1,706.4	151	1,425.9	1,200.1–1,651.7	307	1,451.1	1,290.0–1,612.3
ASR*		1,222.1	1,012.6–1,431.6		1,154.0	950.6–1,357.4		1,191.0	1,044.8–1,337.2

ASR, Age-standardized rates based on the 2010 China population census.

TABLE 3 | Incidence of stroke per 100,000 person-years (with 95% CIs) among Hunan adults (≥20 years) by sex in 2012–2013.

Age group (years)	Men			Women			Total		
	No. of strokes	Rate	95% CI	No. of strokes	Rate	95% CI	No. of strokes	Rate	95% CI
20–29	1	48.3	0–142.8	0	0	0–0	1	22.4	0–66.2
30–39	1	54.9	0–162.6	0	0	0–0	1	28.1	0–83.3
40–49	3	120.4	0–256.6	0	0	0–0	3	62.3	0–132.8
50–59	9	531.0	185.0–877.0	4	251.6	5.3–497.8	13	395.7	181.0–610.4
60–69	16	1,131.5	580.2–1,682.9	15	1,083.0	537.9–1,628.1	31	1,107.5	719.8–1,495.3
70–79	8	1,051.2	326.6–1,775.9	7	885.0	232.3–1,537.6	15	966.5	479.8–1,453.2
≥80	9	3,448.3	1,234.6–5,662.0	14	4,375.0	2,133.9–6,616.1	23	3,958.7	2,373.2–5,544.2
Total	47	447.0	319.5–574.5	40	379.6	262.2–497.0	87	413.3	326.6–499.9
ASR*		376.3	259.3–493.3		287.2	185.0–389.4		333.6	255.7–411.5

ASR, Age-standardized rates based on the 2010 China population census.

All interviewers obtained written informed consent before data collection.

Education, marital status, current occupation, current smoking (≥1 cigarette/per day) and alcohol intake (any dose of alcohol, ≥1 time per week) were defined by the participants' self-reports. A history of hypertension was defined as documented systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or the use of blood pressure-lowering drugs. A history of diabetes mellitus was defined as documented fasting blood glucose ≥7.0 mmol/L and/or 2-h postprandial blood glucose ≥11.1 mmol/L or the use of antidiabetic drugs. Confirmed medical records of atrial fibrillation were diagnosed by electrocardiograph (ECG). Documented medical records of myocardial infarction, angina or hyperlipidemia were used to diagnose coronary heart disease (CHD) or dyslipidemia. To identify differences in the prevalence of risk factors between the two groups, all the risk factors were classified as Yes or No and analyzed as binary variables. The missing data were classified as No because we cannot accurately estimate the prevalence of all risk factors in epidemiological surveys.

Statistical Analysis

Age- and sex-specific prevalence (per 100,000 people), incidence, and mortality rates (per 100,000 person-years) were estimated. Age-standardized prevalence, incidence and mortality rates were calculated with a direct method by using the 2010 China population census as standard, 95% confidence intervals (CIs) and the relative ratio (RR) of 10 years age group of the prevalence, incidence, and mortality of stroke were calculated by using the Poisson distribution. The chi-squared (χ^2) test was used to assess differences in the prevalence, incidence and mortality of stroke between sex, the prevalence of risk factors for prevalent stroke between sexes and between rural and urban populations. All statistical analyses were conducted in SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The characteristics of the study participants are shown in **Table 1**. The response rate was 85.9%. The mean age was 46.2 (SD 16.8) years. An educational background of primary school

TABLE 4 | Mortality (with 95% CIs) of stroke per 100,000 Hunan adults (≥20 years) by sex in 2012–2013.

Age group (years)	Men			Women			Total		
	No. of strokes	Rate	95% CI	No. of strokes	Rate	95% CI	No. of strokes	Rate	95% CI
20–29	0	0	0–0	0	0	0–0	0	0	0–0
30–39	0	0	0–0	0	0	0–0	0	0	0–0
40–49	1	40.1	0–118.8	0	0	0–0	1	20.8	0–61.5
50–59	1	59.0	0–174.6	1	62.9	0–186.0	2	60.9	0–145.2
60–69	4	282.7	6.0–559.3	4	287.2	6.1–568.2	8	284.9	87.8–482.0
70–79	6	789.5	160.3–1,418.7	3	373.1	0–794.6	9	575.4	200.6–950.3
≥80	5	1,915.7	252.7–3,578.7	11	3,188.4	1,334.5–5,042.4	16	2,640.3	1,363.7–3,916.8
Total	17	161.7	84.9–238.5	19	179.4	98.8–260.0	36	170.6	114.9–226.3
ASR*		130.5	61.5–199.5		125.5	57.9–193.1		129.7	81.1–178.3

ASR, Age-standardized rates based on the 2010 China population census.

TABLE 5 | Prevalence of risk factors among 307 people with prevalent stroke by sex and residency in Hunan.

		Sex			Urban and Rural			
		Men *n* (%)	Women *n* (%)	*p*	Urban *n* (%)	Rural *n* (%)	Total *n* (%)	*p*
Hypertension	Yes	113 (72.44%)	106 (70.20%)	0.665	98 (71.01%)	121 (71.60%)	219 (71.34%)	0.911
	No	43 (27.56%)	45 (29.80%)		40 (28.99%)	48 (28.40%)	88 (28.66%)	
Diabetes	Yes	11 (7.05%)	16 (10.60%)	0.273	13 (9.42%)	14 (8.28%)	27 (8.79%)	0.715
	No	145 (92.95%)	135 (89.40%)		125 (90.58%)	156 (91.72%)	280 (91.21%)	
Dyslipidemia	Yes	29 (18.59%)	25 (16.56%)	0.640	27 (19.57%)	27 (15.98%)	54 (17.59%)	0.411
	No	127 (81.41%)	126 (83.44%)		111 (80.43%)	142 (84.02%)	253 (82.41%)	
Atrial fibrillation	Yes	4 (2.56%)	3 (1.99%)	1.000	3 (2.17%)	4 (2.37%)	7 (2.28%)	1.000
	No	152 (97.44%)	148 (98.01%)		135 (97.83%)	165 (97.63%)	300 (97.72%)	
CHD	Yes	22 (14.10%)	30 (19.87%)	0.178	23 (16.67%)	29 (17.16%)	52 (16.94%)	0.909
	No	134 (85.90%)	121 (80.13%)		115 (83.33%)	140 (82.84%)	255 (83.06%)	
Current smoker	Yes	62 (39.74%)	32 (21.19%)	<0.001	49 (35.51%)	45 (26.63%)	94 (30.62%)	0.093
	No	94 (60.26%)	119 (78.81%)		89 (64.49%)	124 (73.37%)	213 (69.38%)	
Alcohol use	Yes	44 (28.21%)	35 (23.18%)	0.314	46 (33.33%)	33 (19.53%)	79 (25.73%)	< 0.01
	No	112 (71.79%)	116 (76.82%)		92 (66.67%)	136 (80.47%)	228 (74.27%)	

or less accounted for 37% of participants; people who were married or had a partner accounted for 79.4% of participants; farmers accounted for 67.5% of participants; and urban residents accounted for 42.6% of participants.

In this study, the diagnostic rate of computed tomography (CT) and/or magnetic resonance imaging (MRI) in stroke patients was 93.1% among incident strokes and 87.9% among prevalent strokes. Of the 21,156 total participants, the number of prevalent strokes was 307 (1451.1 per 100,000), and the 2010 China population census-standardized prevalence was 1191.0 per 100,000 people. The crude prevalence of stroke was 1476.4 per 100,000 people for men and 1425.9 per 100,000 people for women (**Table 2**). The 2010 China population census-standardized prevalence for men was slightly higher than that observed for women (1222.1/100,000 and 1154.0/100,000, respectively). A study of risk factors in 307 people with prevalent stroke showed that hypertension was the most common risk factor (71.34%), followed by smoking (30.62%) and alcohol use (25.73%) (**Table 5**). There were significant differences in smoking between men and women ($p < 0.001$) and in alcohol use between urban and rural subjects ($p < 0.01$). There were no significant differences in hypertension, diabetes, dyslipidemia,

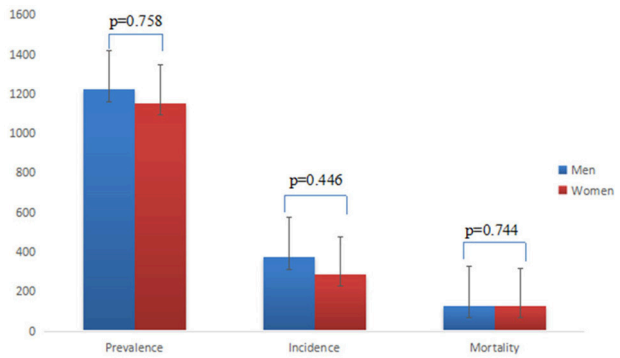

FIGURE 3 | Sex-specific prevalence, incidence, and mortality.

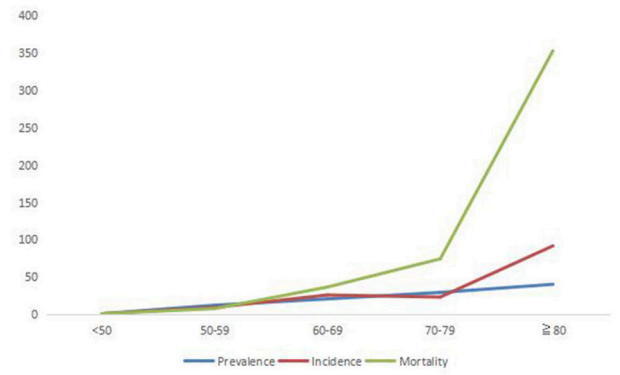

FIGURE 4 | The RR of 10 years age group of the incidence, prevalence, and mortality of stroke.

TABLE 6 | Number and percentage of incident strokes observed in Hunan Province by stroke subtype.

	Strokes	IS (%)	ICH (%)	SAH (%)	UND (%)
Tianxin	13	2 (15.4%)	8 (61.5%)	3 (23.1%)	0
Liuyang	12	4 (33.3%)	7 (58.3%)	1 (8.3%)	0
Pingjiang	14	8 (57.1%)	4 (28.6%)	0	2 (14.3%)
Fenghuang	10	7 (70%)	3 (30%)	0	0
Wuling	5	2 (40%)	3 (60%)	0	0
Hongjiang	12	5 (41.7%)	6 (50%)	1 (8.3%)	0
Suxian	21	16 (76.2%)	5 (23.8%)	0	0
Total	87	44 (50.6%)	36 (41.4%)	5 (5.7%)	2 (2.3%)

IS, ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; UND, stroke of undetermined pathological type.

arterial fibrillation, and CHD between men and women or between urban and rural subjects.

The number of incident strokes was 87, and the crude incidence of stroke in Hunan Province was 413.3 per 100,000 person-years; the 2010 China population census-standardized incidence rate was 333.6 per 100,000 person-years. The crude incidence of stroke was 447.0 per 100,000 people for men and 379.6 per 100,000 people for women (**Table 3**). The 2010 China population census-standardized incidence for men was slightly higher than that observed for women (367.3/100,000 vs. 287.2/100,000, respectively).

The number of deaths due to stroke was 36. The mortality rate of stroke was 170.6 per 100,000 person-years, and the 2010 China population census-standardized mortality was 129.7 per 100,000 person-years. The mortality of stroke was 161.7 per 100,000 person-years for men and 179.4 per 100,000 person-years for women. The 2010 China population census-standardized mortality for men was slightly higher than that observed for women (130.5/100,000 and 125.5/100,000) (**Table 4**).

There is no significant difference between sex-specific prevalence, incidence and mortality ($p > 0.05$) (**Figure 3**). With reference to the age <50 years, the RR of 10 years age group of incidence, prevalence and mortality of stroke are increasing, especially for the RR of mortality of stroke (**Figure 4**).

IS, ICH, SAH, and UND constituted 50.6, 41.4, 5.7, and 2.3% of all incident strokes, respectively. Tianxin, Liuyang, Wuling, and Hongjiang had high proportions of ICH (61.5, 58.3, 60, and 50%, respectively) (**Table 6**).

DISCUSSION

Our study shows that the prevalence, incidence, and mortality of stroke in Hunan Province are much higher than those reported in the survey performed in 1986 (1165.3 vs. 259.86, 324.7 vs. 115.87, and 117.6 vs. 80.94, respectively) (age-standardized rates based on the world standard population) (4, 5). According to the data from the Sixth National Population Census, the total population of Hunan Province is 65.68 million, and the number of people suffering from stroke in Hunan Province is ∼765,000. The synchronous national stroke survey showed that the prevalence of stroke in central China (including Hunan, Jiangxi, Hubei, and Henan) was the highest among the seven regions of China, and the incidence and mortality of stroke in central China ranked second among these regions (10). The incidence of stroke in Hunan Province is close to the incidence in central China (Hunan/Central China 333.6/326.1), and the mortality of stroke in Hunan Province is lower than that in central China (Hunan/Central China 129.7/158.5), which indicates that stroke in Hunan Province is a very serious burden, yet the risk is still increasing. On the other hand, the incidences of stroke are significantly higher in some high-latitude countries than in low-latitude countries (14, 15). Our study confirmed that the stroke incidence of Hunan Province does not follow a north-south gradient, which has been supported by previous studies (7, 16, 17). Environmental or climatic factors may account for a portion of the high incidence of stroke in Hunan Province.

Our data show that hypertension is the most common risk factor in patients with prevalent stroke (71.34%), but no significant differences were found between sexes or between rural and urban areas ($p > 0.05$). Previous studies have also shown that hypertension is highly correlated with stroke incidence and mortality and explains 70% of the geographic variability in stroke incidence and mortality in China (5, 18). Other researchers have found that the prevalence of hypertension among patients with prevalent stroke in China is higher than that in other countries (19). Similarly, Gu (20) showed that the age-specific prevalence of hypertension in men was higher than that in women in the population aged 35 to 64 years but not in the population aged 65–74 years. However, our data were obtained mainly from oral inquiries, and missing data were classified as not having the corresponding disease (No), which may lead to underestimated rates of risk factors. Smoking and alcohol use have been identified as common risk factors for stroke (21, 22). The proportion of smoking in men is higher than that in women ($p < 0.01$), which may partially explain the higher prevalence of stroke in men than in women. The reason why alcohol consumption is more frequent in urban areas than in rural areas may be related to an unhealthy urban lifestyle in Hunan (such as drinking alcohol and eating late at night) ($p < 0.01$). The Global Burden of Disease Study 2013 (GBD 2013) stated that

over 92% of the stroke burden is due to modifiable risk factors, with behavioral factors (i.e., smoking) accounting for 74.2% and metabolic factors (i.e., high systolic blood pressure) accounting for 72.4% of the stroke burden (23). Therefore, controlling risk factors for stroke is important for decreasing the stroke burden.

The main subtypes of incident stroke in Hunan Province are IS and ICH, which account for 50.6 and 41.4% of all strokes, respectively. From a nationwide perspective, IS is still the main subtype and accounts for 45.5–75.9% of strokes, whereas ICH accounts for 17.1–55.4% of strokes (8, 24, 25). In western countries, the proportions of IS and ICH are 67.3–80.5 and 6.5–19.6%, respectively (26). Changsha is the capital of Hunan Province, and it has been reported as the city with the highest prevalence of ICH among the three cities (Changsha, Beijing and Shanghai) (7). A study by Yang et al. (8) showed that ICH accounted for 55.4% of strokes in the Changsha community between 1986 and 2000. In a study by Sun et al. (9), the incidence of IS increased at an annual rate of 3.5%, while the incidence of ICH exhibited no significant changes. This new round of stroke epidemiological studies showed that not only Changsha community (Tianxin) but also other regions of Hunan Province [one urban region (Wuling) and two rural regions (Liuyang and Hongjiang)] have a high proportion of ICH. Hypertension is the most important risk factor for ICH (27, 28), and hypertensive patients are increasing (29). We also found that hypertension is the most common risk factor in patients with prevalent stroke (71.34%). Low awareness, inadequate treatment and an uncontrolled rate of hypertension may explain the high proportion of ICH. According to the 2002 National Nutrition and Health Survey (NNHS), the awareness, treatment and control of hypertension were achieved in only 30%, 25 and 6% of participants, respectively (30). However, not all of the seven investigated regions had a high proportion of ICH. Low awareness and poor control of the rate of hypertension cannot fully explain this phenomenon. Hunan residents tend to eat a spicy and salty diet and to adopt an unhealthy lifestyle of drinking alcohol and eating late at night, and there are also regional differences among these seven regions, which represent potential risk factors for ICH and hypertension. Furthermore, a study by Woo et al. (31) investigated the genetic and environmental risk factors for ICH and found that a third of lobar ICH cases were associated with the apolipoprotein E4 or E2 allele. The fundamental reason for the high proportion of ICH remains unclear, although it may result from a combination of hypertension, diet, lifestyle, and genetic and environmental factors. Further research with a larger sample size should be conducted to investigate blood pressure management status, dietary habits, lifestyle, and genetic risk factors.

LIMITATIONS OF THE PRESENT SURVEY

There are several potential limitations of the present epidemiological survey. First, the risk factor data were obtained from the oral responses of the investigators and were classified as either Yes or No and analyzed as binary variables, which may have incurred bias. Second, recall bias may have affected the evaluation of the prevalence, incidence, and mortality of stroke. However, great efforts have been made to minimize these possibilities by cross-checking the data obtained from the door-to-door interviews and from medical records and by asking neurologists to review the identified and suspected cases. Third, we used only smoking cigarettes as the dominant mode of tobacco use in our survey; this approach may underestimate the proportion of tobacco intake. Fourth, the use of a small monitoring sample (average 3,700 residents per DSP) in a single DSP and the limited medical conditions in some rural areas led to an imbalanced proportion of stroke subtypes, such as a higher proportion of SAH than IS in Tianxin; in addition, the proportion of UND in Pingjiang reached 14.3%, and the number of incident strokes in Wuling was only 5, which led to a 60% proportion of ICH in Wuling.

CONCLUSION

In conclusion, Hunan Province has an extremely heavy stroke burden. The high proportion of ICH is not limited to the Changsha community; it represents an important issue for all of Hunan Province.

AUTHOR CONTRIBUTIONS

YL and YH involved in the study design. DJ, HL, BC were responsible for the first stage data collection. JF, WH, JX, TW, XL, QH, and CY were responsible for the second stage cases confirmation. WH wrote the manuscript. YL and WZ modified and revised the manuscript. All authors have read and approved the final version of the manuscript.

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REVIEW
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Evidence for the Use of Acupuncture in Treating Parkinson's Disease: Update of Information From the Past 5 Years, a Mini Review of the Literature

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Acupuncture is an alternative therapy for Parkinson's disease (PD), but its efficacy and safety are controversial. Our previous study, which reviewed the literature from 1974 to 2012, could not find enough evidence from rigorously designed randomized, controlled trials (RCTs) to make a conclusion about the efficacy of acupuncture. Recently, more RCTs and meta-analyses have been conducted to evaluate the efficacy of acupuncture. The aim of our current study is to provide updated information in brief on this topic. In this study, we analyzed and summarized seven RCTs and four meta-analyses. Although all included studies were not of high quality, we found that there has been a tremendous progress in acupuncture research in treating Parkinson's disease (PD) during the past 5 years, based on our experience and insights into the behavioral assessments of PD. First, the numbers of RCTs and meta-analyses based on RCTs are increasing. Second, non-motor symptoms are increasingly emphasized. Third, objective behavioral assessment tools are being employed. Although recent studies can provide limited evidence for the efficacy of acupuncture, we make the following recommendations for the future investigation: First, large, multicenter, well-designed RCTs should be organized for evaluation of the efficacy of acupuncture. Second, objective assessments using novel computerized technologies should be considered. Third, target symptoms should be selected and evaluated instead of only performing global evaluations. Fourth, attention should be paid to the efficacy of scalp acupuncture. Fifth, the safety of acupuncture should be evaluated and reported.

Keywords: Parkinson's disease, acupuncture, electroacupuncture, non-motor symptoms, efficacy/safety, behavioral assessment

INTRODUCTION

Parkinson's disease (PD), the second most common neurodegenerative disorder, is a major health concern for elderly people. Classical therapies (CTs), such as dopaminergic medication and deep brain stimulation, are far from satisfactory. Before next-generation treatments, such as stem cell and genetic therapy, can be clinically applied, many alternatives are being considered as adjuvant therapies to improve the outcome of patients. Acupuncture, based on the theory of traditional Chinese medicine, has been used to treat PD, especially in the East Asian countries of China, Japan, Korea, and Singapore. Although the action mechanisms of acupuncture for treating PD remain unclear, the therapy may provide relief by affecting the progress of neuron degeneration, improving the dopaminergic system, improving the motor control network, and relieving oxidative stress (1). The included acupuncture studies involved two types of acupunctural methods: classical and electroacupuncture. While classical acupuncture warrants increased experience and skill of a therapist, electroacupuncture has objective parameters that can be easily achieved by a beginner. Therefore, electroacupuncture will be the future of acupuncture. In this study, the term "acupuncture" implies classical and electroacupuncture.

The efficacy of acupuncture for PD is controversial. At present there are no authoritative reports of the efficacy and safety of acupuncture for Parkinson's disease. Our 2013 review (1) covered almost all the available literature on this topic from 1974 to 2012 since the first report of the use of acupuncture in the central nervous system (2). This review could not find enough evidence from rigorously designed, randomized, controlled trial (RCTs) to make a conclusion about the efficacy of acupuncture. Many trials were not convincing because of flaws in the methodology (1, 3). We therefore wrote another review aiming to briefly introduce improved methodology to studies of acupuncture (3). In recent years, with progress in evidence-based medicine and clinical epidemiology, more RCTs and meta-analyses have been conducted to evaluate the efficacy of acupuncture. Moreover, non-motor symptoms of PD have been increasingly emphasized by clinicians. Many subjective assessment tools have been used for evaluation of PD symptoms (4, 5). It is imperative to update the information on the efficacy of acupuncture taking account of these advances in acupuncture studies. Although several systematic reviews have investigated the efficacy of acupuncture, we performed a newer and more comprehensive mini-review [the continuation of our previous study (1)] of these previous studies, as well as the newest RCTs. This review aims to provide updated, brief "take-home messages" about the efficacy of acupuncture in patients with PD.

Abbreviations: Acup, acupuncture; BA, balance area; BDI, Beck Depression Inventory; CT, classical treatment; CTCA, Chorea-tremor controlling area; EA, electroacupuncture; FMSA, foot motor sensory area; MCA, motor controlling area; MFIS, Modified Fatigue Impact Scale; PDQ-39, 39-Item Parkinson's Disease Questionnaire; PDQL, Parkinson's Disease Quality of Life Questionnaire; PDSS, Parkinson's Disease Sleep Scale; PIGD, Postural Instability and Gait Disturbance; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized, controlled trial; TAS, Tension Assessment Scale; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS I, mentation, behavior and mood subscale of the Unified Parkinson's Disease Rating Scale; UPDRS II, activities of daily living subscale of the Unified Parkinson's Disease Rating Scale; UPDRS III, motor symptoms caused by Parkinson's disease subscale of the Unified Parkinson's Disease Rating Scale; UPDRS IV, complications of therapy subscale of the Unified Parkinson's Disease Rating Scale.

MATERIALS AND METHODS

We searched the literature from English (PubMed, EMBASE, and Google Scholar) and Chinese (CNKI, SinoMed, VIP, and Wanfang Data) databases. In order to balance sensitivity and specificity, we also searched related trials via the World Health Organization (WHO) trials portal (ICTRP). Documents from 2013 to 2017 were included. The search results are shown in **Figure 1A**. A total of 171 studies were found. Finally, 11 studies, including 4 meta-analysis studies and 7 RCTs, were approached for further analysis (**Figure 1A**).

RESULTS

Characteristics of Included Literature

A total of 11 studies were included, comprising 4 meta-analysis studies and 7 RCTs. The characteristics of the included studies are shown in **Table 1**. Subjective behavioral assessments employed in this study include the Unified Parkinson's Disease Rating Scale (UPDRS) (6–9, 11–16), the Webster Scale (6, 7, 9, 16), the Tension Assessment Scale (TAS) (9), the Parkinson's Disease Sleep Scale (PDSS) (10, 12, 15), the Postural Instability Gait Disorder (PIGD) (11), the Parkinson's Disease Quality of Life Questionnaire (PDQL) (11), the Beck Depression Inventory (BDI) (11), the Modified Fatigue Impact Scale (MFIS) (12), the 39-Item Parkinson's Disease Questionnaire (PDQ-39) (12, 15), and the Pittsburgh Sleep Quality Index (PSQI) (14). One RCT used gait speed as an objective assessment (13). Besides motor symptoms, non-motor symptoms, such as sleep (12, 14, 15), quality of life (QOL) (12, 15), and fatigue (12), were also evaluated. Objective evaluation and evaluation of non-motor symptoms are increasingly emphasized for evaluation of the efficacy and safety of acupuncture for PD. No serious adverse events were reported.

Quality Assessment of Included Studies

We assessed the quality of the included studies with a Jadad scale (for RCTs) (17) and an Overview Quality Assessment Questionnaire (OQAQ) (for meta-analysis) (18) (**Figure 1B**).

The included meta-analyses were of minor (three studies) and major (one study) flaws because of the possible selection bias and small sample size. Although Lee (6) and Lee (7) used the Physiotherapy Evidence Database scale and Cochrane risk of bias to perform a quality assessment, there was a possible publication and performance bias, and most (80%) of the included RCTs had a serious selection bias. In addition, follow-up and sensitivity analyses were available in this study. The limitations of the study Lee 2013 were that only four RCTs published in China were included and the small sample size in these RCTs hindered drawing a useful conclusion (6). Although RCTs included in

TABLE 1 | Efficacy and safety in the current acupuncture study.

Study	Experimental design treatment vs. control	Number of participants	Acupoints involved	Course	Assessments	Adverse events	Results
META-ANALYSIS OF ACUPUNCTURE FOR PD PATIENTS							
Lee et al. (6)	A1. SA+CT vs. B1. CT alone A2. SA vs. B2. CT alone	184 participants including 4 RCTs	MS (4, 6, 8, 9, 14), MCA, CTCA, FMSA	> 5 weeks average	UPDRS total score 2. Webster Scale	No serious adverse events reported	A1 > B1, $P = 0.01$, $I^2 = 0\%$* 2. A2 > B2, $P = 0.30$, $I^2 = 84\%$
Lee et al. (7)	A1. Acup + CT vs. B1. CT alone A2. Acup vs. B2. No treatment A3. Acup vs. B3. CT alone	1616 participants including 25 RCTs	Taichong (LR-3), Baihui (GV-20), Yanglingquan (GB-34), Fengchi (GB-20), Hegu (LI-4), Sishencong (EX-HN1), Quchi (LI-11) (Freq ≥ 7)	> 6 weeks average	UPDRS I UPDRS II UPDRS III UPDRS IV UPDRS total scores Webster Scale 7.Total efficacy	Unreported	1: A1 > B1, $P = 0.23$, $I^2 = 0\%$ 2: A1 > B1, $P < 0.001$, $I^2 = 0\%$** 3. A1 > B1, $P < 0.001$, $I^2 = 0\%$** 4. A1 > B1, $P = 0.17$, $I^2 = 93\%$ 5. A1 > B1, $P < 0.001$, $I^2 = 0\%$** 6. A2 > B2, $P < 0.001$, $I^2 = 0\%$** A3 > B3, $P < 0.001$, $I^2 = 0\%$** A1 > B1, $P < 0.001$, $I^2 = 93\%$** 7. A3 > B3, $P = 0.06$, $I^2 = 0\%$ A1 > B1, $P < 0.001$, $I^2 = 73\%$**
Liu et al. (8)	A. Acup + Madopar vs. B. Madopar alone	831 participants including 11 RCTs	Unreported	Unreported	Total efficacy UPDRS I UPDRS II UPDRS III UPDRS IV 6. UPDRS total scores	No serious adverse events reported	1: A > B, $P < 0.001$, RR = 1.28** 2: A > B, $P = 0.06$, $I^2 = 47\%$ 3: A > B, $P = 0.006$, $I^2 = 82\%$** 4: A > B, $P = 0.17$, $I^2 = 95\%$ 5: A > B, $P = 0.30$, $I^2 = 96\%$ 6: A > B, $P = 0.002$, $I^2 = 77\%$**
Noh et al. (9)	A1. Acup+CT vs. B1. CT alone A2. EA+CT vs.B2. CT alone A3. EA + Acup + CT vs.B3. CT alone A4. Acup vs.B4. Sham Acup	2625 participants including 42 RCTs	Taichong (LR-3), Fengchi (GB-20), Yanglingquan (GB-34), Hegu (LI-4), Baihui (GV-20), Zusanli (ST-36), Sishencong (EX-HN1)(Freq≥10)	> 4 weeks average	UPDRS total score Webster Scale 3. Tension Assessment Scale	No serious adverse events reported	1: A1 > B1, $P < 0.00001$, I^2=81%** A2 > B2, $P = 0.0006$, I^2=46%** A3 > B3, $P = 0.003$, I^2= 0%** A4 > B4, $P = 0.59$, I^2= 0% 2: A1 > B1, P =0.006, I^2= 81%** A2 > B2, $P = 0.41$, I^2= 97% 3: A2 > B2, $P = 0.08$, I^2= 38%
RCTS OF ACUPUNCTURE FOR PD PATIENTS							
Aroxa et al. (10)	A. Acup + drug vs. B. drug alone	22 participants	Taichong (LR-3), Sanyinjiao (SP-6), Hegu (LI-4), Waiguan (TE-5), Shenmen (HT-7), Neiguan (PC-6), Quchi (LI-11), Fengchi (GB-20)	8 weeks	PDSS score	Unreported	A > B, $P = 0.66$

(Continued)

TABLE 1 | Continued

Study	Experimental design treatment vs. control	Number of participants	Acupoints involved	Course	Assessments	Adverse events	Results
Cho et al. (11)	Acup + BVA vs. Sham + vehicle vs. C. CT	63 participants	Fengchi (GB-20), Quchi (LI-11), Yanglingquan (GB-34), Zusanli (ST-36), Taichong (LR-3)	12 weeks	UPDRS II UPDRS III UPDRS II + III PIGD PDQL 6. BDI	No serious adverse events reported	1: A > C, $P = 0.001$** A > B, $P = 0.257$ 2: A > C, $P = 0.008$** A > B, $P = 0.793$ 3: A > C, $P = 0.001$** A > B, $P = 0.444$ 4: A > C, $P = 0.001$** A > B, $P = 0.244$
Kluger et al. (12)	A. Acup vs. B. Sham Acup	89 participants	Baihui (GV-20), Shenting (GV-24), Qihai (CV-6), Shousanli (LI-10), Shenmen (HT-7), Zusanli (ST-36), Sanyinjiao (SP-6)	6 weeks	MFIS: Total MFIS: Physical MFIS: Cognitive MFIS: Psychosocial UPDRS III PDQ-39 Total 7. PDSS	No serious adverse events reported	1: A > B, $P = 0.4388$ 2: A > B, $P = 0.1881$ 3: A > B, $P = 0.9222$ 4: A > B, $P = 0.5638$ 5: A > B, $P = 0.9343$
Lei et al. (13)	A. EA vs. B. sham Acup	15 participants	FMSA, BA, Baihui (GV-20), Dazhui (GV-14), Hegu (LI-4), Zusanli (ST-36), Yanglingquan (GB-34), Weizhong (BL-40), Sanyinjiao (SP-6), Taixi (KI-3), Taichong (LR-3)	3 weeks	Gait-Speed UPDRS I UPDRS II 4. UPDRS III	No serious adverse events reported	1: A > B, $P = 0.001$** 2: A > B, $P = 0.005$** 3: A > B, $P = 0.02$* 4: A > B, $P < 0.001$**
Wang 2015 (14)	A. EA + drug vs. B. drug alone	50 participants	Fengchi (GB-20), Hegu (LI-4), Dazhui (GV-14), Fengfu (GV-16)	2 months	UPDRS III 2. PSQI	Unreported	1: A > B, $P = 0.036$* 2: A > B, $P = 0.034$*
Liang and Chen (15)	A. Acup vs. B. drug	70 participants	Fengchi (GB-20), Wangu (GB-12), Tianzhu (BL-10), Yamen (GV-15)	6 months	PDQ-39 UPDRS II 3. PDSS	Unreported	1: A > B, $P < 0.001$** 2: A > B, $P = 0.041$* 3: A > B, $P < 0.001$**
Zhao 2017 (16)	A. Acup + drug vs. B. drug	108 participants	Taichong (LR-3), Fengchi (GB-20), Hegu (LI-4), Sishencong (EX-HN1)	3 months	UPDRS total scores 2. Webster Scale	No serious adverse events reported	1: A > B, $P = 0.005$** 2: A > B, $P = 0.001$**

*$p < 0.05$; **$p < 0.01$.

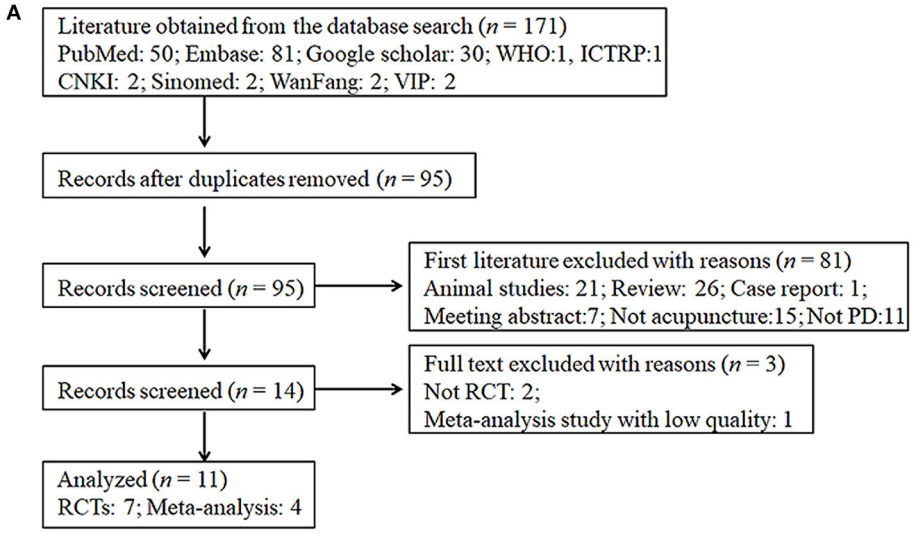
the study by Liu were published in Chinese, these were not based on a double-blind design and reported no follow-ups. Of the 11 RCTs, nine had a serious selection bias and three reported data loss. Moreover, the sensitivity analysis was not performed (8). In Noh's study, all RCTs had a performance bias and 39 of 42 RCTs had a selection bias. In addition, most studies included had a small sample size, and only seven out of 42 RCTs reported a follow-up (9). Of note, some overlaps occurred among the four meta-analyses. For example, four RCTs by Lee (6) were included in Lee (7). Of note, two studies of Lee (6) were also included in Noh's study, and four RCTs were included in the studies by Lee (7), and Noh and Liu. In addition, Liu's study comprised four studies overlapping with Lee's study (7) and six with Noh's study. Furthermore, Lee's study (2017) had 18 RCTs overlapped with the Noh's study.

The primary limitations of the included RCTs were small sample size and unreported adverse events. One progress compared with previous acupuncture studies was that placebo acupuncture was performed in four studies and objective behavioral assessment tool was used in one study **Figure 1B**.

Efficacy of Acupuncture for Global Evaluation

For global evaluation, we used the total UPDRS score and the Webster Scale. UPDRS is the most widely used scale for evaluation of the PD symptoms. The classic UPDRS has six parts: UPDRS I- mentation, behavior and mood; Part II—activities of daily life (ADLs); Part III—motor evaluation; Part IV—complications of therapy; Part V—staging of severity of PD; and Part VI—Schwab and England ADL scale. This is a clinician-report scale. Most items have scores ranged from 0 (normal) to 4 (severest). The Webster Scale is another commonly used self-report scale, which is briefer than UPDRS. It has 10 items (bradykinesia of hands, rigidity, posture, upper extremity swing, gait, no detectable tremor, tremor, seborrhea, speech, and self-care). The scores range from 0 (normal) to 3 (severest) (5). We found that all the measurements using the total UPDRS score showed good efficacy of acupuncture, regardless of whether the protocol acupuncture + classical treatment vs. classical treatment or acupuncture vs. classical treatment was used. A meta-analysis by Lee and Lim analyzed seven RCTs with 425 participants and found that the protocol acupuncture + classical treatment showed superior efficacy to classical treatment

A



B

	Studies	Quality Evaluation	Strengths	Weaknesses
Meta-analysis	Lee 2013	Major flaws (OQAQ Score: 4)	E	SB, RB, SS
	Lee 2017	Minor flows (OQAQ Score: 6)	QE	SB, PB, NR,NS
	Liu 2017	Minor flows (OQAQ Score: 5)	QE	SB, PB, NS
	Noh 2017	Minor flows (OQAQ Score: 6)	E	SB, SS
RCTs	Aroxa 2017	Jadad Score: 2		SS, NR
	Cho 2017	Jadad Score: 3	PA	SS, NR
	Kluger 2017	Jadad Score: 3	PA	SB
	Lei 2016	Jadad Score: 3	PA, Objective assessment tool	SS, NR
	Wang 2015	Jadad Score: 2		SB
	Liang 2014	Jadad Score: 3	PA	NF
	Zhao 2017	Jadad Score: 1	RCTs	SS, NF, PB

FIGURE 1 | Information of the included literatures. **(A)** Flow chart of the literature selection protocol. PD, Parkinson's disease; RCT, randomized, controlled trial; WHO, World Health Organization. **(B)** Quality evaluation of included studies. OQAQ, Overview Quality Assessment Questionnaire. Strengths: E, Good searching strategy including enough RCTS; QE, Qualify of involved RCTs was evaluated; PA, Placebo acupuncture. Weaknesses: SB, Selection bias; RB, reporting bias; PB, Publication bias; SS, Small samples; NR, Adverse events unreported; NS, No sensitivity analysis NF, No follow up.

(weighted mean difference [WMD] = −10.73; 95% CI, −8.38 to−13.07; $P < 0.001$; $I^2 = 0\%$) (7). These results are similar to those of Liu et al. from 11 RCTs with 831 participants [standardized mean difference [SMD] = −1.15; 95% CI, −1.63 to −0.67; $P < 0.001$] (8), of Noh from five RCTs with 407 participants (WMD = −10.48; 95% CI, −13.61 to −7.34; $P < 0.00001$, $I^2 = 47\%$) (9), and of Lee from two RCTs with 60 participants (WMD = −3.94; 95% CI, −6.05 to −1.84; $P = 0.01$; $I^2 = 0\%$) (6).

A study by Lee et al. also employed the Webster Scale for global evaluation. The study found no significant differences between patients treated by acupuncture and controls (three RCTs with 154 participants; WMD = 1.29; 95% CI, 0.79 to 2.12; P = 0.30, $I^2 = 84\%$). However, the authors commented that the quality of the studies was low and the results were not convincing (6).

Only one recent RCT of 108 PD patients in China found efficacy of acupuncture + pramipexole + L-dopa vs. L-dopa. However, acupuncture + pramipexole + L-dopa had significantly better efficacy than L-dopa alone. The poor experimental design of this study could not distinguish whether the efficacy was from acupuncture, pramipexole, or both (16).

Efficacy of Acupuncture for Motor Symptoms

UPDRS III is the most commonly used score for measuring motor performance. An RCT with 15 participants conducted by Lei et al. evaluated improvement in motor performance due to electroacupuncture in 15 participants (13). They found that electroacupuncture significantly decreased UPDRS scores and improved gait speed. To the best of our knowledge, this is the first experiment using an objective task for evaluating the effects of acupuncture, which may provide rigorous evidence for evaluation of the efficacy of acupuncture. These results were in accordance with those of other studies by Cho et al. (one RCT with 63 participants) (11) and Lee et al. (a meta-analysis with five RCTs and 366 participants) (7). Only one study found no efficacy. A meta-analysis by Liu et al. that analyzed two RCTs with 240 participants did not found any efficacy of acupuncture in improving UPDRS scores (SMD = −0.93; 95% CI, −2.28 to 0.41; $P = 0.17$; $I^2 = 95\%$). Their explanation was that the high heterogeneity influenced the reliability of the results (8).

The Webster Scale is another subjective tool for assessment of motor performance. Only one poorly designed RCT with 108 participants evaluated the efficacy of acupuncture by this scale. The authors suggested that reduction of the Webster Scale score was significantly higher in the acupuncture group (16). Several meta-analyses, including those of Lee et al. (6) [three RCTs with 154 participants; WMD = −1.29; 95% CI,−0.79 to−2.12; $P = 0.30$; $I^2 = 84\%$] (6), Noh et al. (WMD = −1.99; 95% CI, −3.43 to −0.56; $P = 0.006$; $I^2 = 81\%$) (9), and Lee and Lim (7), came to the same conclusion that acupuncture has good efficacy for improving the motor symptoms as assessed by the Webster Scale. Lee and Lim found that acupuncture had good efficacy in comparison with no treatment (two studies with 74 participants; WMD = −7.36; 95% CI, −5.58 to −9.14; $P < 0.001$; $I^2 = 0\%$) and classical treatment (two studies with 260 participants; WMD = −3.08; 95% CI,−2.81 to −3.35; $P < 0.001$; $I^2 = 0\%$). They also found that acupuncture + classical treatment was better than classical treatment (four studies with 208 participants; WMD =-3.78; 95% CI,−2.17 to−5.40; $P < 0.001$; $I^2 = 93\%$) (7).

Efficacy of Acupuncture for Non-motor Symptoms

Tension/Stress

The study of Noh et al. also investigated the efficacy of acupuncture for tension related to PD. They analyzed two RCTs with 121 participants and used the TAS to evaluate the efficacy of electroacupuncture to treat tension. They found that electroacupuncture + classical treatment had better efficacy than classical treatment alone (WMD = −1.85; 95% CI,−3.91 to−0.20; $P = 0.08$; $I^2 = 38\%$) (9). Although this is a stirring result, the limited number of RCTs ($n = 2$) and the small sample size ($n = 121$) limit the strength of the evidence.

Fatigue

Kluger et al. employed MFIS in an RCT to evaluate fatigue symptoms related to PD (12). They recorded MFIS for 6 weeks in 89 participants and found that acupuncture and sham acupuncture both had satisfactory efficacy ($p < 0.0001$). However, there was no evidence that acupuncture was superior to sham treatment ($p < 0.34$). In conclusion, acupuncture is good for relief from fatigue, regardless of it being PD-related or not. However, limitations of the experimental design, such as the lack of a wait-list control arm and potential selection bias (participants were highly educated), could have affected the reliability of this study. More rigorously designed RCTs are needed (19).

PD-Related Sleepiness

Three RCTs evaluated the efficacy of acupuncture for PD-related sleepiness. Aroxa et al. used the PDSS to compare the efficacy of acupuncture + drug with that of classical treatment alone in 22 participants. Although acupuncture produced a significant improvement, there was no evidence that acupuncture + drug was superior to drug alone (10). However, an RCT by Liang and Chen with 70 participants used PDSS and found that acupuncture was more efficacious than drug alone (15). Wang et al. used the PSQI to evaluate the efficacy of electroacupuncture for PD-related sleepiness in 50 participants. They found that electroacupuncture + drug significantly improved PSQI scores, whereas drug alone did not (14). The three RCTs revealed contradictory results. While one RCT ($n = 22$) denied any efficacy, the other two ($n = 70$ and 50) confirmed the efficacy. Hence, further well-designed, extensive studies are warranted for rigorous validation.

PD-Related Psychiatric Symptoms

Based on the UPDRS I Scale (for examination of mentation, behavior, and mood), the results of a recent RCT were different in two meta-analysis studies. The RCT, with 15 participants, found that the acupuncture group achieved a significant improvement ($p < 0.01$), whereas the sham group did not ($p = 0.21$) (13). However, the meta-analysis studies (7, 8) found no significant improvement with acupuncture. Liu examined 240 patients in two trials and did not report any significant change in UPDRS I (SMD = −0.37; 95% CI: −0.77 to 0.02; $P = 0.06$) (8), Lee analyzed two studies (one was overlapped with Liu's study) and reported the same result (weighted mean difference = 0.27; 95% CI: 0.17–0.72; $P = 0.23$; $I^2 = 0\%$; $n = 228$) (7). However, the results were debatable. As the sample size in the RCT ($n = 15$) was too small, the efficacy of acupuncture in treating PD-related psychiatric symptoms warrants further validation by large, multicenter, well-designed RCTs.

QOL

Three RCTs using the UPDRS Scale found that acupuncture had significant efficacy for improving QOL in PD patients (11, 13, 15). Using a PDQ-39 questionnaire, Kluger et al. reported the scores of acupuncture in weeks 1 and 6 as 27.4 ± 10.0 and 21.6 ± 12.2, respectively, confirming a significant amelioration in PD symptoms (12). Lei's study mentioned that the QOL can be improved by improving the hypokinetic rigid gait of PD (13). A Chinese study by Liang and Chen reported PDQ-39 scores of 20.41 ± 11.64 and 27.48 ± 8.69 in the acupuncture and control groups, respectively. This difference was

significant. Furthermore, all five items of the QOL in PDQ-39 were significantly improved in the acupuncture group (15).

DISCUSSION

As a continuation of our previous studies (1, 3), the present study indicated that several studies, including RCTs and meta-analysis studies, provided limited evidence for the efficacy of acupuncture to treat PD, including motor and non-motor symptoms. There is no authoritative evidence from rigorously designed, large-scale, multicenter RCTs. However, compared with the previous study (1) 5 years ago which we could not make a conclusion regarding the efficacy of acupuncture, the situation has been improved.

Improvements/Characters in Acupuncture Studies During the Past 5 Years

RCTs and Meta-Analysis Studies Based on RCTs Are Increasing

More rigorously designed RCTs and meta-analyses following PRISMA rules were used to evaluate the efficacy of acupuncture. This will provide more convincing evidence for the efficacy of acupuncture. Increasing numbers of acupuncture investigators have accepted the principles of evidence-based medicine and recognized that only well-designed RCTs can provide powerful and convincing evidence for the efficacy of acupuncture, which is the only way for acupuncture to step into mainstream medical academia. In the present study, seven recent RCTs and four meta-analysis studies evaluated the efficacy of acupuncture. Although some studies did not reach a satisfactory quality (**Figure 1B**), the data obtained from RCTs cannot be ignored.

Non-motor Symptoms Are Increasingly Emphasized

In addition to the motor symptoms of PD, more clinicians are paying attention to the non-motor symptoms (4, 5). We found several studies that evaluated the efficacy of acupuncture for non-motor symptoms. Noh et al. found that acupuncture was effective against PD-related stress (9); Kluger reported that acupuncture could relieve PD-related fatigue (19); studies by Liang et al. (15) and Wang et al. (14) showed that acupuncture could relieve PD-related sleepiness; and QOL in PD patients could be improved by acupuncture (11, 13, 15). The non-motor symptoms of PD are quite complex. More investigations can be expected to verify the efficacy of acupuncture for various non-motor symptoms in PD.

Objective Behavioral Assessment Tools Are Employed in Acupuncture Studies

Behavioral assessments play a crucial role in evaluation of PD symptoms. Selection of different assessment tools may lead to different results. Currently, most acupuncture studies have employed subjective scores such as UPDRS. However, this may cause observation bias. In the present study, we found that one study used an objective task (gait speed) to evaluate the efficacy of acupuncture (13). Because of the peculiarity of acupuncture, it is difficult to use a double-blind design in the studies (1). Objective indexes in the experimental design are required to avoid observation bias (3). On the other hand, the principles of objectification, multipurpose, and simplification (OMS) (4, 5) have been the tendency of behavioral assessments in PD. We believe objective assessment tools will be developed and employed in future studies.

Recommendations for Future Studies

Based on the recent acupuncture studies summarized here, we make several recommendations for future studies.

1. The quality assessments (**Figure 1B**) suggested that some studies were of low quality and some items (such as PD-related psychiatric symptoms and sleepiness) provided inconsistent results in different studies. Thus, it is time to organize large, multicenter, well-designed RCTs to evaluate the efficacy of acupuncture. Although many RCTs have provided evidence for the efficacy of acupuncture, flaws of methodology (small sample size, statistical flaws, etc.) have reduced the value of the evidence. Acupuncture needs authoritative evidence to step into the mainstream of medical academia. Once acupuncture has been authoritatively proved to be efficacious and accepted by clinicians, it should be considered as a method of "peripheral stimulation" to treat PD (20). Peripheral stimulation has no surgical risks, which will greatly benefit PD patients in the world.

2. Objective assessments using novel computerized technologies, such as wearable devices, virtual reality, and augmented reality technologies and robot assistant technology, which can realize real-time, programmable, and safe measurements of the motor fluctuations in PD, should be developed and used in future acupuncture studies to provide more powerful evidence for the efficacy of acupuncture, since it may bring great revolutionary in the behavioral assessments in PD (5).

3. Because of the complicated nature of PD symptoms, we suppose that different acupuncture parameters (acupoints, duration time, current intensity, and frequency, etc.) may correspond to different symptoms. Future investigations should evaluate the efficacy of acupuncture according to the target symptoms observed, instead of only performing global evaluations.

4. The safety of acupuncture should be evaluated. Recent studies have emphasized the evaluation of efficacy. In this study, none of the enrolled studies reported serious adverse events. However, to our knowledge, acupuncture is not totally harmless. Adverse events such as stabbing pain, hematoma, and bleeding have been reported (1). Perhaps, insufficient reporting of adverse events could decrease the reliability of studies; albeit some scientists believe that the safety of acupuncture is not a problem as evidenced by the lack of adverse events, the health risks cited are basically similar to venipuncture.

CONCLUDING REMARKS

In the past 5 years, progress has been made in providing limited evidence for the efficacy of acupuncture in treating PD. However, there is still no authoritative evidence, which has prevented acupuncture from stepping into the mainstream of medicine.

More innovations, including experimental design and assessment tools, are recommended for the future validation of acupuncture. Acupuncture research should also keep pace with mainstream PD research.

AUTHOR CONTRIBUTIONS

TY, FJ, ZS, and TA got the original idea. TY, FJ, HY, HN, ZS, and TA searched for the literatures. TY and FJ performed the data analysis. TA wrote the draft. TY, FJ, HY, HN, ZS, and TA revised and approved the final manuscript. TA and ZS supervised the study.

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Hypertension and High Blood Pressure Are Associated With Dementia Among Chinese Dwelling Elderly: The Shanghai Aging Study

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Background: To explore the association between blood pressure and cognition in older participants in the Shanghai Aging Study.

Methods: Data were drawn from 3,327 participants at the baseline of Shanghai Aging Study. History of hypertension was inquired and confirmed from participants' medical records. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by research nurses in the early morning. Participants were diagnosed with "cognitive normal," "mild cognitive impairment (MCI)," or "dementia" by neurologists using DSM-IV and Petersen criteria. Multivariate logistic regression was used to evaluate the association between history of hypertension, duration of hypertension, SBP, DBP, or classification of blood pressure and cognitive function. Generalized linear model was used to assess the relation between duration of hypertension, SBP, or DBP and Mini Mental State Examination (MMSE).

Results: A significantly higher proportion of hypertension [78 (76.5%)] was found in participants with dementia than in those with MCI [347 (59.3%)] and cognitive normal [1,350 (51.1%)] ($P < 0.0001$). Participants with dementia had significantly higher SBP [157.6 (26.1) mmHg] than those with MCI [149.0 (23.7) mmHg] and cognitive normal [143.7 (22.6) mmHg] ($P < 0.0001$). After adjusting for sex, age, education, living alone, body mass index, anxiety, depression, heart disease, diabetes, and stroke, the likelihood of having dementia was positively associated with history of hypertension ($OR = 2.10$; 95% CI: 1.22, 3.61), duration of hypertension ($OR = 1.02$ per increment year; 95% CI: 1.01, 1.04), higher SBP ($OR = 1.14$ per increment of 10 mmHg; 95% CI: 1.04, 1.25), higher DBP ($OR = 1.22$ per increment of 10 mmHg; 95% CI: 1.02, 1.45), moderate hypertension ($OR = 2.09$; 95% CI: 1.10, 3.99), or severe hypertension ($OR = 2.45$; 95% CI: 1.20, 4.99). The MMSE score was inversely correlated to duration of hypertension ($\beta = -0.0088$ per increment year; 95% CI: −0.0158, −0.0018, $P = 0.0132$), SBP ($\beta = -0.0655$ per increment of 10 mmHg; 95% CI: −0.1022, −0.0288, $P = 0.0005$), and DBP ($\beta = -0.1230$ per increment of 10 mmHg; 95% CI: −0.1915, −0.0545, $P = 0.0004$).

Conclusion: Our results suggest that hypertension and high blood pressure may be potential risk factors for dementia. Blood pressure management for the elderly may be important for maintaining cognitive vitality.

Keywords: cognitive function, dementia, mild cognitive impairment, hypertension, blood pressure, community-based study

INTRODUCTION

Cognitive impairment has a great impact on disability and mortality among the elderly, while it also reduces the quality of life for both patients and their caregivers. Approximately, there have been 24.3 million prevalent dementia cases, with 4.6 million new cases worldwide every year (1). China had 9.2 million cases of dementia in 2010 (2), and the case number will rise to the world's top by 2025 (1).

Hypertension is a highly prevalent condition, occurring in one-third of the world's adults and in two-thirds of adults over 65 years of age (3, 4). Both hypertension and dementia are age-related comorbidities which may induce considerable disabilities (1, 5–7). Some epidemiological studies showed that hypertension is an important risk factor of dementia (8, 9), which was evident from the positive relationship between blood pressure at midlife and the subsequently higher risk of cognitive impairment or dementia late in life (10–12); however, some other studies provided contradictory evidence that low blood pressure was a risk factor for dementia and cognitive decline (13–15). Until now, the relationship between hypertension and dementia or cognitive decline has been inconsistent, and mixed findings have been reported from cross-sectional and longitudinal studies (6, 16–18).

Epidemiological dementia research in China is still far behind developed countries. Only two epidemiological studies examined the relation between hypertension and cognitive impairment in the elderly in China, but it was inconclusive because of small sample size and simple neuropsychological assessments (19, 20). The Shanghai Aging Study intended to identify the prevalence and the incidence of dementia and mild cognitive impairment (MCI) among a cohort of old adults in an urban community in Shanghai, China (21). We, therefore, intend to explore the association between blood pressure and cognition in this cohort by analyzing the baseline data of the Shanghai Aging Study.

MATERIALS AND METHODS

Recruitment of Participants

From January 2010 to December 2012, the Shanghai Aging Study recruited 3,836 permanent residents aged ≥50 years in the Jingansi community, Shanghai. Participants were excluded if they were (1) residing in nursing homes or other institutions; (2) suffering from severe schizophrenia or mental retardation, based on the data abstracted from their medical record or diagnosed by neurologists; or (3) suffering from severe vision, hearing, or verbal impairment and could not participate in the neuropsychological evaluation. Detailed process of the participant recruitment has been published elsewhere (21). In this study, we used the dataset of 3,327 participants aged 60–85 years.

This study was approved by the Medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China. All the participants and/or their legal guardians provided their written informed consent to participate in the study.

Demographic Characteristics and Medical History

Participants were interviewed face-to-face by neurologists and research nurses to collect information on their demographic characteristics, including age, sex, and education. The participants' weight and height were measured and used to calculate the body mass index (BMI: the weight in kilograms divided by the square of the height in meters). We also obtained lifestyle factors, such as living alone, cigarette smoking, and alcohol drinking. Their history of chronic diseases, such as diabetes, stroke, and heart disease (including coronary artery disease and arrhythmia), was inquired and confirmed from their medical records.

Blood Pressure Measurement

From 7:30 to 8:00 a.m., after at least 5 min of rest in a seated position blood pressure was measured twice, with a standard sized cuff placed on the right arm at heart level of the seated subject, by trained research nurses using a validated and calibrated digital electronic tensiometer (M4; OMRON Corp., Kyoto, Japan) (22). We recorded the blood pressure as the mean of two measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Hypertension and Classification of Blood Pressure

Hypertension was defined as the reported physician-diagnosed hypertension, with or without treatment. Duration of hypertension was also inquired and confirmed from the participants' medical records (19, 23). According to the 2010 Chinese guidelines for the management of hypertension, blood pressure was classified into four categories: severe hypertension: SBP ≥180 mmHg or DBP ≥110 mmHg; moderate hypertension: SBP of 160–179 mmHg or DBP of 100–109 mmHg; mild hypertension: SBP of 140–159 mmHg or DBP of 90–99 mmHg; and normal blood pressure: SBP <140 mmHg and DBP <90 mmHg (23).

Neuropsychological Assessments

Cognitive function of each participant was assessed by a neuropsychological test battery, which covers domains of global cognition, executive function, spatial construction function,

memory, attention, and language. The battery contained (1) Mini Mental State Examination (MMSE); (2) Conflicting Instructions Task (Go/No Go Task); (3) Stick Test; (4) Modified Common Objects Sorting Test; (5) Auditory Verbal Learning Test; (6) Modified Fuld Object Memory Evaluation; (7) Trail-making test A&B; and (8) RMB (Chinese currency) test. Neuropsychological tests were administered by study psychometrists according to the different education levels of each participant. Test 1, 2, 3, 4, 5, and 7 in the battery were used in participants with education $\geq$6 years; test 1, 2, 3, 4, 6, and 8 were used in those with education <6 years. All tests were conducted in Chinese within 90 min. A pilot validation study was conducted for each cognitive measure using corrections for gender, age, and years of education in a community of healthy elderly people, and the normative data and the detailed description of these tests were reported elsewhere (24, 25).

Neurological Exams

Neurologists examined each participant for their reflexes and motor responses. They also administered the Center for Epidemiologic Studies Depression Scale (CES-D) (26) and the Zung Self-Rating Anxiety Scale (SAS) (27) to evaluate whether each participant met the criteria of having a major depression (CES-D $\geq$ 16) or anxiety (SAS > 44) episode within the past week. Neurologists also administered the Clinical Dementia Rating (CDR) (28, 29) and Activities of Daily Living (ADL) (30) scale to obtain information on cognitive complaints and activities of daily living.

Consensus Diagnoses

After each clinical assessment, two study neurologists, one neuropsychologist, and one neuroepidemiologist reviewed the functional, medical, neurological, psychiatric, and neuropsychological data and reached a consensus regarding the presence or absence of dementia using DSM-IV criteria (31). Only those who were not diagnosed with dementia were considered for the diagnosis of MCI, which was defined according to Petersen's criteria (32). Diagnostic procedures were reported elsewhere (21). Based on the consensus diagnoses, the subjects were classified into three groups with dementia, MCI, and cognitive normal.

APOE Genotype Assessment

DNA was extracted from blood or saliva collected from the study participants. *Apolipoprotein E (APOE)* genotyping was conducted by the TaqmanSNP method (33). The presence of at least one *ε4 allele* was defined as being *APOE-ε4* positive.

Statistical Analyses

Continuous variables were expressed as the mean ± standard deviation (SD) or median (25%, 75%), and categorical variables were expressed as frequencies (%). The analysis of variance (ANOVA) and Kruskal-Wallis test were used to compare the continuous variables; the Cochran-Mantel-Haenszel Chi-squared test was used to compare the categorical variables. Multivariate logistic regression model was used to detect the association between history of hypertension, duration of hypertension, SBP, DBP, or blood pressure categories and different clinical cognitive diagnoses, which were adjusted for confounders. Measurement of the association was presented as odds ratio (OR) and 95% confidence interval (CI). Generalized linear model was used to evaluate the relation between duration of hypertension, SBP, or DBP and MMSE, which were adjusted for confounders. Systolic and diastolic blood pressures were regarded as continuous variables and were expressed in units of 10 mmHg (original blood pressure value divided by 10) in the multivariate logistic regression model and in the generalized linear model.

All the *P*-values and 95% CIs were estimated in two-tailed tests. Differences were considered to be statistically significant at $P < 0.05$. The data analysis was conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographic, Lifestyles, and Medical History of the Participants

Among the 3,327 participants, 1,519 (45.7%) were males. The mean age of all the participants was 70.1 (SD 7.2) years, and the mean year of education was 11.7 (SD 4.2) years. Five hundred and eighty-five (17.6%) participants were diagnosed as MCI, while 102 (3.1%) were diagnosed as dementia. Age, education, MMSE score, alcohol drinking, *APOE-ε4 allele*, history of heart disease, diabetes, stroke, anxiety, and depression were found to be significantly different across groups with different diagnosis of cognition (**Table 1**).

Hypertension and Blood Pressure of Groups With Different Cognition

One thousand seven hundred and seventy-five (53.4%) participants were suffering from hypertension. Participants with dementia had a significantly higher proportion of having hypertension (76.5%) than those with MCI (59.3%) and cognitive normal (51.1%) ($P < 0.0001$). Participants with dementia had significantly longer duration of hypertension (median 10 years) than those with MCI (median 4 years) and cognitive normal (median 1 year) ($P < 0.0001$). Participants with dementia had significantly higher SBP [157.6 mmHg (SD 26.1)] than those with MCI [149.0 mmHg (SD 23.7)] and cognitive normal [143.7 mmHg (SD 22.6)] ($P < 0.0001$). The distribution of blood pressure category was significantly different across the three groups ($P < 0.001$). More moderate and severe hypertension (47.0%) was seen in participants with dementia than those with MCI (33.4%) and cognitive normal (23.5%) ($P < 0.001$; **Table 2**).

Association Between Blood Pressure and MMSE

After adjusting for age, sex, education, BMI, living alone, anxiety, depression, heart disease, diabetes, and stroke in the generalized linear model, the decline in MMSE score was significantly correlated with duration of hypertension ($\beta = -0.0088$ per increment year; 95% CI: −0.0158, −0.0018; $P = 0.0132$), SBP ($\beta = -0.0655$ per increment of 10 mmHg: 95% CI: −0.1022,

TABLE 1 | Demographic, lifestyles, and medical history of the participants with cognitive normal, MCI, and dementia.

	All (n = 3,327)	Cognitive normal (n = 2,640)	MCI (n = 585)	Dementia (n = 102)	*P*-Value*
Age, years, mean ± SD	70.1 ± 7.2	69.2 ± 6.9	73.1 ± 7.3	77.4 ± 6.0	<0.0001
Education, years, mean ± SD	11.7 ± 4.2	12.2 ± 3.8	9.9 ± 4.8	8.0 ± 6.0	<0.0001
MMSE, scores, mean ± SD	27.9 ± 2.8	28.6 ± 1.7	26.5 ± 2.9	17.5 ± 4.8	<0.0001
BMI, kg/m^2, mean ± SD	24.4 ± 3.6	24.3 ± 3.4	24.6 ± 4.2	23.9 ± 3.9	0.1635
Sex, males, *n* (%)	1519 (45.7)	1216 (46.1)	261 (44.6)	42 (41.2)	0.2815
Cigarette smoking, *n* (%)	359 (10.8)	280 (10.6)	71 (12.2)	8 (7.8)	0.8389
Alcohol drinking, *n* (%)	261 (7.9)	219 (8.4)	40 (6.9)	2 (2.0)	0.0193
Anxiety, *n* (%)	74 (2.2)	51 (1.9)	18 (3.1)	5 (5.0)	0.0118
Depression, *n* (%)	564 (17.0)	408 (15.5)	126 (21.7)	30 (29.4)	<0.0001
Heart disease, *n* (%)	407 (12.3)	289 (11.0)	97 (16.6)	21 (20.6)	<0.0001
Diabetes, *n* (%)	459 (13.8)	338 (12.8)	104 (17.8)	17 (16.7)	0.0028
Stroke, *n* (%)	413 (12.4)	272 (10.3)	102 (17.5)	39 (38.2)	<0.0001
Living alone, *n* (%)	287 (8.6)	219 (8.3)	63 (10.8)	5 (4.9)	0.5353
APOE-ε4 *allele* positive, *n* (%)	564 (18.1)	437 (17.5)	106 (19.9)	21 (25.0)	0.0403

SD, standard deviation; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; BMI, body mass index; APOE, Apolipoprotein.
**P-Value is for the comparison among three groups of participants with cognitive normal, MCI, and dementia.*

TABLE 2 | Hypertension and blood pressure of the participants with cognitive normal, MCI, and dementia.

	All (n = 3,327)	Cognitive normal (n = 2,640)	MCI (n = 585)	Dementia (n = 102)	*P*-Value*
History of hypertension, *n* (%)	1775 (53.4)	1350 (51.1)	347 (59.3)	78 (76.5)	<0.0001
Duration of hypertension, year, median (25%, 75%)	2 (0, 13)	1 (0, 11)	4 (0, 17)	10 (1, 21.5)	<0.0001
SBP, mmHg, mean ± SD	145.0 ± 23.1	143.7 ± 22.6	149.0 ± 23.7	157.6 ± 26.1	<0.0001
DBP, mmHg, mean ± SD	77.3 ± 11.7	77.5 ± 11.6	76.3 ± 12.1	78.4 ± 14.0	0.0735
Classification of BP, *n* (%)					<0.0001
Normal	1390 (41.8)	1151 (43.6)	212 (36.2)	27 (26.5)	
Mild	1072 (32.2)	867 (32.9)	178 (30.4)	27 (26.5)	
Moderate	608 (18.3)	447 (16.9)	135 (23.1)	26 (25.5)	
Severe	257 (7.7)	175 (6.6)	60 (10.3)	22 (21.5)	

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MCI, mild cognitive impairment; SD, standard deviation.
**P-Value is for the comparison among three groups of participants with cognitive normal, MCI, and dementia.*

−0.0288; $P = 0.0005$), and DBP (β = −0.1230 per increment of 10 mmHg; 95% CI: −0.1915, −0.0545; $P = 0.0004$; **Table 3**).

Association Between Hypertension, Blood Pressure, and Cognition

After adjusting for age, sex, education, BMI, living alone, anxiety, depression, heart disease, diabetes, and stroke, the likelihood of having dementia was positively associated with history of hypertension (OR = 2.10; 95% CI: 1.22, 3.61), duration of hypertension ($OR = 1.02$ per increment year; 95% CI: 1.01,1.04), higher SBP ($OR = 1.14$ per increment of 10 mmHg; 95% CI: 1.04, 1.25), higher DBP ($OR = 1.22$ per increment of 10 mmHg; 95% CI: 1.02, 1.45), moderate hypertension ($OR = 2.09$; 95% CI: 1.10, 3.99), or severe hypertension ($OR = 2.45$; 95% CI: 1.20, 4.99), but it was not associated with mild hypertension ($OR = 1.31$; 95% CI: 0.70, 2.45). There was no significant association between MCI and hypertension or blood pressure (**Table 4**).

DISCUSSION

Our study indicated that history of hypertension, duration of hypertension, and high blood pressure were positively associated with dementia among older Chinese people living in an urban community. The MMSE score, which represented the global cognition, was inversely correlated to duration of hypertension, SBP, and DBP. One advantage of the current study was the reliable diagnosis, which was conducted by neurologists with consensus diagnosis at one of the top institutions of neurology in China. Other advantages included the population-based study design with a large sample and the adjustment for confounders, such as sociodemographic characteristics, health behaviors, and medical conditions.

Result from our study was consistent with most of the previous studies which suggested that blood pressure and hypertension are key risk factors for cognitive impairment. In a cross-sectional epidemiological study with 19,836 participants

TABLE 3 | Adjusted association between blood pressure and MMSE.

Blood pressure	β	95% CI	Wald Chi-square	*P*-Value
Duration of hypertension (per increment year)	−0.0088	(−0.0158, −0.0018)	6.14	0.0132
SBP (per increment of 10 mmHg)	−0.0655	(−0.1022, −0.0288)	12.22	0.0005
DBP (per increment of 10 mmHg)	−0.1230	(−0.1915, −0.0545)	12.38	0.0004

MMSE, Mini-Mental State examination; SBP, systolic blood pressure; DBP, diastolic blood pressure; β, beta coefficient; CI, confidence interval.
Generalized linear model adjusted for sex, age, education, body mass index, living alone, anxiety, depression, heart disease, diabetes, and stroke.

TABLE 4 | Adjusted odds ratios for hypertension and blood pressure among participants with dementia vs. cognitive normal, and with MCI vs. cognitive normal [OR (95% CI)].

	Model 1	Model 2
DEMENTIA VS. COGNITIVE NORMAL		
History of hypertension	3.11 (1.95, 4.94)	2.10 (1.22, 3.61)
Duration of hypertension (per increment year)	1.04 (1.02, 1.05)	1.02 (1.01, 1.04)
SBP(per increment of 10 mmHg)	1.27 (1.18, 1.38)	1.14 (1.04, 1.25)
DBP(per increment of 10 mmHg)	1.06 (0.90, 1.25)	1.22 (1.02, 1.45)
Classification of BP		
Normal	1 (reference)	1 (reference)
Mild	1.33 (0.77, 2.28)	1.31 (0.70, 2.45)
Moderate	2.48 (1.43, 4.30)	2.09 (1.10, 3.99)
Severe	5.36 (2.99, 9.62)	2.45 (1.20, 4.99)
MCI VS. COGNITIVE NORMAL		
History of hypertension	1.39 (1.16, 1.67)	1.09 (0.89, 1.34)
Duration of hypertension (per increment year)	1.02 (1.01, 1.02)	1.01 (0.99, 1.01)
SBP(per increment of 10 mmHg)	1.10 (1.06, 1.15)	1.03 (0.99, 1.08)
DBP(per increment of 10 mmHg)	0.91 (0.84, 0.98)	0.98 (0.90, 1.06)
Classification of BP		
Normal	1 (reference)	1 (reference)
Mild	1.12 (0.90, 1.39)	0.99 (0.79, 1.26)
Moderate	1.64 (1.29, 2.09)	1.28 (0.98, 1.67)
Severe	1.86 (1.34, 2.58)	1.11 (0.77, 1.60)

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MCI, mild cognitive impairment; OR, odds ratio; CI, confidence interval.
Univariate logistic regression model 1 didn't adjust any confounder.
Multivariate logistic regression model 2 adjusted for sex, age, education, body mass index, living alone, anxiety, depression, heart disease, diabetes, and stroke.

in India/America, an increment of 10 mmHg in DBP was associated with a 7% (95% CI: 1–14%; $P = 0.0275$) higher odds of cognitive impairment based on 6-Item Screener. No independent association was identified between impaired cognitive status and SBP ($OR = 1.02$; 95% CI: 0.99–1.06) or pulse pressure ($OR = 0.99$; 95% CI: 0.95–1.04) (34). However, some studies showed inverse association. A cross-national epidemiological study was conducted in India and America with 4,810 subjects of 55 years and older; in Ballabgarh, India, for every 10 mmHg increase in SBP there was a 10% reduction in cognitive impairment based on a set of cognitive tests ($OR = 0.90$; 95% CI: 0.83–0.97), and there was a 13% reduction in cognitive impairment ($OR = 0.87$; 95% CI: 0.76–0.99) with every 10 mmHg increase in DBP; in the Monongahela Valley, America, a similar association between DBP and cognitive impairment was observed, but it did not remain significant after adjustment for confounders ($OR = 0.83$; 95% CI: 0.65–1.06) (35).

Few studies were reported in the Chinese population. In a cross-sectional study with 1,799 participants (aged 40–85) in a rural area of Xi'an, stratified multivariate analysis revealed a positive relation between SBP (when regarded as continuous data) and cognitive impairment (MMSE) in patients aged 40–49 years ($OR = 1.35$ per 10 mmHg; 95% CI: 1.04–1.75; $P = 0.025$) and 50–59 years ($OR = 1.19$ per 10 mmHg; 95% CI: 1.03–1.37; $P = 0.019$). The analysis turned out to be insignificant for patients aged 60–69 years ($OR = 0.88$ per 10 mmHg; 95% CI: 0.73–1.06; $P = 0.171$) and ≥70 years ($OR = 0.93$ per 10 mmHg; 95% CI: 0.77–1.11; $P = 0.416$). Results similar to those obtained for SBP were obtained for DBP, mean arterial blood pressure, and high blood pressure as well (20). In a prospective observational study with four rural counties in China, 2,000 rural Chinese people aged 65 years and older (median age 70, range 65–92) participated in a baseline evaluation. Two and a half years after baseline the evaluation, a follow-up evaluation of 1,737 subjects was conducted. Cognitive decline based on a set of cognitive tests was derived as the difference between baseline and follow-up scores. Untreated hypertension was associated with greater cognitive decline in this Chinese cohort (19).

The possible mechanism explaining the effect of hypertension on cognitive impairment is not yet clear. A number of autopsy studies (36, 37) have shown that the probability of dementia manifestation for a given level of Alzheimer's disease (AD) pathology is increased by the presence of cerebrovascular pathology, which is strongly linked to hypertension (38–45). Animal studies suggest that cerebral ischemia may be involved in the initiation of AD through upregulation of amyloid precursor protein gene expression (46–48), promotion of amyloid precursor protein cleavage into beta-amyloid peptides (49), or reduction in beta-amyloid peptide clearance (50). Uncontrolled hypertension appears to predict the level of neurofibrillary tangles and neuritic plaques (pathologic indicators of AD) in the brain (51–53), which could be a direct effect of hypertension on AD pathology. Blood pressure may be related to AD initiation or progression through mechanisms that involve beta-amyloid peptides (54), which aggregate to form neuritic plaques.

Some limitations existed in our study. Firstly, we failed to draw conclusions about causal relationship between hypertension and cognitive impairment, especially in the case of the disease that is both age-related and associated with a biased participation rate, from this cross-sectional study design. Secondly, we have adjusted as many potential confounders as possible in the logistic regression model, but we still could not exclude the possible influence of uncollected confounders, such as life experience (e.g., interests, hobbies, leisure activities) and ones' innate intelligence, which could also reflect cognitive reserve. Thirdly, spot blood

pressure measurement might not represent the whole situation of blood pressure level. But for each participant, we measured the blood pressure at the same time in the early morning; therefore, it is better than those measured at other time points. Finally, our study site lies in the urban center of Shanghai, and the participants had higher education than most of the others in China. Therefore, the results could not be generalized to the whole Chinese population.

Our results suggest that hypertension and high blood pressure may be potential risk factors for dementia. Blood pressure management for the elderly may be important for maintaining cognitive vitality. The association between blood pressure and risk of cognitive impairment needs to be further studied and validated by prospective studies with longer follow-up time in older population.

AUTHOR CONTRIBUTIONS

This work was conceptualized by DD, YS, and ZH and all of them approved the protocol. Data collection was done by DD, QZ, QG, XL, and LZ. Statistical analysis was undertaken by XL, WD, and JL. XL, YS, LT, and DD prepared the manuscript. YS and DD are the guarantors of this paper.

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Acute Effects of Particulate Air Pollution on Ischemic Stroke and Hemorrhagic Stroke Mortality

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Background and Purpose: A large body of literature reported the association of particulate matter (PM) with stroke in high-income countries. Few studies have examined the association between PM and stroke in middle- and low-income countries and considered the types of stroke. In this study, we examined the short-term effects of particulate matter $<2.5\,\mu m$ in diameter ($PM_{2.5}$) and particulate matter $<10\,\mu m$ in diameter (PM_{10}) on ischemic stroke mortality and hemorrhagic stroke mortality in Beijing, China.

Methods: We used an ecological study design and quasi-Poisson generalized additive models to evaluate the association of $PM_{2.5}$ and PM_{10} and cerebrovascular diseases mortality, as well as ischemic- and hemorrhagic stroke mortality. In the model, we controlled long-term and season trends, temperature, and relative humidity, the day of the week and air pollution. For cerebrovascular diseases mortality, we examined the effects stratified by sex and age with different lag days.

Results: A total of 48,122 deaths for cerebrovascular disease (32,799 deaths for ischemic stroke and 13,051 deaths for hemorrhagic stroke) were included in the study. $PM_{2.5}$ was associated with stroke mortality. The 10 $\mu g/m^3$ increase of $PM_{2.5}$ was associated with the increase of mortality, 0.27% (95% CI, 0.12–0.43%) for cerebrovascular diseases, 0.23% (95% CI, 0.04–0.42%) for ischemic stroke and 0.37% (95% CI, 0.07–0.67%) for hemorrhagic stroke -. The associations between PM_{10} and mortality were also detected for cerebrovascular diseases and ischemic stroke, but not in hemorrhagic stroke. The stratified analysis suggested age and gender did not modify the effects of PM on mortality significantly.

Conclusions: Our study suggested that short-term exposure to ambient PM was associated with the risk of stroke mortality.

Keywords: particulate matter, risk, stroke, ischemic, hemorrhagic, mortality

INTRODUCTION

Globally, stroke is the second leading cause of premature mortality in 2015 (1). In the past two decades, age-standardized rates of stroke mortality have decreased; however, the absolute numbers have been increasing. It is estimated that there are 113 million disability-adjusted life-years (DALYs) due to stroke, 6.5 million deaths from stroke. Compared to the developed countries, there is an evident increase in DALYs and deaths in the developing countries (2). Due to higher stroke incidence and mortality rates, the burden of stroke is substantial in developing countries. According to a nationwide population-based survey, there are approximately 2.4 million new strokes, and 1.1 million people died from stroke annually in China (3). It is of significant public health interest to identify modifiable risk factors for stroke.

Apart from modifiable risk factors, air pollution has emerged as the third significant contributor to global stroke burden, accounting for 29.2% of the burden of stroke (4). One of the main priorities to reduce the stroke burden is to reduce exposure to air pollution, especially in low-income and middle-income countries (4). During the last two decades, numerous studies have performed to investigate associations between air pollution and daily admission or mortality (5–8). Besides gaseous pollutants, solid particles are an essential component of ambient air pollution. Recently, particulate matter (PM), especially ambient fine particulate matter air pollution (particulate matter with an aerodynamic diameter less than 2.5 μm, $PM_{2.5}$), has received particular attention for its high toxicity. Identification of specific air pollutant which is a potential risk factor for stroke, is important for policy making, risk assessment and intervention takes. However, the epidemiologic findings on PM and the risk of stroke were inconsistent, from no significant associations to positive associations (9–12). Moreover, few studies conducted in developing countries and distinguished the effects of PM on types of stroke (9, 11, 13). It is still not clear whether the effect of PM on ischemic stroke is the same with hemorrhagic stroke (12, 14, 15).

In the present study, we conducted a time-series study to evaluate the association between PM and the mortality by stroke types and to determine potential effect modifiers of the relationship between of PM and stroke mortality.

MATERIALS AND METHODS

Study Area and Population

Beijing is the capital of China and located at 39°26–41°03 north latitude, 115°25–117°30 east longitude, covers 16411 km^2. The population of Beijing registered residence was about 13 million during the study period (Jan 2014 to Dec 2016). The study area contains sixteen urban and suburban districts. Beijing has a temperate monsoon climate and features a four season. The primary air pollution source is automobile exhaust emissions, industrial emissions and wind-blown dust (16).

The study was approved by the ethics committee of Beijing Tiantan hospital. Because all of the data were de-identifier and the data were analyzed at the aggregate level, informed consent from the participant has been waived in this study.

Stroke Mortality Data

The daily mortality counts of stroke from 1 January 2014 to 31 December 2016 were obtained from Beijing Center for Diseases Prevention and Control. At the time of death, death certificates are issued by community doctors for the deaths at home, or by hospital doctors for the deaths at hospitals (17). The death reasons were coded according to the International Classification of Diseases 10th version (ICD-10). I60-I69 were used for cerebrovascular disease, I63 and I63.9 for ischemic stroke, and I60-I62 and I69.1 for hemorrhagic stroke-. The Chinese Center for Disease Control and Prevention implemented strict quality control procedures to ensure of the accuracy and completeness of the death data (18). Moreover, in order to explore the susceptible populations, we divided mortality data - by age group (<45 years, 45–64 years and 65 years or older) and gender.

Environmental Data

We obtained daily air pollution data from January 2014 to December 2016, including $PM_{2.5}$, PM <10 μm in aerodynamic diameter (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3) from China Air Quality Online Analysis Platform (https://www.aqistudy.cn/). The data displayed on the platform was from the Beijing Environmental Protection Monitoring Center. There were 35 automated monitoring stations located in Beijing. In this study, except O_3 that 8 h average concentration was used, for other air pollutants, we used 24 h average concentrations, which were calculated form all valid monitoring stations. At each monitoring station, the local government has mandated detailed quality assurance and quality control programs (17). In order to control the effect of weather conditions on stroke mortality, meteorological data containing daily mean temperature and relative humidity were obtained from the China Meteorological Data Sharing Service System (http://data.cma.cn/).

Statistical Analysis

We applied the generalized additive models with quasi-Poisson regression to estimate the associations between ambient $PM_{2.5}$ and PM_{10} and the risk of stroke mortality, as previously described (19). In order to control the long-term and seasonal trends of daily stroke mortality, we used natural cubic spline with 8 degrees of freedom (df) per year in the model. The day of the week was introduced as an indicator variable in the model. Additionally, we - applied natural smooth spline with 3 df for temperature and humidity to control the confounding effects. $PM_{2.5}$ or PM_{10} was incorporated in the established basic model to examine its effects on stroke mortality, as well as ischemic stroke and hemorrhagic stroke separately.

The main model structure is:

$$In\left[E\left(Y_t\right)\right] = \beta_0 + \beta_1 PM + \beta_2 DOW + s_1\left(temp, df = 3\right) + s_2\left(hum, df = 3\right) + s_3\left(time, df = 8/year\right),$$

where $E(Y_t)$ is the expected stroke mortality count on day t, PM is particular matter, DOW is the day of the week, temp is the average temperature on the current day, hum is the

relative humidity of the current day, time is calendar time, β is the regression coefficient and s indicates a smoothing spline. The results were summarized as percent change in daily mortality per 10 $\mu g/m^3$ increase of PM. Furthermore, in order to examine whether gender and age modify the effect of PM on cerebrovascular deaths, - we evaluated the association stratified by gender and age. We tested the significance of subgroup differences through calculating$(\hat{Q}_1 - \hat{Q}_2) \pm 1.96\sqrt{S\hat{E}_1 + S\hat{E}_2}$, where $\hat{Q}_1$and $\hat{Q}_2$ were estimates of the categories and $S\hat{E}_1$ and $S\hat{E}_2$ were their corresponding standard errors (20, 21).

In order to examine the stability of our results, we also performed sensitivity analyses. First, we fitted 2-pollutant models with adjustment for other air pollutants' (NO_2, SO_2, O_3) effects respectively, to control the confounding effects of other pollutants. Second, different lag periods, containing single-day lags (from lag0 to lag2) and multiday lags (lag01 to -lag02) were used to investigate the lag patterns of air pollution. In single-day lags, a lag of 0 day (lag0) meant the concentration of current day and a lag of 1 day (lag1) referred to the concentration of the previous day. In multiday lags, lag01 corresponded to the average concentration of the current day and previous day, and lag02 referred to 3-day moving mean concentration of current day and previous 3 days (19). Additionally, we applied different df values for time trends to estimate the effects of air pollution.

All the analyses were conducted using the GAM procedure in SAS 9.4 (SAS Institute Inc, Cary, NC) and all reported P values are based on two-sided tests at the 0.05 level.

RESULTS

There were a total of 48,122 deaths of cerebrovascular disease from 1 January 2014 to 31 December 2016, including 32,799 ischemic strokes and −13,051 hemorrhagic strokes. The daily numbers of stroke deaths ranged from 11 to 76. The mean ages (SD) for cerebrovascular diseases, ischemic stroke and hemorrhagic stroke were 76.7 (11.6), 78.7 (10.0), and 71.7 (13.7), respectively. The percentage of male was 55.7% for cerebrovascular patients, 55.4% for ischemic strokes and 57.5% for hemorrhagic strokes. The mean daily average concentrations for $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 were 79.1, 103.8, 50.6, 14.4, and 110.4 $\mu g/m^3$, respectively. During the study period, the mean temperature was 13.8°C and relative humidity was 53.1% (**Table 1**).

In the single-pollutant model, we observed a significant association between daily cerebrovascular diseases mortality and $PM_{2.5}$ and PM_{10}. When we examined the effects by the type of stroke, the associations between $PM_{2.5}$ and ischemic stroke and hemorrhagic stroke death were positive. However, exposure to PM_{10} was related to increase the risk of ischemic stroke but not hemorrhagic. Each 10 $\mu g/m^3$ increase of $PM_{2.5}$ was associated with the increases of mortality, 0.27% (95% CI, 0.12–0.43%) for cerebrovascular diseases, 0.23% (95% CI, 0.04–0.42%) for ischemic stroke and 0.37% (95% CI, 0.07–0.67%) for hemorrhagic stroke. However, each 10 $\mu g/m^3$ increase of PM_{10} was associated with the increases of mortality for cerebrovascular diseases and ischemic stroke [0.19% (95% CI, 0.07–0.32%), 0.16% (95% CI, 0.01–0.32%), respectively], but not in hemorrhagic stroke [0.20% (95% CI, −0.04 to 0.44%)].

After we adjusted NO_2 or O_3 in the two-pollutant models, the associations between $PM_{2.5}$ and cerebrovascular diseases remained statistically significant, and the consistent result was observed for ischemic stroke (**Table 2**). The association between $PM_{2.5}$ and hemorrhagic stroke was attenuated after adding NO_2 in the model. When NO_2 and SO_2 were adjusted, the associations

TABLE 1 | Distribution of Daily Stroke Mortality, Air Conditions and Air Pollution Variables.

	Mean	Minimum	25%	50%	75%	Maximum
Cerebrovascular disease, N per day	43.9	11.0	38.0	43.0	50.0	76.0
Ischemic stroke, N per day	29.9	10.0	25.0	30.0	34.0	55.0
Hemorrhagic stroke, N per day	11.9	1.0	9.0	12.0	14.0	24.0
$PM_{2.5}$, $\mu g/m^3$	79.1	5.2	29.8	60.0	106.4	477.5
PM_{10}, $\mu g/m^3$	103.8	1.7	47.0	86.8	135.9	480.8
NO_2, $\mu g/m^3$	50.6	8.1	33.5	44.5	61.4	153.5
SO_2, $\mu g/m^3$	14.4	1.8	3.6	7.9	17.4	133.1
O_3, $\mu g/m^3$	110.4	3.0	57.0	92.0	158.5	343.0
Temperature, °C	13.8	−14.3	2.8	15.6	24.0	32.6
Humidity, %	53.1	8.0	37.0	53.0	68.5	99.0

$PM_{2.5}$ indicates particulate matter <2.5 μm in aerodynamic diameter, PM_{10} indicates particulate matter <10 μm in aerodynamic diameter, NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone.

TABLE 2 | Percentage increase (mean and 95%confidence intervals) of stroke mortality associated with 10 $\mu g/m^3$ increase of $PM_{2.5}$ and PM_{10}.

	$PM_{2.5}$			PM_{10}		
	Mean	95% CI	*P*	Mean	95% CI	*P*
Cerebrovascular Disease	0.27	0.12–0.43	0.0007	0.19	0.07–0.32	0.003
Adjusted SO_2	0.18	0–0.37	0.0550	0.11	−0.04–0.26	0.1572
Adjusted NO_2	0.28	0.05–0.51	0.0194	0.16	−0.03–0.35	0.1035
Adjusted O_3	0.25	0.09–0.42	0.0020	0.18	0.06–0.31	0.0047
Ischemic Stroke	0.23	0.04–0.42	0.0191	0.16	0.01–0.32	0.0363
Adjusted SO_2	0.10	−0.13–0.33	0.4056	0.05	−0.13–0.23	0.5666
Adjusted NO_2	0.33	0.05–0.61	0.0228	0.22	−0.02–0.45	0.067
Adjusted O_3	0.20	0.01–0.40	0.0396	0.16	0–0.31	0.0482
Hemorrhagic Stroke	0.37	0.07–0.67	0.0167	0.20	−0.04–0.44	0.1082
Adjusted SO_2	0.46	0.10–0.82	0.0131	0.22	−0.06–0.51	0.1303
Adjusted NO_2	0.29	−0.16–0.73	0.2083	0.03	−0.34–0.40	0.8732
Adjusted O_3	0.35	0.04–0.66	0.0272	0.19	−0.05–0.44	0.1279

$PM_{2.5}$ indicates particulate matter <2.5 μm in aerodynamic diameter; PM_{10} indicates particulate matter <10 μm in aerodynamic diameter, NO_2, nitrogen dioxide; SO_2, sulfur dioxide, O_3, ozone.

of PM_{10} with cerebrovascular disease and ischemic stroke were not statistically significant. Using different lag periods, we found at lag 0, 1 and 0 to 1 days, the concentrations of $PM_{2.5}$ were significantly associated with cerebrovascular diseases and ischemic stroke (**Figure 1**). A significant association of PM_{10} with cerebrovascular diseases and ischemic stroke was detected at lag 0 and 0 to 1 days (**Figure 2**). Results were essentially unchanged when the df for time trend was changed from 6 to 10 (data not shown).

The stratify analyzes by gender and age groups showed that female and the elder people were more likely to be vulnerable to $PM_{2.5}$ and PM_{10}. However, this did not hold at different lag days (**Table 3**).

DISCUSSION

To our knowledge, this is contemporary- study to analyze the association between $PM_{2.5}$ and PM_{10} and the mortality by stroke types in the area with a high concentration of PM. Our present study suggested that short-term exposures to ambient $PM_{2.5}$ and PM_{10} were associated with increased mortality of cerebrovascular diseases. When stratified by stroke types, we did not find evidence of an association between PM_{10} exposure and hemorrhagic stroke mortality.

We observed 0.27% (95% CI, 0.12–0.43%) and 0.19% (95% CI, 0.07–0.32%) increase in cerebrovascular diseases mortality with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10}, respectively. Due to large population exposure to ambient PM, it was of great benefits, though the effect was small. If the annual mass concentration of PM2.5 achieved the World Health Organization (WHO) Air Quality Guidelines (10 $\mu g/m^3$) (22), about 400 stroke deaths will be avoided yearly in Beijing. The magnitude of the associations was lower than the results from a meta-analysis (1.1%, 95%CI 1.1–1.2% for each 10 $\mu g/m^3$ increase of $PM_{2.5}$; 0.3%, 95%CI 0.2 to 0.4% for each 10 $\mu g/m^3$ increase of PM_{10}) (23). The main reasons for this disparity may be that admission or mortality was to be recorded as an endpoint and most of the studies contained in this meta-analysis were

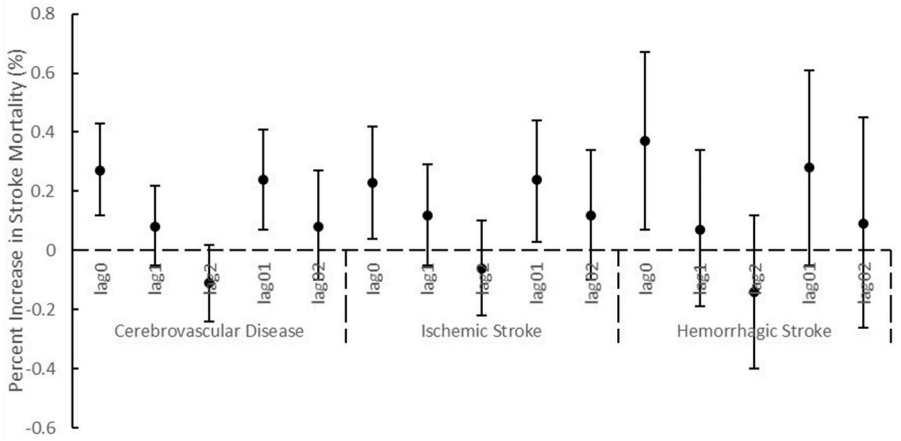

FIGURE 1 | Percentage increase (mean and 95% confidence intervals) of stroke mortality associated with 10 $\mu g/m^3$ increase of $PM_{2.5}$ using different lag structures.

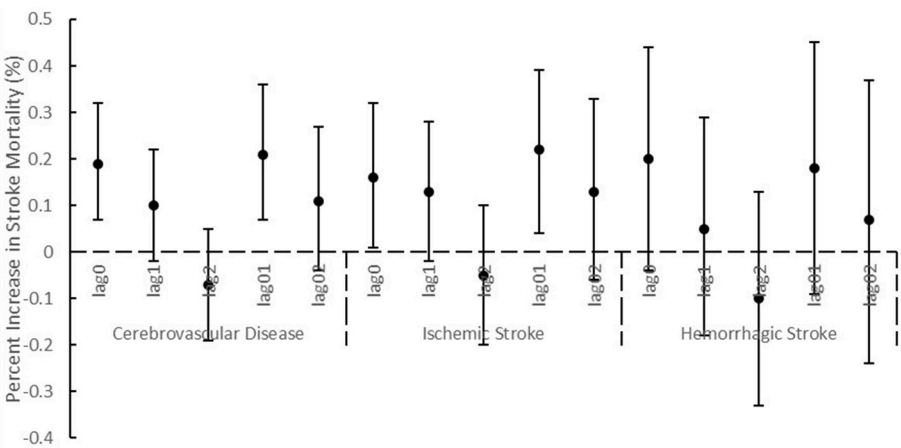

FIGURE 2 | Percentage increase (mean and 95% confidence intervals) of stroke mortality associated with 10 $\mu g/m^3$ increase of PM_{10} using different lag structures.

TABLE 3 | Percentage increase (mean and 95% confidence intervals) of stroke mortality associated with 10 $\mu g/m^3$ increase of $PM_{2.5}$ and PM_{10} using different lag structures by gender and age.

		Gender		Age		
		Male	Female	~ <45	45~ <65	>=65
$PM_{2.5}$	lag0	0.24 (0.03–0.45)	0.32 (0.08–0.56)	0.25 (−1.03–1.54)	0.24 (−0.16–0.64)	0.28 (0.1–0.45)
	lag1	0.09 (−0.10–0.27)	0.08 (−0.13–0.29)	0.62 (−0.48–1.73)	−0.1 (−0.45–0.25)	0.11 (−0.04–0.26)
	lag2	−0.11 (−0.28–0.07)	−0.12 (−0.32–0.08)	0.44 (−0.62–1.51)	−0.38 (−0.72–0.03)	−0.06 (−0.2–0.09)
	lag01	0.22 (−0.01–0.45)	0.25 (0–0.51)	0.7 (−0.66–2.08)	0.05 (−0.38–0.48)	0.26 (0.07–0.45)
	lag02	0.08 (−0.17–0.32)	0.09 (−0.19–0.37)	0.86 (−0.6–2.34)	−0.26 (−0.72–0.21)	0.14 (−0.06–0.35)
PM_{10}	lag0	0.14 (−0.03–0.31)	0.25 (0.06–0.44)	−0.46 (−1.5–0.58)	0.23 (−0.09–0.55)	0.19 (0.05–0.33)
	lag1	0.07 (−0.09–0.23)	0.14 (−0.04–0.32)	0.47 (−0.51–1.46)	−0.03 (−0.34–0.28)	0.12 (-0.02–0.25)
	lag2	−0.11 (−0.27–0.05)	−0.03 (−0.21–0.15)	0.38 (−0.59–1.35)	−0.41 (−0.72–0.1)	−0.01 (−0.14–0.13)
	lag01	0.15 (−0.04–0.35)	0.28 (0.07–0.5)	0.08 (−1.08–1.25)	0.13 (−0.23–0.49)	0.22 (0.07–0.38)
	lag02	0.04 (−0.17–0.25)	0.2 (−0.04–0.44)	0.35 (−0.92–1.65)	−0.2 (−0.6–0.2)	0.17 (0–0.35)

$PM_{2.5}$ indicates particulate matter <2.5 μm in aerodynamic diameter, PM_{10} indicates particulate matter <10 μm in aerodynamic diameter.

from high-income countries. Additionally, the specific risks were volatile ranging from −2.9 to 31.4%. However, the the impact of PM on mortality in the present study was similar to that at another city in China (0.44%, 95%CI 0.16–0.72%) (24). This may occur due to the characteristic of air pollution, weather patterns and the economy. Hence, it is reasonable to summarize the effect according to geographical location.

Though ischemic stroke and hemorrhagic stroke share similar risk factors, they are different clinical entities (23, 25). In order to examine whether the effect of PM on different types of stroke was the same, ischemic stroke and hemorrhagic stroke was evaluated respectively. Our data showed that short-term elevations in $PM_{2.5}$ increased the risk of death in both ischemic stroke and hemorrhagic stroke. Nevertheless, we found a significant association between ischemic stroke death and PM_{10} exposure, but not in hemorrhagic stroke. The studies of PM and hemorrhagic stroke were limited, and the outcomes were inconsistent (15, 26, 27). The mechanisms of hemorrhagic stroke and air pollution might be different from that of ischemic stroke and air pollution (23). Several mechanisms had been proposed, including exposure to particulate air pollution may induce inflammation (28), endothelial injury (29), atherosclerosis (30, 31), and can lower cerebral blood flow velocity (32).

There was not well documented referring to whether gender and age were effect modifiers. In the subgroup analysis, we did not find evidence that gender or age can modify the effect of PM on stroke. However, in some previous studies, it was suggested that females and the elderly were more likely to be vulnerable to air pollution (7, 33, 34). For instance, Kan et al. found that the effect of PM_{10} on total mortality among females was about twice those among males, though the difference was insignificant. Some stated that the gender difference could be partly explained by differences in particulate deposition, airway size (35), inflammatory response (36). Hong et al. found the elderly were more susceptible to PM_{10} (33). In the elderly, atherosclerosis is the main reason for ischemic stroke (37). Through pro-oxidant and pro-inflammatory effects, particulate matter modulates the progression of atherosclerosis, as a result of increasing the risk of ischemic stroke (38). However, the exact mechanisms of gender and age difference are unclear and deserve further investigation.

Several potential limitations of our study should be considered. First, as an ecological study, population level exposure was used, which may not reflect actual individual level exposure. The measurement error contains three components: the difference between an individual's deviation and the average personal exposure; the difference between the average personal exposure and the true ambient level; and the difference between the measured and the true ambient level. The first and third components are of the Berkson type and they are likely to have a small effect on the risk estimation (39). The effect of the second component may cause substantial bias, however, it tends to bias the results toward to null and underestimates the air pollutant effect (32, 40). Hence, the results should be interpreted with cautions and we cannot make causal inference form this study. Second, misclassification of cause of death may exist due to diagnostic or coding errors. However, the misclassifications seem to be unrelated with the air pollution levels and the errors may reduce the accuracy of the risk estimation (7). Third, because of data limitations, smoking-, drinking-, education- and complication-specific stroke mortality cannot be accessed, which prevented us from further exploring potential modifiers of association between air pollutants and ischemic stroke and hemorrhagic stroke.

In conclusion, PM exposure was associated with cerebrovascular death in Beijing, China. $PM_{2.5}$ was associated with both ischemic stroke and hemorrhagic stroke death. However, short-term exposure to PM_{10} increased the risk of death in ischemic stroke but not in hemorrhagic stroke.

Our study adds the evidence of the effect of PM on stroke in low-income countries, and it may have implications for public and environmental healthy policies.

AUTHOR CONTRIBUTIONS

GL and YOW: study design; GL, JW, and ZW: data acquisition; YJ, YP, and RZ: data analysis and interpretation; RZ: drafting; GL, YIW, and YOW: revising and final approval.

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Treating People With Epilepsy in Rural Low-Income Countries Is Feasible. Observations and Reflections From a "Real Life Experience" After a Long Lasting Intervention in the Rural Chaco

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Introduction: Epilepsy represents an important public health issue, in particular in low and middle-income countries where significant disparities are present in the care available for patients with epilepsy. Treatment cost and unavailability of drugs represent important barriers in treating people with epilepsy especially in rural setting. Aim of the study was to evaluate, by means of routine data, the current real-life clinical practice in epilepsy in the rural communities of the Plurinational State of Bolivia. Treatment activity followed educational campaigns and an anthropological fieldwork over more than 20 years.

Material and Methods: Medical records of people with epilepsy (PWE) living in the rural communities of the Bolivian Chaco who received antiepileptic drugs (AEDs), from 2012 to 2016, and were followed-up for at least 1 year were analyzed. Treatment delivery and follow up visits were managed by a neurologist with the support of rural health care workers.

Results: From 2012 to 2016, 157 PWE (76 men with a mean age of 24.2 ± 15.7) have been included in the study. Structural epilepsy was the most common type, recorded in 54 cases (34.4%) and the most common reported causes were perinatal factors, present in 11 subjects (20.0%). Almost all patients presented epilepsy with generalized tonic-clonic seizures (91.4%). The most common AED prescribed was phenobarbital followed by carbamazepine. During the follow-up, a dramatic seizures reduction was observed, with 31 subjects (19.7%) being seizures-free at the last follow-up. However, 48 subjects (30.6%) did not assume the medication regularly and 10 interrupted the drug intake. More than 20% of PWE did not receive any financial supports for AEDs. During the follow-up period 10 patients died but only in one case the death was probably caused by epilepsy.

Conclusion: Our study demonstrated that PWE in rural areas of the Bolivian Chaco are willing to seek medical attention and to receive antiepileptic treatment. However, improvement in care is needed to assure compliance to AED treatment, including activity to increase awareness toward epilepsy among community members and health staff of the rural communities and to guarantee the coverage of treatment costs and drug supply.

Keywords: epilepsy, treatment, low-income countries, management, real-life

INTRODUCTION

Throughout the world, epilepsy represents an important public health issue, accounting for an estimated 0.7% of the global burden of diseases. It affects approximately 70 million people worldwide of whom the majority live in low and middle-income countries (LMIC) (1). In particular, about 5 million people living in Latin American Countries (LAC) are affected by epilepsy (2). In the Chaco region, which is part of the Plurinational State of Bolivia, it was found a prevalence of lifetime epilepsy of 12.3/1,000 and a prevalence of active epilepsy of 11.1/1,000. In a recent study the life-time prevalence of epilepsy associated with generalized tonic-clonic seizures (GTCS) was found to be 7.2/1,000 and the prevalence of its active form 6.6/1,000 with a crude incidence risk of 55.4/100,000 in the same area (3–5). According to a recent meta-analysis in Latin American countries the treatment gap (TG) is 60.6% (95% CI 45.3–74.9), with high differences between rural (77.8%; 95% CI 67.4–86.8) and urban (26.2%; 95% CI 10.2–46.4) areas (5). In LMIC there are significant disparities in the care available for patients with epilepsy (PWE). Most neurologists work in the urban private sector, where the level of care is similar to that found in developed countries. However, in the poorer urban and rural areas this level of care is rarely available (6). In this latter setting, indeed, general practitioners (GPs) have an important role in providing care and support to PWE. However, in rural areas non-medical health workers such as nurses and community health workers (CHWs) are often the only health care staff present who can diagnose epilepsy with GTCS. As pointed out by recent WHO recommendations, in LMIC settings epilepsy with GTCS, should be recognized and treated at primary care level by trained non-specialist health care providers (7).

Thus, education of primary health workers and other clinicians working in the rural areas represents a key action in the reduction of the treatment gap. Nonetheless treatment cost and unavailability of drugs represent a further important barrier in treating PWE in rural setting (6). Consequently, specific programs for the improvement of knowledge and awareness about epilepsy in these settings are not sufficient if not accompanied by governmental actions aimed to support the treatment cost and drug supply. The reduction of epilepsy TG in the area of Chaco has been the main aim of many different projects performed by our group over the last 20 years in this area (3, 4, 8–12). However, even if a reduction of TG was recorded over the time by the subsequent studies carried-out (3, 4, 13), the real impact of our activity in the clinical practice of PWE has never been evaluated until now.

Aim of the present study was to evaluate, by means of routine data coming from the rural communities of the Bolivian Chaco, the current real-life clinical practice in epilepsy in the rural communities of the Plurinational State of Bolivia.

MATERIALS AND METHODS

Study Area

The study has been conducted in the Chaco area of the Plurinational State of Bolivia, which is a low-middle income country where about 4 million people live under the "poverty line" (14). In particular in rural areas the access to the health system is still difficult (15). However, a slight economic improvement has been recorded in the last few years, since the approval of the 2016-2020 National Economic and Social Development Plan by the Government of Bolivia aimed at maintaining growth of 5% and reducing poverty (16, 17). Indeed, with the application of policies to improve the economy, the social and health services and thanks to specific programs such as Bono Juana Azurduy, Programa Mi Salud, Ley de Gratuidad, Seguros departamentales, there was an increase in the social security and an improvement of the Bolivian health system (18).

PWE involved in this study come from three Departments of the Plurinatinal State of Bolivia: the Department of Santa Cruz (municipalities of Boyuibe, Cabezas, Cuevo, Lagunillas, Gutierrez, Eiti, Camiri and S. Antonio Parapetí), the Department of Chuquisaca (municipalities of Macharetí and Muyupampa or Villa Vaca Guzmán) and the Department of Tarija (municipality of Villamontes). These Departments are part of the Chaco region (**Figure 1**), that is a subtropical area, inhabited mainly by indigenous Guaraní people. They live in communities that often lack basic services such as running water or electricity, basing their economy on animal husbandry and agriculture.

Study Population

About 190,000 people live in the Bolivian Chaco and among them about 80,000 are indigenous Guarani. It is estimated that 49% of the population live in rural areas with 68.9% of the population living in conditions of poverty, the majority of them still presenting unresolved issues such as energy and sanitation supplies[1]. In the last 25 years, many

[1] *OPS/OMS Paraguay - Rostros, Voces y Lugares: El Chaco Sudamericano*. Available online at: https://www.paho.org/par/index.php?option=com_docman&view=document&layout=default&alias=139-rostros-voces-y-lugares-el-chaco-sudamericano&category_slug=salud-familiar-y-comunitaria&Itemid=253 (Accessed September 4, 2018).

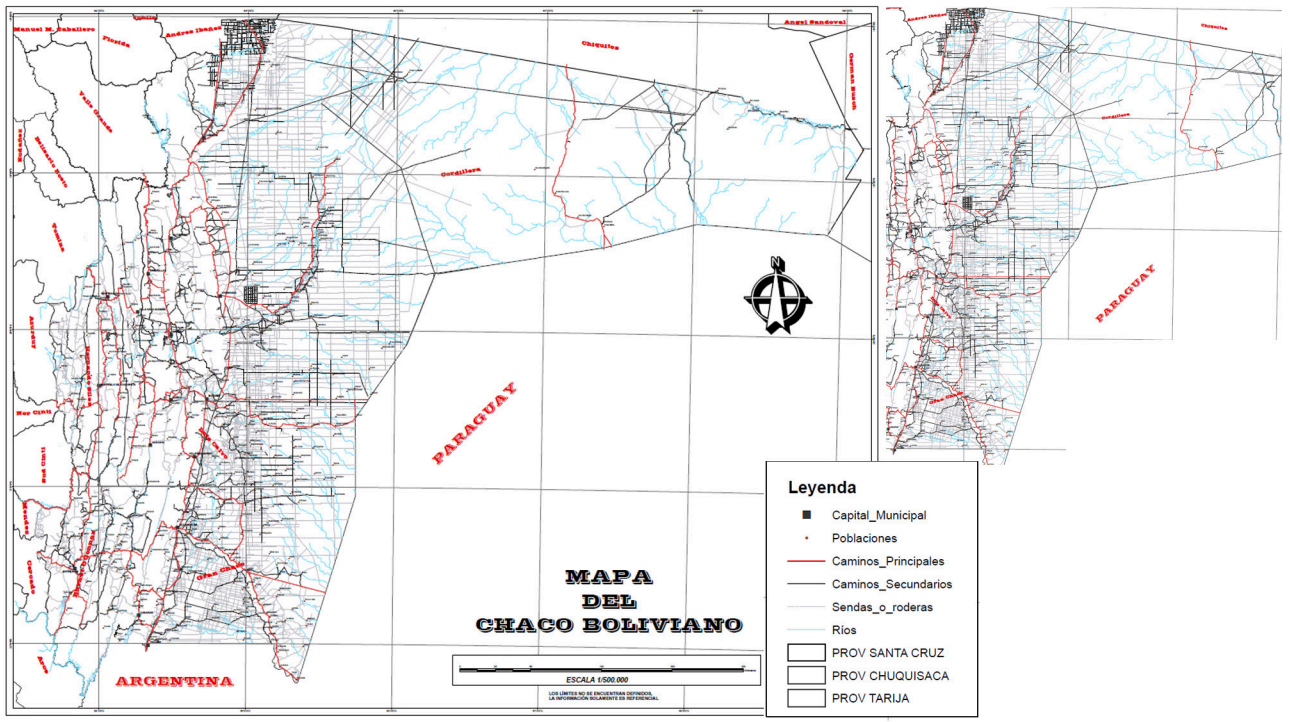

FIGURE 1 | Map of the Plurinational State of Bolivia with highlighted on the top left the area of the Chaco region and the three departments of Santa Cruz, Chuquisaca and Tarija.

activities aimed at improving knowledge about epilepsy and reducing TG have been conducted by our group in the rural communities of the Chaco region. (8–14). After the assessment of the prevalence, incidence, mortality and the most frequent causes of epilepsy, the evaluation of the sociocultural dimension of epilepsy and epilepsy-associated stigma among members of the Guaraní communities, many training courses about epilepsy have been organized directed to the health staff and all the members of the communities (3, 4, 8–13, 19). In particular an educational campaign directed to GPs and non-medical health staff has recently been implemented with teaching courses regarding the main causes of epilepsy, epilepsy diagnosis and treatments, first aid, prevention of the secondary forms of epilepsy and psychosocial aspects such as social stigma and discrimination (10, 19).

From 2012 to 2016 a Bolivian neurologist, working in Santa Cruz, participated to the teaching activity, organized in collaboration with the "Convenio de Salud" and the "Escuela Tekove Katu." The "Convenio de Salud," located in Camiri, works through cooperation projects with the University of Florence in Italy and the Pan American Health Organization. Its objective is to improve the health conditions of the indigenous Guaraní population through the development of health projects in primary care. The "Tekove Katu" school, located in Gutierrez, carries out training courses since 1985 and is an integral part of the educational and health system of the Plurinational State of Bolivia[2]. The neurologist guaranteed a bimonthly service of neurological visits to PWE living in the rural communities of the Chaco region.

Subjects identified by trained nurses or CHWs, as well as PWE already diagnosed by the GPs working in the rural areas or identified during the different epidemiological surveys, were attended in the main health centers located in the different areas.

When the diagnosis of epilepsy was confirmed, AEDs were prescribed and for PWE already in AED treatment, prescription was confirmed according to the neurologist's judgement.

This clinical activity was not part of a specific scientific programme and clinical data were routinely collected without the aim to be analyzed. Consequently, due to the lack of a standardized data collection, often incomplete information was gathered with a certain amount of missing data.

All medical records of all PWE coming from rural communities who received AEDs treatment and were followed-up for at least 1 year were analyzed by two independent observers (LG, CEC). Those patients for whom not sufficient information was available or who underwent only one neurological visit without follow-up have been excluded (**Figure 2**).

Diagnosis of epilepsy was generally performed just on the bases of the clinical history because the majority of cases never underwent EEG recording or neuroimages. On the bases of

[2]*Home - Scuola di Salute Pubblica Tekove Katu.* Available online at: http://www.tekovekatu.org/ (Accessed January 30, 2018).

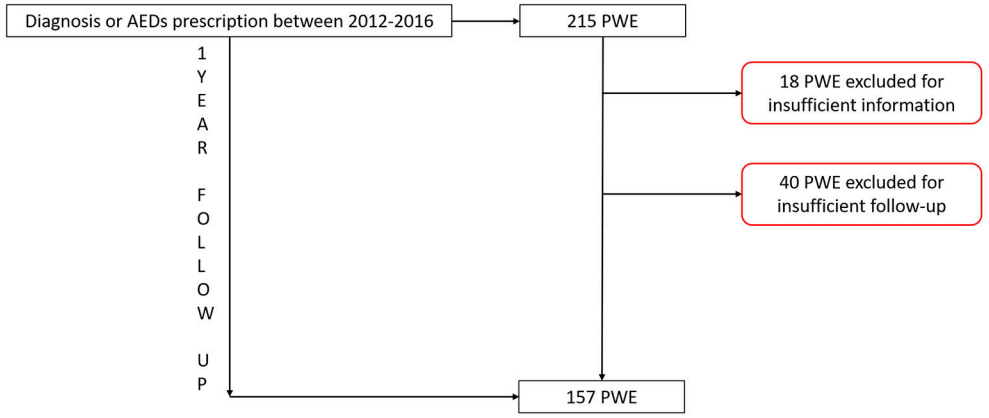

FIGURE 2 | Flow chart describing the study population. AEDs, antiepileptic drugs; PWE, people with epilepsy.

the clinical history, epilepsy was defined according to the ILAE definition and classification proposed in 2017 (20). In particular, according to the causes, epilepsy was classified as "structural" when an imaging abnormality was the likely cause of the patient's seizures; "genetic generalized" when an idiopathic form with a genetic predisposition was suspected on the bases of the clinical history; "of unknown etiology" when the cause of the epilepsy was not yet known; "unknown" when there was not adequate information to classify epilepsy type into a category (20).

Among the causes of structural epilepsy, perinatal factors were defined when there was an evidence of a hypoxic-ischemic encephalopathy (21); traumatic brain injury was defined as an insult to the brain from an external mechanical force, with an associated diminished or altered state of consciousness (22); neurocysticercosis (NCC) was defined according the most recent criteria (23); for the other possible causes we based our diagnosis on the previous clinical report.

Data Management and Statistical Analysis

Medical records were revised twice by two different operators (CC, LG) and relevant data were collected in an *ad hoc* created standardized form. Data were double entered into the database and statistical analysis was performed using the software STATA 12 (version 12.0, College Station, TX). Data cleaning was performed before the data analysis considering range and consistency checks. Quantitative variables were described as mean and standard deviation (SD) while frequencies using percentages. The frequency comparisons were performed using the chi-squared test.

Ethical Approval

The study has been approved by the Ethical committee of the Bolivian Neurological Society.

RESULTS

From 2012 to 2016, 215 PWE from the rural communities of the Gran Chaco area underwent a neurological examination and received at least an AED prescription. Of these, 18 were excluded from the analysis because no sufficient information was available, while 40 were excluded due to the lack of a follow-up visit. Finally, 157 PWE (76 men with a mean age of 24.2 ± 15.7) who had had at least 1 year of follow up were included in the analysis. The majority of them came from the areas of Camiri, Gutierrez and Eiti as shown in **Table 1.** Baseline characteristics are shown in **Table 1.**

The mean age at epilepsy onset was 9.6 ± 12.2. Seizure types were classified on the bases of the clinical history which was available in 113 cases (72%). Almost all patients presented epilepsy with GTCS of whom 26 (23.0%) focal to bilateral tonic-clonic seizures, while 81 (71.7%) were classified as generalized tonic-clonic. Only 6 (5.3%) presented focal seizures (**Table 2**). Structural epilepsy was the most common type of epilepsy, recorded in 54 cases (34.4%) followed by epilepsy of unknown etiology (22 cases, 14.0%) and genetic generalized epilepsy (21, 13.4%). Nonetheless, for 60 cases (38.2%) epilepsy was defined as unknown (**Table 2**).

Concerning the causes of structural epilepsy, perinatal factors were the most commonly reported, being present in 11 subjects (20.4%), followed by head trauma (11.1%). A diagnosis of meningitis was reported in 5 cases, NCC in 3 while other structural causes such as stroke or cysts were reported in 6 cases. For 22 cases (14.0%) "known" causes were not reported and were then classified as epilepsy of unknown etiology. Clinical characteristics of epilepsy are shown in **Table 2.**

Presence of co-morbidities was reported in 24 cases (15.3%) and the majority (17 subjects; 10.8%) presented developmental delay; however, for 22 cases this information was missing.

Overall, the most common AED prescribed was phenobarbital followed by carbamazepine and by the association of phenobarbital and carbamazepine. AEDs treatment during the follow-up period (2012–2016) is reported in **Figure 3**.

Information about seizure frequency before and after the treatment were available only for 47 patients. Before the AEDs treatment only 13% of cases presented sporadic seizures (2–3 per year) while the majority (55%) presented monthly or weekly seizures and 32% reported to have seizures every day. During the follow-up, a dramatic seizures reduction was observed and,

TABLE 1 | Demographic features of the patients.

	N = 157 (%)
Sex (M)	76 (48.4)
Mean age	24.2 ± 15.7
Mean age at onset	9.6 ± 12.2
OCCUPATION	
Unemployed	30 (19.1)
Student	39 (24.8)
Housewife	29 (18.5)
Farmer	15 (9.5)
Other	10 (6.4)
Not known	34 (21.7)
AREA OF ORIGIN	
Boyuibe	12 (7.6)
Cabezas	13 (8.3)
Camiri	45 (28.7)
Cuevo	4 (2.5)
Eiti	30 (19.1)
Gutierrez	25 (15.9)
Lagunillas	9 (5.7)
Macharetí	9 (5.7)
Muyupampa	2 (1.3)
San Antonio Parapetí	8 (5.1)

N, number; M, men.

TABLE 2 | Classification and causes of epilepsy.

	N (%)
CLASSIFICATION OF EPILEPSY	
Focal epilepsy	76 (48.4)
Generalized epilepsy	21 (13.4)
Unknown epilepsy	60 (38.2)
CLASSIFICATION OF EPILEPSY BASED ON THE ETIOLOGY	
Structural epilepsy	54 (34.4)
Genetic generalized epilepsy	21 (13.4)
Epilepsy of unknown etiology	22 (14.0)
Unknown epilepsy	60 (38.2)
CLASSIFICATION OF SEIZURES (*N* = 113)	
Focal	6 (5.3)
Focal to bilateral tonic-clonic	26 (23.0)
Generalized tonic-clonic	81 (71.7)

N, number.

in particular, 14/47 (30%) were seizure-free during the last year of follow-up, while 19% presented only sporadic seizures, and most of them just when they did not take the AEDs regularly. Frequency of seizures before and after treatment for these patients is reported in **Figure 4**. Of 157 PWE, 31 (19.7) were seizure-free at the last follow-up.

It should be underlined that 48 subjects (30.6%) stated to not assume regularly the medication and that 10 (6.4%) interrupted the drug intake. Of these, 8 (13.8%) interrupted AED treatment due to the absence of seizures, while for the others the most common reason for an irregular intake or interruption was the lack of medication, in part due to economic reasons. The cost of AEDs, in fact, was covered by the Ministry of Health programmes (Mi Salud and Seguro Universal Materno Infantil, SUMI) or by the municipality ("alcaldia") for 21 (13.4%) patients, by the local Strategic Partner Organizations (SPOs) of the Non-governmental Organization (NGO) "Liliane Fonds" (20.4%) and by the Convenio de Salud (11.5%). At any rate, more than 20% of PWE did not receive any financial supports.

During the follow-up period, 10 (6.4%), of the 157 PWE, died. Of them, 9 died due to causes not directly related to seizures, while only in one case a seizure-related cause was identified. In particular, the causes of death were the followings: severe malnutrition in four cases, malnutrition and pneumonia in two cases, pneumonia in one case, alcohol addiction complications in two cases, severe burn following a fall during a seizure in another case. Five of the 10 subjects suffered from structural epilepsy and six (60%) had also other comorbidities. Among these subjects, three had suspended the treatment, while five declared an irregular intake. The patient for whom a seizure-related death has been suspected was suffering from epilepsy with GTCS and alcoholism and he had suspended his treatment because of alcohol abuse.

DISCUSSION

Epilepsy treatment gap is an important public health problem in LMICs and in particular in the rural areas. Inadequate trained staff, cost of antiepileptic treatment and its unavailability, cultural misbeliefs about epilepsy, use of traditional medicine, and distance from the health posts represent its main causes (6) and appropriate interventions have been suggested to reduce it (24).

Among the suggested interventions, the core actions are represented by training nurses and community health workers, in order to be able to identify people with epilepsy, and training GPs working in the rural communities in order to diagnose and initiate epilepsy treatment (10). Indeed, according to the WHO guidelines, in LMICs settings epilepsy with GTCS should be diagnosed at primary care level by trained non-specialist health care providers (7). Moreover, increasing communities' awareness about epilepsy represents a further important action in order to reduce stigma and improve the adherence to the epilepsy treatment, even if misconceptions about epilepsy and recourse to traditional healers are challenging to change.

During our long-lasting activity in rural Bolivia, in agreement with the ILAE and WHO recommendations, from 1994 up to date we performed several epidemiological and interventional surveys including an anthropological survey, training programs directed to GPs, nurses and CHWs of the rural communities of the Chaco region as well as communities awareness programs (ongoing activity). Training activities were mainly directed to the Knowledge, Attitudes and Practice (KAP) and management of epilepsy with GTCS. The activities conducted by our group during these last 25 years, have surely increased the level of knowledge and awareness about epilepsy in this region as

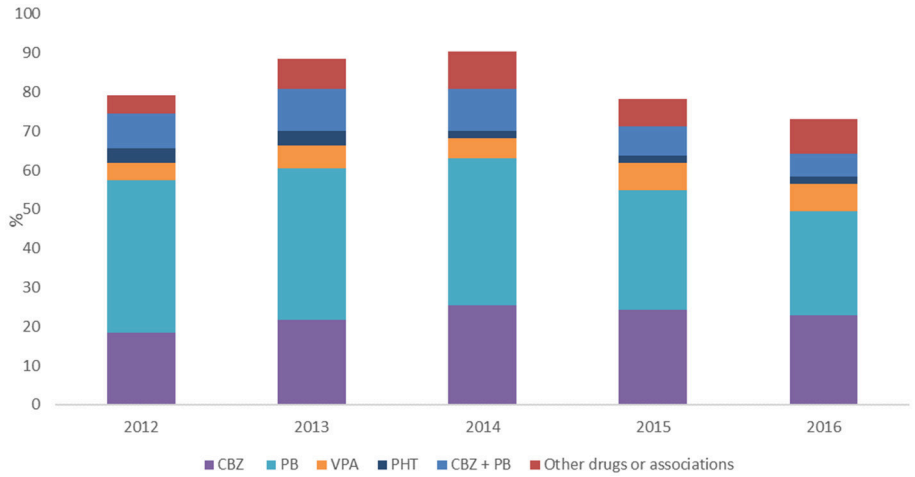

FIGURE 3 | Percentage of subjects treated with different AEDs per year. CBZ, carbamazepine; PB, phenobarbital; VPA, valproic acid; PHT, phenytoin.

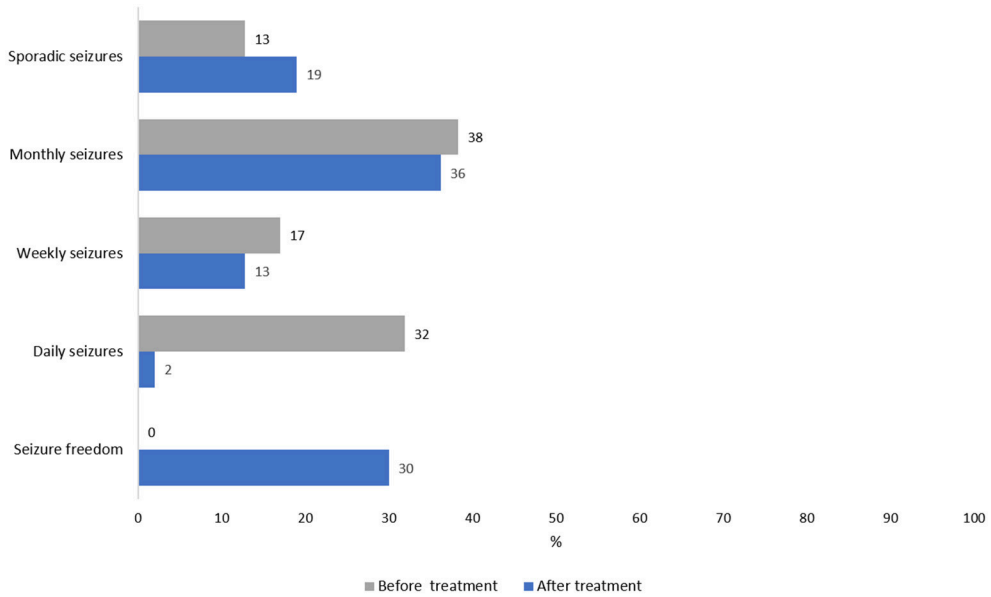

FIGURE 4 | Frequency of seizures before and after treatment in 47 patients with epilepsy.

demonstrated by the drop in the level of treatment gap recorded during different epidemiological survey over the time. Indeed, in our first survey performed in 1994 a treatment gap of about 90% was recorded while in 2010 a reduction of TG to values of about 70% has been found; finally in 2016 a value of TG of 45% has been recorded (3, 4, 13).

Although recognizing the importance of data coming from well-designed epidemiological studies, we believe that it can be worthwhile to evaluate the impact of our activity on the "real life" and not only under experimental conditions. Several trials have already demonstrated the feasibility of the treatment of epilepsy with GTCS under experimental conditions (25), but few data are available regarding the following step, namely the clinical practice in these settings. In experimental conditions, in fact, PWE are strictly monitored, the treatment is guaranteed and often delivered directly in the communities; furthermore, sometimes the costs of the AEDs have been directly covered by the project. However, what happens after the trial? Which is the real adherence to the treatment and the risk of an abrupt interruption? Which are the main causes of an irregular intake? All these important questions can be addressed only by the analysis of routine data, taking into account all the limits related to this kind of study. In fact, routine data collected for the clinical practice have the fault of lacking information with possible missing data for many subjects and many variables. Moreover, we are absolutely aware about the possible selection bias related

to the fact that PWE treated and included in the analysis can have different characteristics with respect to those never treated. Nonetheless, from our point of view, despite all the possible limits, important food for thought comes from this study.

As expected on the bases of our activities that, in agreement with the WHO guidelines, have been focused on the management of GTCS, more than 90% of PWE on treatment presented convulsive epilepsy. Concerning the epilepsy causes, it was possible to define the epilepsy type only in a minority of cases, since in 14% of cases epilepsy was defined as of unknown etiology and in 38.2% of patients, epilepsy diagnosis was not possible. This high level of diagnostic uncertainty, with consequent underestimation of the most frequent recognized epilepsy causes, such as NCC (11), is certainly due to the low availability of reliable diagnostic tools in these areas. Treating epilepsy with GTCS in rural communities, regardless of its causes, is feasible as demonstrated by the high frequency of a regular intake and the dramatic seizures reduction. Nonetheless 30% of subjects reported an irregular intake often due to irregular AEDs supply and economic reasons. On the other hand, AEDs adherence does not seem to be influenced by stigma or cultural beliefs. Thus, when we increase knowledge and awareness about epilepsy, the treatment is well accepted and sought by PWE. However, cost and supply still represent an important barrier in these areas. Currently, the costs of AEDs are in part covered by NGOs or other non-governmental institutions. An effort should be made to extend the cost coverage of AEDs by national and departmental health institutions since the cost of the most common AEDs used in Bolivia is very low. In fact, considering the most common drugs used, the annual cost of a treatment with the average dosage used of 100 mg of PB daily would be only about 50 $ per person a year, as well as the annual treatment with 400 mg of CBZ, which would cost about 95 $ per person a year. Only 21.6% of cases are currently taken in charge by the municipality and Ministry of Health (Mi Salud and SUMI). Furthermore, the follow-up depends entirely by the volunteer action of local neurologists. It should be underlined that even if the follow-up can be performed by the GPs working in the rural area, in Bolivia, as well as in other countries, phenobarbital, that represents the first line drug, can be prescribed only by neurologists. In this perspective, the presence of a neurologist should be considered as an essential element within a team attending PWE, acting as prescriber and reference specialist for GPs. Programs should consider this presence and the relative costs.

Mortality rate for epilepsy in the Chaco area was 10/1,000 (12) and even if, due to the different study design, a direct comparison cannot be made, the number of deaths recorded in this sample (10 out of 157 PWE) is probably higher than expected. As already reported it is possible that patients seeking treatment and consequently included in the study were the most severe ones, thus leading to a possible selection bias. Indeed, patients who died were affected by more severe forms of disease as demonstrated by a high rate of comorbidities present in 60% of subjects, mainly represented by developmental delay. Moreover, all patients presented a structural epilepsy with only GTCS and with a frequency higher with respect to the rest of the sample (57.15% with weekly or daily seizures before treatment). In agreement with this observation, nine patients died due to causes not directly related to seizures, such as severe malnutrition, pneumonia and alcohol addiction, while only in one case a seizure-related cause was identified (severe burn following a fall during a seizure). Nonetheless, this latter patient interrupted his treatment intake because of alcohol abuse.

We are aware that our study includes only a part of PWE residing in this area. Indeed, considering the total rural population of the study areas (about 75,000 inhabitants according to the 2012 census) and according to the prevalence of active epilepsy associated with GTCS (6.6/1,000) (4) which is the most common type, about 495 PWE are expected in this population. Thus, we can conclude that about 50% of PWE ($n = 215$) received medical attention and were treated with an AED in this area, percentage that is roughly close to the last TG recorded in the same area (13). Nonetheless, this is not a population survey and, as reported, selection bias is probable. It is possible to hypothesize, in fact, that PWE affected by more severe forms were more prone to seek medical attention and treatment. To these reasons, our data do not allow to reach any conclusion regarding the effective TG. According to our experience, after improving knowledge and awareness in the rural population, PWE are willing to seek medical attention and to receive antiepileptic treatment, and these considerations can be extended to other similar settings.

At this point governmental and departmental actions are urgently needed in order to guarantee an adequate treatment and medical attention in these areas. In particular, local government should strengthen specific training programs for the GPs and CHWs living in the rural area and should support supply of generic, low-cost, first-line AEDs. These actions could lead to a significant improvement of epilepsy care in rural areas.

Furthermore, the national organizations and international official epilepsy institutions should reinforce their actions in order to obtain equal conditions people with epilepsy in the different parts of the world.

AUTHOR CONTRIBUTIONS

LG and AN contributed to conception and design of the study. SP, EV, DR, and MM contributed to the organization of the project. LG, AN, CC, and CEC organized the database. LG and AN performed the statistical analysis. LG and AN wrote the first draft of the manuscript. CC, CEC, and AB wrote sections of the manuscript. MZ, MC, AB, and EC critically reviewed the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Validation of a Questionnaire for Distinguishing X-Linked Dystonia Parkinsonism From Its Mimics

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Objectives: X-linked dystonia parkinsonism (XDP) is a neurodegenerative movement disorder endemic to the island of Panay in the Philippines. We undertook a population-based prevalence study to enumerate all cases of XDP in Panay. We first developed a 4-item questionnaire to distinguish XDP suspects from the general population. In the present study we aimed to revalidate this questionnaire to distinguish XDP from similar conditions so as to give it greater utility in the clinical setting.

Patients and Methods: A total of 306 subjects (114 cases and 192 controls) were screened in from the 16 towns and 1 city of Capiz province. Their responses to the previously developed 4-item questionnaire were collected and multivariable logistic regression was performed to develop a predictive model. The accuracy of the model was determined by using it on a subset of patients; then, a scoring system based on the model coefficients was established.

Results: With a cut-off score of 6, the questionnaire had an accuracy of 70.7% (95% CI 0.57-0.82), a sensitivity of 84.6 % (95% CI 0.65-0.96) and a specificity of 59.4 % (95% CI 0.41-0.76). The item on "shuffling of feet" was the strongest predictor in distinguishing XDP from its common mimics.

Conclusion: We were able to revalidate a simple, four-item questionnaire that could distinguish XDP from its common mimics with fair accuracy. The questionnaire along with other clinical features can be used to determine which patients need specialty evaluation and genetic testing to verify a diagnosis of XDP.

Keywords: XDP, dystonia, questionnaire, parkinsonism, genetic, prevalence, epidemiology

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INTRODUCTION

X-linked dystonia parkinsonism (XDP) is a neurodegenerative movement disorder endemic to Panay island in the Philippines, with recessive inheritance and a genetic founder effect. Molecular genetic studies suggest reduced expression of a neural isoform of *TAF1* in the striatum of patients (1). The disease initially manifests with focal dystonia, which then progresses to generalized dystonia and overlaps with symptoms of parkinsonism about 5–10 years after onset. Parkinsonism predominates after about 10 years of disease (2). Some XDP patients have may have predominantly parkinsonian symptoms initially (3), causing diagnostic confusion with idiopathic Parkinson

Disease. Among inherited forms of isolated dystonia, XDP stands out with its overlapping parkinsonian features and X-linked mode of inheritance (4). The disease was brought to the attention of the international scientific community in 1975 when it was presented in the Second Dystonia Meeting held in New York City (5).

A population-based prevalence study was initiated in 2016 in order to do a complete enumeration of all XDP cases in Panay. The first phase involved the development of a 4-item screening questionnaire that can be used by community health workers (CHWs). The second phase involved screening by the CHWs of all the households in the island using this questionnaire. Individuals who were screened in were then evaluated by neurologists and movement disorder specialists. All consenting patients deemed to have probable XDP underwent genetic testing. Only Capiz province in Panay island has undergone all four phases of the study.

The first phase of the prevalence study was accomplished in 2015. A questionnaire with four items was validated to be highly sensitive and specific for screening patients with possible XDP in a general population where XDP is endemic. The questions screened for sustained twisting, repetitive jaw opening and closing, slowness in movement, and feet shuffling (6). Since the questionnaire was designed for screening at-risk individuals in a healthy population, the validity of this tool is unknown in patients with symptoms similar to XDP, such as Parkinson's disease, stroke, and cerebral palsy (6). A questionnaire that can distinguish genetically confirmed XDP from its clinical mimics is therefore lacking.

New diagnostic criteria for another genetic movement disorder, Huntington Disease, have recently been established. The criteria are based on motor scoring systems, genetic testing and historical findings that classify the patients into six strata (7). Similarly, a questionnaire for another neurologic condition, myotonic dystrophy (MD), identified 5 questions predictive of MD among healthy controls and diseases that mimic MD. The study emphasized the importance of such questionnaires especially in neurologic conditions such as MD that may be missed by non-neurologists (8). Common neurologic diseases, such as stroke, migraine, dementia and Parkinson disease also have screening tools used by non-specialists that lead to more definitive investigations (9–12).

The main objective of our study is to develop a weighted questionnaire that will differentiate XDP from other neurological diseases with similar symptoms. Many patients reside in remote areas of Panay, accessible only by long treks on foot and boat rides. General health professionals who are first to see patients with possible XDP will need to know which ones will need specialist assessment. The present questionnaire, if validated, can help direct meager community resources toward diagnosing and treating patients most likely to have XDP.

MATERIALS AND METHODS

The study design involved the development of a predictive model using retrospectively obtained data from the ongoing Population-Based Prevalence Study of XDP in Panay. Over a period of 2 months, data was gathered from all the 16 towns and 1 city of Capiz province. The CHWs screened the entire province of about 440,000 adults[1] using the previously validated 4-item questionnaire. In brief, the questionnaire was adapted from existing screening tools and tested on a random sample of 64 genetically confirmed and 64 normal healthy individuals (7). Responses to the questionnaire, the clinical diagnoses made by the movement disease specialists and the results of genetic testing provided data for the current study. Multivariable logistic regression was performed on a training subset of the data ($n = 248$) to create a predictive model and scoring system. The predictive model's performance was evaluated by applying the scoring system on another subset of data ($n = 56$). Sensitivity, specificity, and accuracy of the predictive model were obtained with 95% CI.

To be included in the dataset, subjects needed to be patients of the ongoing Population Based Prevalence Study of XDP in Panay, screened in by the CHWs in the second phase of the study. The subjects had a "yes" answer to at least one question in the 4-item questionnaire and a final disposition which is either a diagnosis of XDP or an alternative diagnosis, based on results of clinical and genetic testing.

Cases were defined as subjects with at least one positive response to the 4-item questionnaire and a positive genetic test result for XDP with the SVA retrotransposon insertion using a polymerase chain reaction (PCR) based genetic test (13). On the other hand, controls were defined as subjects with at least one positive response to the 4-item questionnaire and one of the following: a negative genetic test result or a more likely alternative diagnosis (in which case genetic testing was no longer done).

The patient's age, sex, and responses to the 4-item questionnaire, final clinical diagnosis and genetic testing results, where available, were tabulated on data collection sheets and subsequently, tabulated in an Excel file (Microsoft Excel for Mac v15.35). Anonymity was maintained by ensuring that only the codes were used in data gathering.

The collected data was randomly partitioned into two: a training set and a test set. The training set (248 subjects: 88 cases and 160 controls) was used to develop a predictive model through multivariable logistic regression analysis, which was appropriate to model the data because the output variable (whether or not a subject has XDP) was based on a set of predictor variables (responses to the screening questions) Each of the four questions in the screening tool was assigned a score based on the raw coefficients of the logistic regression model. A simulated dataset consisting of a list of all the possible combinations of answers to the four questions was used to determine the total score cut-off value. The resulting model was then run on the test set (58 subjects: 26 cases and 32 controls) to estimate its prediction abilities (diagnostic accuracy). The predicted probability cut-off value used in the estimation of the diagnostic accuracy, sensitivity, and specificity was chosen

[1] Philippine Statistics Authority. *Capiz Quickstat*.

as the point on the ROC curve that maximizes sensitivity and specificity.

To allow for the predictive model to be used at the point of clinical encounter, a scoring system for the 4-item questionnaire was developed based on the model coefficients of the logistic regression model. All calculations and statistical analysis were done in R version 3.2.4 (www.R-project.org). **Figure 1** provides a graphic summary of the experimental design.

The identity of all the subjects were concealed throughout the process. They were only referred to by their codes. The study obtained approval from the Expanded Health Research Office of the Philippine General Hospital prior to data collection. Also, a memorandum of agreement with the primary author of the Population Based Prevalence Study was signed to allow review of the study's de-identified data.

RESULTS

The baseline characteristics of all patients involved in the study is summarized in **Table 1**. Of all those seen by the CHWs during the second phase of the Population Based Prevalence Study, 306 subjects were screened in with an answer of "yes" to at least one item in the 4-item questionnaire. Out of all these patients, 114 had genetic confirmation of XDP, hence were labeled as cases. Of these, five were female. The average age was 53.14 years old (±10.79) with a range of 23 to 77 years old.

On the other hand, 192 either had a negative genetic test or a likelier alternative diagnosis after clinical evaluation, hence were labeled as controls. The diagnoses of the control group composed mainly of other neurologic diseases mimicking XDP are illustrated in **Figure 2**. Cerebral palsy (18.75%) was the most common XDP mimic. Forty one of the 192 patients in the control group also underwent genetic testing and had a negative result. Of the 12 Parkinson Disease patients, all in the control group, 5 underwent genetic testing and tested negative.

Based on the logistic regression model, the question on feet shuffling and taking smaller steps was found to be the single strongest predictor in distinguishing XDP from conditions that mimic it. The receiver operating characteristic (ROC) curve is shown in **Figure 3**. A cut-off probability of 0.179 for a "positive" result of the questionnaire was set, which was determined to be the best cut-off threshold maximizing the model's sensitivity and specificity. The area

TABLE 1 | Baseline Characteristics of Study Subjects.

Characteristic	Value
Total Number of patients	306
MEAN AGE—YEARS (STANDARD DEVIATION)	
All patients	47.6 (±18.3)
SEX	
No. of males (%)	229 (74.8)
No. of females (%)	77 (25.2)
NUMBER OF PATIENTS WITH A "YES" RESPONSE TO:	
Sustained twisting (%)	171 (55.9)
Repetitive jaw opening and closing	124 (40.5)
Slowness in movement (%)	209 (68.3)
Feet shuffling (%)	198 (64.7)
All four symptoms (%)	69 (22.5)

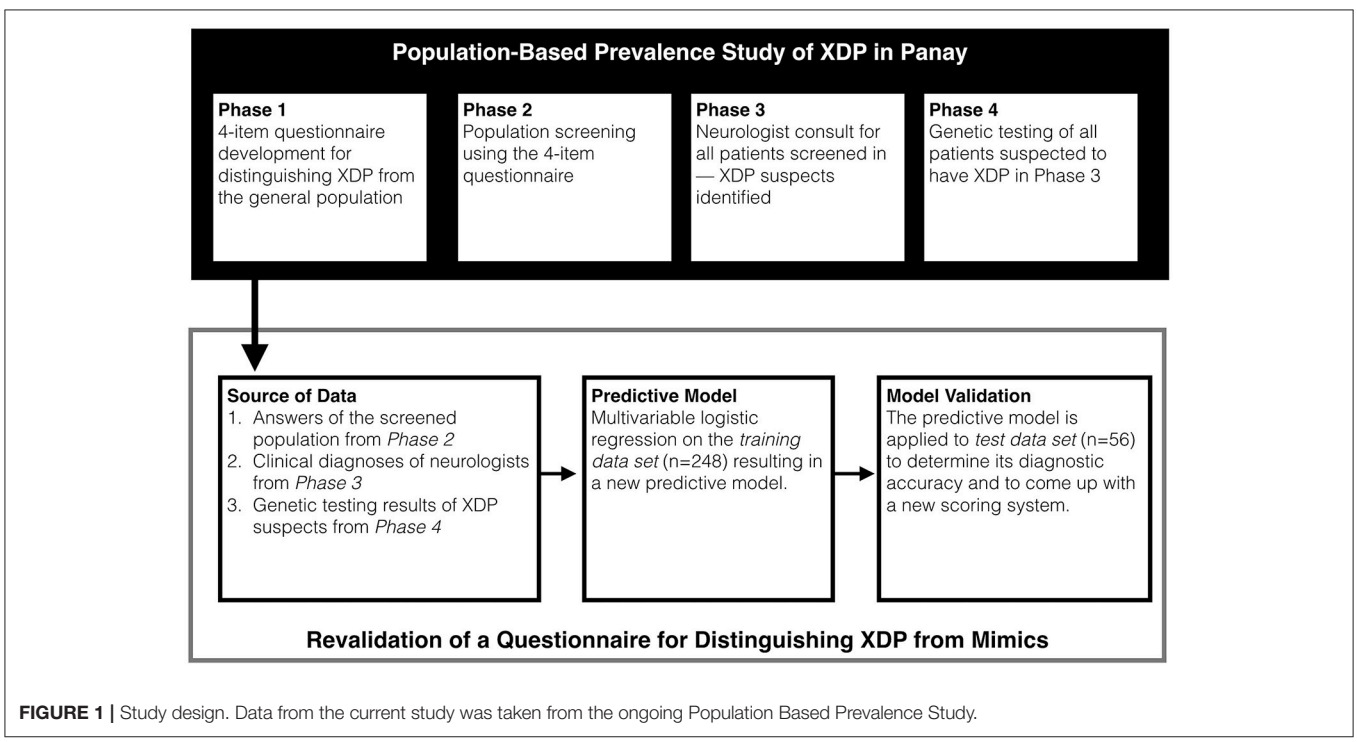

FIGURE 1 | Study design. Data from the current study was taken from the ongoing Population Based Prevalence Study.

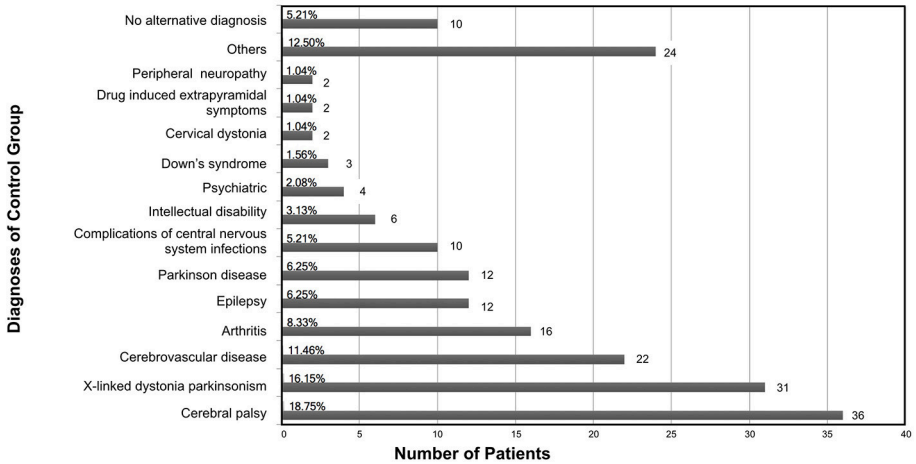

FIGURE 2 | Breakdown of the diagnoses of the control group.

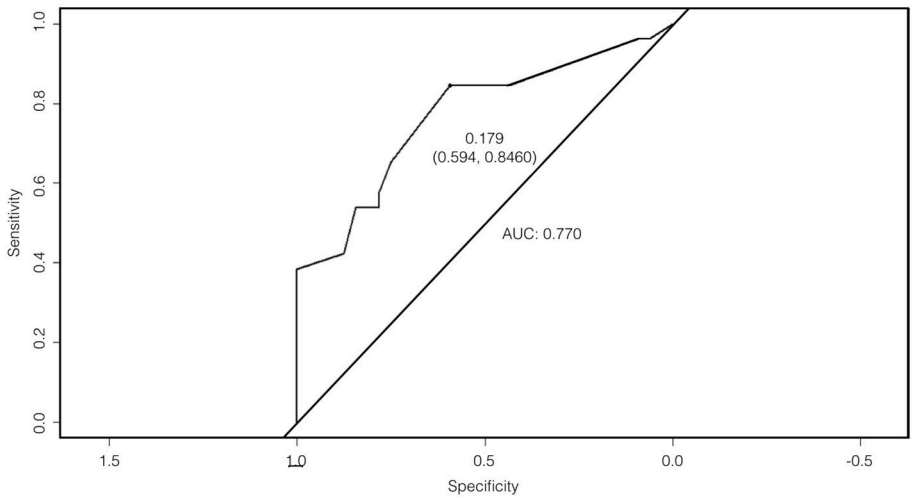

FIGURE 3 | Receiver operating characteristic (ROC) curve with an area under the curve (AUC) of 0.770.

under the curve (AUC) is 0.770—reflecting a fair ability of the questionnaire to distinguish XDP from its mimics (14).

The final scoring system based on raw coefficients of the logistic regression model is shown in **Table 2**. The total scores for each combination of answers were compared with the predicted probabilities generated by running the model on the simulated dataset. The predicted probabilities of the simulated dataset are shown in **Supplementary Material**. The total score can range from 0 to 13. A score of 6 or more is considered "positive" i.e., the patient has a high likelihood of having XDP.

The over-all accuracy of the model in separating XDP from non XDP individuals in the test set is 71%, which is statistically different from the accuracy that will be achieved if all subjects are classified as XDP without regard to their answer to the questions (no information rate). The model can correctly identify 85% of subjects with XDP as having XDP (sensitivity) and can correctly identify 59% of subjects without XDP as not having XDP (specificity). On the other hand, a positive identification made by the model will be correct 63% of the time (positive predictive value) and a negative identification made by the model will be correct 83% of the time (negative predictive value). The negative predictive value (NPV) of the test, 83%, ensures that most of those excluded by the test are true negatives.

DISCUSSION

In this study we attempted to validate a four-item questionnaire originally for use by lay workers to screen a population endemic for XDP, in a group of individuals with signs and symptoms that may be misdiagnosed as XDP by non-specialists. We found that

TABLE 2 | Questionnaire items with corresponding weights.

Questions	Score	Coefficient	95% CI	*p*-value
1. Do you experience sustained twisting movements of any body part?	3	4.26	2.17	<0.001*
2. Do you experience constant jaw opening and closing?	3	3.20	1.64	0.001*
3. Do you experience slowness in movement?	2	1.51	0.59	0.392
4. Do you shuffle your feet or take smaller steps when you walk?	5	7.61	2.99	<0.001*

**Statistically significant ($p < 0.05$).*

though highly sensitive and specific in the general population, it was fairly accurate in this subset of XDP mimics.

Experience from the Population-Based Prevalence Study reveals that many patients who were suspected to have XDP could not even be brought to the municipal health centers for screening because of time and financial constraints. This emphasizes the great resources that need to be mobilized to get expert opinion for XDP suspects. Once this study ends, evaluation by a movement disorder specialist and genetic testing will become even more elusive. The questionnaire we developed can be used to screen for patients most likely to have XDP. Identifying this subset of patients will enable a more focused use of resources for those most likely to benefit. The questionnaire can be used by both lay workers and general health professionals.

Up to a quarter to one half of patients with dystonia may be misdiagnosed or undiagnosed (15). Even among neurologists the correct diagnosis of movement disorders may be difficult to make. The rate of accurate diagnosis correlates with the physician's experience—with movement disorder specialists arriving at the right diagnosis more consistentl (16). Unfortunately, in the Philippines, for a population of 100,981,437 (17), there are only about 10 movement disorder specialists with formal training. This questionnaire can be used to assist general health professionals and CHWs in Panay in selecting patients who are most likely to benefit from subspecialty consult and genetic testing.

The developed questionnaire has a fair ability to distinguish XDP from its common mimics with an accuracy of 71% (0.57-0.82, 95% CI). It has a relatively high negative predictive value of 83% (0.61-0.95, 95% CI), which makes it useful for first line health workers in selecting patients that need to be triaged for further work-up and evaluation in tertiary institutions with neurologists and movement disorder specialists. A patient with a score of 6 or more would likely benefit from further evaluation by a movement disorder specialist and subsequent genetic testing. While a score of less than 6 would identify patients who probably have an alternate diagnosis. The earlier validation study that distinguished XDP patients from the healthy general population only required that any one of the 4 identified questions be positive for the screened individual to move to the next phase of the study (6).

Perhaps the main differential diagnosis for XDP is idiopathic parkinsonism. Multivariable logistic regression analysis reveals that the question on feet shuffling and taking smaller steps has the biggest weight for determining XDP in this population but is not by itself able to distinguish between genetically positive XDP and its mimics. A previous review on the phenomenology of XDP revealed that only 5.7% of XDP patients begin with parkinsonian symptoms, including shuffling of gait, and that only 18.6% are predominantly parkinsonism throughout the course of the illness (5). This study suggests that shuffling of feet and parkinsonism may be more important than previously thought. In contrast, the original validation study for the 4-item questionnaire gave constant jaw opening and closing the largest weight for distinguishing XDP from the general population (6).

A screening questionnaire for Parkinsonism found the following questions most predictive: stiffness and rigidity in legs, tremor and shaking, troublesome arm swing and feet stuck to floor (18). It is interesting to note that two of these items relate to lower extremity mobility as well. This fact emphasizes the need for the other 3 components not found in the PD questionnaire to come up with a scoring system that can distinguish XDP from PD. The original version of the 4-item questionnaire found the question on "shuffling of feet" to have excellent positive and negative clinical utility in differentiating XDP from the normal population (6). It is not surprising then that the same symptom is found to be most important in differentiating XDP from its mimics.

The most interesting aspect of the results perhaps is the 31 clinically diagnosed XDP patients who had a negative genetic test. In this study we used a PCR-based test that detected the presence of the SVA retrotransposon insertion in intron 32 of the TATA binding protein factor 1 (*TAF1*) in the XDP critical region in Xq13.1 (13). This retrotransposon insertion however, is not the only variant associated with XDP in the XDP haplotype on the X chromosome. Six other variants have been identified: single-nucleotide changes (DSC1, DSC2, DSC3, DSC10, DSC12) and one 48-bp deletion (19), although previous data has shown that all these genetic variants are in tight linkage disequilibrium (i.e., no variant has been described in patients in isolation from the rest).

Theoretically, each of the 31 patients with clinical features consistent with XDP but a negative genetic test could have any of the other 6 genetic variants apart from the SVA retrotransposon insertion; however, a previous study that investigated the genetic features in 166 clinically diagnosed XDP patients found that all 7 disease-associated genetic variants always occurred together with each other in all but 5 individuals. These 5 patients, clinically diagnosed to have XDP, had none of the 7 genetic variants, and were classified as phenocopies (19). The 31 clinically diagnosed XDP patients that were negative for the XDP haplotype on genetic testing may harbor a yet unidentified genetic variation that may be common to the 5 phenocopies in the previous study. Unfortunately, details on the individual phenomenology of the XDP in these 31 patients apart from their answers to the questionnaire were not documented. We recommend that further clinical evaluation be done for these subjects. Features such as age of onset of the disease and initial neurologic

manifestations may determine if this subset of patients has a phenotype that is unique from genetically confirmed XDP patients.

Further modifications to the questionnaire can be made that can utilize other questions from an expanded list of screening questions (6). The test-retest reliability of the questionnaire can also be explored in future studies. New questions can be added from focused group discussions involving movement disorder specialists, health workers and patients. A questionnaire with better diagnostic performance (i.e., higher sensitivity and specificity) can thus be produced. Involvement of stakeholders will also improve the acceptability of the questionnaire later. All these can help produce a more accurate and acceptable questionnaire. In addition, a convenient electronic application can also be developed.

Similar to developments in Parkinson Disease research, the principles of objectification, multi-purpose design and simplification should be applied to future assessment tools for XDP (20). Further modification of the tool can include an objective assessment of the pathologic movements of XDP by clinical observation or the use of wearable movement analysis devices. Doing so would make the evaluation adhere to an objective multipurpose design that gathers data for XDP phenomenology research (20).

There are several limitations of this study. The prevalence study only screened those able to understand and respond to a "yes or no" questionnaire-type interview. The new scoring tool was developed using subjects who had already been screened-in using the 4-item XDP screening questionnaire developed in phase 1 of the Prevalence Study. Only the same 4 questions were used to develop the new scoring tool. The questionnaire by itself cannot be used to decide which patients merit genetic testing. A careful evaluation by a movement disorder specialist is needed to elicit clinical clues that cannot be provided by the questionnaire.

All data was only collected through review of the database of an ongoing study. Because not all controls were genetically tested, some patients, especially those thought to have PD, may be XDP patients with predominant parkinsonian symptoms. Besides answers to the four questions no other clues to the patients' clinical features were found; hence, correlations between signs and symptoms to the genetic variant tested for could not be done. Most importantly, XDP patients without any of the currently known 7 mutations may not have been selected by the questionnaire.

CONCLUSIONS AND RECOMMENDATIONS

We were able to revalidate a simple, four-item questionnaire that can be used to distinguish XDP from its common mimics with fair accuracy. The questionnaire is intended for use by local health workers and general practitioners to determine which patients need specialty evaluation and genetic testing to ascertain or dispute the diagnosis of XDP. Doing so would direct time and finances to the patients most likely to have XDP and need specialty care.

The clinical features of all subjects classified as cases should be more completely characterized. Doing so would contribute greatly to data regarding the phenomenology of XDP. Further genetic profiling should be done on the 31 clinically diagnosed XDP patients with negative genetic testing, as they could be harboring a yet to be discovered genetic mutation associated with XDP. A follow-up study that includes more controls with genetic testing may perhaps improve the accuracy of this questionnaire.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

JD, MM, MA, and PP were all equally responsible for the conception and design, acquisition of data or analysis and interpretation of data. MA designed and carried out the statistical analysis of the data. JD and MM drafted the article while MA and PP took charge of critical revisions for important intellectual content. JD, MM, MA, and PP agreed to be accountable for the article and to ensure that all questions integrity of the article are investigated and resolved.

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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.2018.00830/full#supplementary-material

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Corrigendum: Validation of a Questionnaire for Distinguishing X-Linked Dystonia Parkinsonism From Its Mimics

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A Corrigendum on

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In the original article, we neglected to include the funder, Collaborative Center for X-linked Dystonia Parkinsonism (CCXDP) of the Massachusetts General Hospital. CCXDP is responsible for the funding of the Population-based prevalence study of X-Linked Dystonia Parkinsonism (XDP) in Panay Island, an ongoing study whose database our raw data is from.

In addition, we neglected to acknowledge the neurologists and genetic counselors who examined the patients of the study. The corrected Acknowledgment appears below:

We wish to acknowledge Dr. Roland Dominic Jamora for his review of the study design during the conception of this research. We would also like to thank the neurologists and genetic counselors who were instrumental in the implementation of this study. But most of all we are grateful to the health workers of Panay who bear the daily burden of caring for our XDP brothers and sisters. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

Conflict of Interest Statement: 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.

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A Retrospective Analysis of the Clinical Features of Inpatients With Epilepsy in the Ganzi Tibetan Autonomous Prefecture

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Background: There is limited detailed clinical information for patients with epilepsy in Tibet. This study sought to provide data about the clinical features of epilepsy in the Ganzi Tibetan Autonomous Prefecture to improve strategies for epilepsy prevention and management in this region.

Methods: We reviewed the clinical record of patients with epilepsy in the Neurology Department, Ganzi Tibetan Autonomous Prefecture People's Hospital and compared the clinical features and compared it with control, from West China Hospital in Chengdu.

Results: This retrospective study included 165 patients with epilepsy admitted between January 2015 and February 2018. Majority of patients (97%) in this study had active epilepsy; 28.5% had generalized onset seizures and 68.5% had focal onset seizures. Fifty-four patients had received anti-epileptic drug (AED) treatment prior to hospitalization, however, 38 (70.4%) patients took the medication irregularly. The leading etiology of this cohort was head trauma (20.6%), followed by stroke (10.9%), neurocysticercosis (7.9%), brain hydatidosis (6.7%) and tuberculous infection (5.5%). Compared with in-patients in Chengdu, epilepsy in Ganzi was more frequently caused by infection (OR = 4.216, 95% CI, 2.124–8.367), including neurocysticercosis (OR = 29.301, 95% CI, 1.727–497.167) and brain hydatidosis (OR = 24.637, 95% CI, 1.439–421.670).

Conclusions: These data suggest that the control of cerebral infections, especially parasite infection, is essential for the prevention of epilepsy in the Ganzi Tibetan Autonomous Prefecture. Education of local primary doctors and patients about the literacy of epilepsy will enable better management of epilepsy in this population.

Keywords: cerebral infection, clinical features and atiology, epilepsy, Ganzi Tibetan Autonomous Prefecture, retrospective study

INTRODUCTION

Epilepsy is one of the most common neurological disorders in the world that affects people of all nations and socioeconomic classes. The Tibetan area, which is on the Qinghai-Tibetan plateau, is ∼4,000 m above sea level. There are very few studies of epilepsy in this area (1, 2). A survey done in one of the counties in Tibet found that the lifetime prevalence of convulsive epilepsy was ∼2.5 per 1,000 with a treatment gap of up to 97%. No EEG or imaging data were available in this study (1). Another study summarized 180 cases of patients with epilepsy (PWE) and reported that the etiology was unknown in 145 cases (80.6%) and no EEG or imaging data were available (2). Detailed clinical information, such as MRI and EEG results in the Tibet area, remains limited.

This study sought to provide data about the clinical features of epilepsy in the Ganzi Tibetan Autonomous Prefecture. Ganzi Tibetan Autonomous Prefecture is on the South-eastern edge of the Qinghai-Tibetan plateau, in the Western part of Sichuan Province. The average altitude is 3,500 meters above sea level. Tibetan is the primary ethnic group. With a population of one million, Ganzi Tibetan Autonomous Prefecture is the second largest inhabited region of Tibetan people in China. Many locals earn their living by farming or yak herding (3).

In this study, clinical records of patients admitted to Ganzi Tibetan Autonomous Prefecture People's Hospital and diagnosed with epilepsy were retrospectively reviewed. The study aimed at providing an updated information on the clinical features of epilepsy in the Tibetan area to help improve strategies for epilepsy prevention and management in this region.

MATERIALS AND METHODS

Study Location and Population

The Ganzi Tibetan Autonomous Prefecture People's Hospital is in Kangding City, Sichuan province, the capital of the Ganzi Tibetan Autonomous Prefecture. It is the only hospital equipped with MRI and Video EEG in Ganzi. West China Hospital, a large tertiary referral center in West China, has been sending a neurologist to the Ganzi Tibetan Autonomous Prefecture People's Hospital every year since 2014 to live and work with the local neurologists.

Study Design

Patients with epilepsy that were admitted to the Neurology Department of Ganzi Tibetan Autonomous Prefecture People's Hospital, between January 2015 and February 2018, were retrospectively and consecutively included in this study. To explore the clinical features of inpatients with epilepsy in Ganzi, demographic and clinical data collected were compared with the data from West China Hospital in Chengdu (control group). Controls' data were retrieved from in-patient epilepsy database of West China Hospital in Chengdu City between June 2017 and February 2018. PWE in Ganzi were identified and matched for gender, age (±2 years) in the controls database. In cases where there were several matched controls, the one with early admission date would be included.

The following definitions were considered: epilepsy is defined according to the 2014 International League Against Epilepsy (ILAE) as two spontaneous seizures with one occurring within the last 6 months, or one seizure with an epileptiform discharge shown by EEG or an enduring relevant lesion shown by imaging (4, 5).

Status epilepticus (SE) is defined according to the 2015 ILAE as a condition resulting from the failure of the mechanisms responsible for seizure termination or initiation of mechanisms which lead to abnormally prolonged seizures. Convulsive SE is defined as more than 5 min of continuous seizure or two or more discrete seizures with incomplete recovery between them (6).

Patients were excluded if they reported symptomatic seizures occurring <2 weeks after the onset of acute cerebral insults and if they lived outside of the Ganzi Tibetan Autonomous Prefecture.

Controls were excluded if they reported symptomatic seizures occurring <2 weeks after the onset of acute cerebral insults.

Socio-Demographic Status and Clinical Information

Data were collated retrospectively using a structured data collection form by reviewing the medical charts. All patients recruited had been diagnosed with epilepsy by two neurologists, from both the Ganzi Tibetan Autonomous Prefecture People's Hospital and West China Hospital. Differences in opinion were resolved by consensus. Demographic information included gender, age, marriage status, living area, education, job, and ethnicity were collected.

Clinical information was collected from all patients and the control. This included: age at the seizure onset, seizure frequency, and AEDs. The results of EEG and MRI/CT scans were reviewed and recorded. The MRI prescribed was a 1.5-T imaging system (Philips Achieva, Holland & Sonata, Siemens, Germany). Most patients in our clinic underwent neuroimaging as part of routine checks. Local or generalized slow waves in the EEG recording were considered non-specific abnormalities, while local or generalized paroxysms of sharp waves, spike waves, sharp and slow waves, or spike and slow waves were considered epileptiform discharges. Epileptic seizures were classified according to ILAE 2017 classification as focal seizures (focal aware seizures, focal impaired awareness seizures, or focal to bilateral tonic-clonic seizures), generalized seizures (non-motor, other motor or tonic-clonic), and unknown (7). Etiology was defined as the presence of remote brain injury that causes seizure episodes (8). Diagnosis was typically established on the basis of clinical history, past medical records, and laboratory results, and was further confirmed by neuro imaging. Etiology was classified according to ILAE 2017 classification as structural, infectious, genetic, metabolic, immune, and unknown etiology (7, 9). Specific etiologies were also listed, including neurocysticercosis, brain hydatidosis, stroke, head trauma, cerebral tumor, hippocampal sclerosis, cortical dysplasia, unclear intracranial space-occupying lesions, and so on.

The study was approved by the West China Hospital clinical trial and biomedical ethics committee and the ethics committee of the Ganzi Tibetan Autonomous Prefecture People's Hospital.

Data Analysis

Descriptive statistics of the patients and controls were conducted. Quantitative data were expressed as the mean ± SD. Qualitative data were summarized as proportions. A comparison of demographic and clinical data between the two groups was done using Student's *T*-tests/Mann Whitney *U* test for continuous variables and Chi-squared tests for categorical variables, respectively.

IBM SPSS 23.0 was used to perform all analyses. All of the tests were two-tailed, and *p*-values <0.05 were considered to be statistically significant.

RESULTS

Demographic Data of the Participants

One hundred and sixty-seven PWE were admitted to the Neurology Department of the Ganzi Tibetan Autonomous Prefecture People's Hospital from January 2015 to February 2018. Out of these, two patients were excluded because they were travelers living outside the Ganzi Tibetan Autonomous Prefecture. Hence, 165 patients were included in the study.

Our patient population included 96 (58.2%) men and 69 (41.8%) women. Other demographic features are listed in **Table 1**. The mean patient age was 39.4 ± 16.8 years. Forty-one (24.8%) patients lived in an urban location, and 124 (75.2%) lived in a rural/pastoral location. Most patients were Tibetan ($n = 128$, 77.6%) or Han Chinese ($n = 34$, 20.6%). The number of illiterate patients was 104 (63.0%), and 60.6% of the total patients were farmers.

A comparison of the demographic characteristics of the in-patients in Ganzi and gender and age-matched controls in Chengdu was done (**Table 1**). The comparison indicates that there were more patients in Ganzi who lived in rural/pasture areas compared to the controls (75.2 vs. 36.4%, $p < 0.001$) as well as lower education levels (the illiterate up to 63.0 vs. 1.2%, $p < 0.001$). There was also a significant difference in job groups ($p < 0.001$) and ethnic group distribution (77.6% Tibetan in Ganzi patients, $p < 0.001$). No differences were detected for the age, gender, and marital status.

TABLE 1 | Demographic features of PWEs in the neurology department of Ganzi people's hospital and control group from West China hospital.

Variable	PWEs in Ganzi $N = 165$	Control group $N = 165$	*P*-value
Gender, *n* (%)	–	–	1.000
Female	69 (41.8%)	69(41.8%)	–
Male	96 (58.2%)	96 (58.2%)	–
Age (year, mean ± SD)	39.4 ± 16.8	40.0 ± 17.0	0.721
Age group, *n* (%)	–	–	0.996
≤14 years	5 (3.0%)	5 (3.0%)	–
15–44 years	99 (60.0%)	97 (58.8%)	–
45–59 years	37 (22.5%)	38 (23.0%)	–
≥60 years	24 (14.5%)	25 (15.2%)	–
Marriage, *n* (%)	–	–	0.729
Married	109 (66.1%)	106 (64.2%)	–
Single	56 (33.9%)	59 (35.8%)	–
Living area, *n* (%)	–	–	0.000*
Urban	41 (24.8%)	105 (63.6%)	–
Rural/pastoral	124 (75.2%)	60 (36.4%)	–
Education status, *n* (%)	–	–	0.000*
Illiterate	104 (63.0%)	2 (1.2%)	–
Primary school and middle school	38 (23.0%)	77 (46.7%)	–
High school	15 (9.1%)	37 (22.4%)	–
College	8 (4.8%)	49 (29.7%)	–
Job, *n* (%)	–	–	0.000*
Not employed[b]	9 (5.5%)	41 (24.8%)	–
Student	17 (10.3%)	26 (15.8%)	–
Farmer	100 (60.6%)	30 (18.2%)	–
Employment	21 (12.7%)	46 (27.8%)	–
Retirement	7 (4.2%)	11 (6.7%)	–
Other	11 (6.7%)	11 (6.7%)	–
Ethnic Group, *n* (%)	–	–	0.000*[a]
Han	34 (20.6%)	158 (95.8%)	–
Tibetan	128 (77.6%)	5 (3.0%)	–
Yi	3 (1.8%)	2 (1.2%)	–

*$P < 0.05$.
[a] *Fisher exact test.*
[b] *Including housewife.*

Clinical Features

The mean age at the time of seizure onset was 34.5 ± 18.0 years. No significant difference was noted when this was compared with the data from the control group (**Table 2**). In addition, there were more patients newly diagnosed with epilepsy 104 (63.0%) compared to the control group (63.0 vs. 33.3%, $p < 0.001$). The different seizure types were as follows: focal aware seizures ($n = 5$, 3.0%); focal impaired awareness seizures ($n = 12$, 7.3%); focal to bilateral tonic-clonic seizures ($n = 96$, 58.2%); and generalized tonic-clonic seizures ($n = 46$, 27.9%). Thirty-three (20%) out of 165 patients were diagnosed with SE, while 2 (1.2%) died following prolonged SE. No significant difference in seizure type fund between groups (focal/generalized/unknown, $p = 0.087$). Most (98.8%) patients underwent an MRI or CT scan; abnormalities were noted in 102 (61.8%) patients. These were more than those in the control group (61.8 vs. 38.2%, $p < 0.001$). EEG or video EEG was performed in 51 (30.9%) patients. These were less than those in the control group (30.9 vs. 91.5%, $p < 0.001$). The results of the EEG studies revealed that 27 (52.9%) and 19 (37.3%) patients showed epileptiform discharge and normal EEG, respectively.

TABLE 2 | Clinical features of PWEs in neurology department of Ganzi people's hospital and control group from West China hospital.

Variable	PWEs in Ganzi *N* = 165	Control group *N* = 165	*P*-value
Age of onset (year, mean ± SD)	34.5 ± 18.0	31.9 ± 19.0	0.208
Admitted for status epilepticus, *n* (%)	33 (20.0%)	17 (10.3%)	0.014*
Death after status epilepticus	2 (6.1%)	0 (0%)	0.517[a]
Newly diagnosis	104 (63.0%)	55 (33.3%)	0.000*
Seizure type, *n* (%)	–	–	0.087*[b]
Generalized onset	47 (28.5%)	66 (40%)	–
Tonic-clonic	46 (27.9%)	65 (39.4%)	–
Nonmotor	1 (0.6%)	1 (0.6%)	–
Focal onset	113 (68.5%)	95 (57.6%)	–
Impaired awareness	12 (7.3%)	32 (19.4%)	–
Aware	5 (3.0%)	7 (4.2%)	–
Focal to bilateral tonic-clonic	96 (58.2%)	56 (33.9%)	–
Unknown onset	5 (3.0%)	4 (2.4%)	–
EEG, *n* (%)	51 (30.9%)	151 (91.5%)	0.001*
Normal	19 (37.3%)	87 (57.6%)	–
Non-specific abnormality	5 (9.8%)	26 (17.2%)	–
Epileptiform discharge	27 (52.9%)	38 (25.2%)	–
MRI/CT scan, *n* (%)	–	–	0.000*
Abnormal	102 (61.8%)	63 (38.2%)	–
Normal	61 (37.0%)	100 (60.6%)	–
Anti-epileptic drugs at the time of discharge, *n* (%)	–	–	0.000*
No treatment	18 (10.9%)	24 (14.5%)	–
Mono-therapy	129 (78.2%)	90 (54.5%)	–
Poly-therapy	18 (10.9%)	51 (31.0%)	–

*$P < 0.05$.
[a]*Haldane–Anscombe correction.*
[b]*Fisher exact test.*

The data collected also revealed that 61 (36.9%) patients had been diagnosed with epilepsy prior to hospitalization with 54 of these patients receiving prescriptions for AEDs. However, 38 (70.4%) patients reported irregular use of medication, significantly higher than the control group (70.4 vs. 22.5%, $p < 0.001$). Moreover, 5 cases of SE were precipitated by nonadherence to the medication regime. The mean duration of status epilepticus before admission was 15.5 h (range 0.5–48). Most patients in this study (97.0%) had active epilepsy (seizure free <1 year) (10).

Etiology

The etiological factors of epilepsy in Ganzi are summarized in **Table 3**. With the ILAE 2017 classification, 39.4% had a structural etiology, 24.8% had an infectious etiology, 4.8% had a presumed genetic cause, and 29.7% was classified as unknown.

As to specific causes of epilepsy, the leading cause was head trauma ($n = 34$, 20.6%), followed by stroke ($n = 18$, 10.9%), neurocysticercosis ($n = 13$, 7.9%), brain hydatidosis ($n = 11$, 6.7%) and tuberculous infection ($n = 9$, 5.5%). Other etiologies included presumed genetic cause ($n = 8$, 4.8%), viral infection ($n = 6$, 3.6%) and unclear intracranial space-occupying lesions ($n = 5$, 3.0%). Less common etiologies included tumor ($n = 3$, 1.8%), cortical dysplasia ($n = 4$, 2.4%), and hippocampal sclerosis ($n = 1$, 0.6%).

When compared with the control group, PWEs in Ganzi significantly had more frequent infectious etiology (OR = 4.216, 95% CI, 2.124–8.367). And epilepsy in Ganzi was caused more frequently by head trauma (OR = 1.994, 95% CI, 1.084–3.666), neurocysticercosis (OR = 29.301, 95% CI, 1.727–497.167) and brain hydatidosis (OR = 24.637, 95% CI, 1.439–421.670). Epilepsy in Ganzi was less frequently caused by hippocampus sclerosis (OR = 0.094, 95% CI, 0.012–0.747). The percentage of patients with unknown etiology in Ganzi was lower compared with the control group (OR = 0.532, 95% CI, 0.338–0.838).

DISCUSSION

The present study focused on the clinical features of epilepsy in the Ganzi Tibetan Autonomous Prefecture, which is currently under-studied. The aim is to obtain clinical information that would lead to improved strategies in prevention, management, education, and treatment of epilepsy in this region.

Status Epilepticus

Thirty-three PWE who were admitted to the hospital had SE. Two of them (6.1%) died in the hospital. The reported overall mortality is ∼20% in the first month after SE (11). However, in SE without provoked factors, the reported rate of death is ∼10% (11, 12). In the current study, we excluded acute symptomatic cases from our cohort. For the two fatalities recorded, it was noted that the SE lasted for more than 1 day before proper treatment was initiated. In addition, some people living in the remote county of the Ganzi Autonomous Tibetan Prefecture would require 2 days drive to reach the People's Hospital. This may have been the reason for delayed diagnosis and treatment. The mean duration of SE before admission was 15.5 h (range 0.5–48). It is therefore important that primary hospital physicians have to provide early diagnosis and control of SE. A survey done on attitudes and management practices of epilepsy among 100 primary practitioners in Ganzi, 2017, revealed that 49% did not know how to treat SE (unpublished data). It is therefore important to train primary practitioners and equip them with skills to control these cases.

TABLE 3 | General etiologic features of the epilepsy patients.

Etiology classification	PWEs in Ganzi $N = 165$	Control group $N = 165$	OR (95% CI)
Infectious	41 (24.8%)	12 (7.3%)	4.216 (2.124–8.367)*
Neurocysticercosis	13 (7.9%)	0 (0.0%)	29.301 (1.727–497.167)*[a]
Brain hydatidosis	11 (6.7%)	0 (0.0%)	24.637 (1.439–421.670)*[a]
Tuberculous	9 (5.5%)	3 (1.8%)	3.115 (0.828–11.721)
Viral infection	6 (3.6%)	8 (4.8%)	0.740 (0.251–2.183)
Brain abcess	2 (1.2%)	1 (0.6%)	1.974 (0.177–22.001)
Structural	65 (39.4%)	60 (36.4%)	1.137 (0.728–1.775)
Head trauma	34 (20.6%)	19 (11.5%)	1.994 (1.084–3.666)*
Stroke	18 (10.9%)	11 (6.7%)	1.714 (0.783–3.752)
Ischemic	11 (6.7%)	5 (3.0%)	2.285 (0.776–6.731)
Hemorrhage	7 (4.2%)	6 (3.6%)	1.174 (0.386–3.571)
Cerebral tumor	3 (1.8%)	6 (3.6%)	0.490 (0.120–1.996)
Hippocampus sclerosis	1 (0.6%)	10 (6.0%)	0.094 (0.012–0.747)*
Cortical dysplasia	4 (2.4%)	8 (4.8%)	0.487 (0.143–1.651)
Unclear intracranial space-occupying lesions	5 (3.0%)	3 (1.8%)	1.687 (0.396–7.179)
Other structural changes	0 (0.0%)	3 (1.8%)	0.143 (0.007–2.737)[a]
Metabolic	0 (0.0%)	0 (0.0%)	1.000 (0.019–50.699)[a]
Immune[b]	2 (1.2%)	3 (1.8%)	0.662 (0.109–4.018)
Presumed genetic cause[c]	8 (4.8%)	17 (10.3%)	0.443 (0.186–1.058)
Unknown	49 (29.7%)	73 (44.2%)	0.532 (0.338–0.838)*

*$P < 0.05$.
[a]*Haldane–Anscombe correction.*
[b]*Autoimmune encephalitis.*
[c]*Included Genetic Generalized Epilepsies.*

AED, Seizure Control and Medication Compliance

The findings of this study indicate that 63.0% of patients were newly diagnosed. Most of the patients who had been diagnosed with epilepsy previously had received AED treatment prior to hospital admission (54 out of 61 patients). However, 38 (70.4%) out of 54 patients reported irregular treatment. Majority of the of the 165 patients (97.0%), reported having active epilepsy (seizure free <1 year) (10). Previous studies have shown that medication compliance is poor in this region. One study reported that 87.5% of patients were not taking regular treatment (1). The factors that may contribute to non-compliance include: patients' perception of the importance of the medication or lack of regular doctor's appointments (13). Furthermore, many patients turn to traditional Tibetan treatment in the Tibet Autonomous Region (2). A survey on the attitudes toward epilepsy among the general population in Ganzi, 2017, revealed that up to 67% of patients preferred traditional Tibetan medicine because they thought it would work (unpublished data). The current study revealed that 78.2% of patients had mono-therapy prescriptions when discharged from Ganzi People's Hospital. However, follow up was not done to ascertain their compliance to the medication. Medication reminders (14) and educational programmes (13) may increase compliance in these patients.

Etiological Factors and Prevention of Parasite Infection

Two previous population-based studies from the Tibet Autonomous Region did not conclusively describe the etiology of epilepsy in the patient populations studied. This may be due to the unavailability of EEG and CT/MRI data (1, 2). One study reported that seven and three patients developed epilepsy due to head trauma and neurocysticercosis, respectively (1). Another study (2) identified one patient with head trauma, one with neurocysticercosis, and 35 patients with seizures associated with heavy drinking or alcohol withdrawal. However, about 80% of patients in both studies have unknown etiologies. A strength of the current study is that most patients in our study underwent CT/MRI scans, hence, we were able to identify more etiological factors than previous study. The leading cause in this study was head trauma (20.6%), followed by stroke (10.9%), neurocysticercosis (7.9%), brain hydatidosis (6.7%), and tuberculous infection (5.5%). Head trauma, stroke, cerebral infection are common causes for epilepsy. In the epidemiological survey of epilepsy in Rochester, Minnesota described the following etiological factors, such as cerebrovascular diseases (6%), neurologic deficits from birth (5%), trauma (5%), and infection (4%) (15). Head trauma, intracranial infection, and cerebrovascular diseases were the leading causes of epilepsy in a large population-based study in China in the 1980s (16). In comparison, the inpatient sample in Ganzi Tibetan area had parasite infection of the brain accounting for about 14.6% percent of all epilepsy patinets in this sample. This was higher than the age and gender matched control group. It was also significantly higher when compared with another etiology study in Chengdu (neurocysticercosis: 7.9 vs. 1.3%, OR 6.271, 95% CI 2.808–14.004; Brain hydatidosis: 6.7 vs. 0%, OR 132.864, 95% CI 7.788–2,266.400) (17). The adult of tapeworm live in the human intestine, and the intermediate hosts are pigs or yaks often found in this area. Humans often develop neurocysticercosis when they ingest raw meat containing cysts (18, 19). The adult of Echinococcus live in dogs or Tibetan foxes. Yaks serve as the intermediate hosts. Humans often get infected when they eat food contaminated with echinococcus eggs. Hydatidosis

could occur in liver, lung or brain (20). Both cysticercosis and hydatidosis are endemic diseases in Ganzi. One study has shown that 22.5% of the study participants had positive serology positive for cysticercosis in Yajiang County, Ganzi. Half of the seropositive patients were noted to experience seizures (18). Approximately an eighth (12.9%) of screened people were infected with hydatidosis in Shiqu County, Ganzi (21).

In the high pastures, many locals still live a traditionally pastoralism and semi-nomadism lifestyles, keeping dogs for herding animals. The domestic dog appears to be a key risk factor for both cystic and alveolar echinococcosis (20). Rates of echinococcosis infection in domestic dogs have been reported to be 5–15% in Tibetan area (22). Controlling the number of dogs and monthly praziquantel dog dosing programme is essential in preventing echinococcosis (20). Improvement of hygiene and promotion of hand-washing could also help in reducing infections (18).

Human taeniasis is acquired by eating uncooked or poorly cooked pork or beef infected with the larval form of the human taeniid tapeworms (19), there is a habitual consumption of undercooked beef and air-dried raw beef in this Tibetan community. Strategies to educate the locals on proper cooking of meat are important in the prevention of taeniasis (18).

Suprisely, the percentage of patients with unknown etiology was higher in the control group, suggesting that in-patients in Ganzi might have more identifiable seizure etiologies, such as infectious and structural changes. Hydatidosis is a critical and often fatal disease if left untreated (23). This study therefore proposes that all patients in this area with a new diagnosis of epilepsy should undergo a hydatidosis screen test.

The average altitude is 3,500 meters above sea level in Ganzi Tibetan Autonomous Prefecture. Excepted the two study in Tibet Autonomous Region which had been described above (1, 2), epidemiology of epilepsy in high altitude region was few (24), though there have been multiple case reports of seizures occurring in non-epileptic individuals and well-controlled epileptic patient at altitude (25–27). Still, the effect of altitude on the seizure threshold has not been studied in depth. This issue need to be explored more in future studies.

Gender and Age

Our study cohort comprised 58.2% male patients (male: female, 1.39:1). A door-to-door survey of six cities in China in 1987 regarding PWE reported a male-to-female ratio of 1.15:1 (16). An additional population-based survey in the Tibet Autonomous Region reported a male-to-female ratio of 1.73:1 (2). Our study may have a higher number of man than the number that is in the general population; however, our ratio is similar to those observed in previous studies that note a greater number of male patients than female patients.

Mean age of patients was 39.4 $\pm$ 16.8 years. The mean onset age was 34.5 $\pm$ 18.0. Our age group distribution was similar to that observed in previous population-based surveys in Tibetan area, with over half of the patients in the 15–44 years age group (1, 28). However, the predominant middle-age group in this study is unusual as compared to the bimodal age distribution reported in the literature (15, 28). This may be because many of them had infectious etiology, as the mean onset age of infectious etiology was 34.3 $\pm$ 15.1. Besides, Children <14 years of age were directed to the pediatrics department and hence most were not included in this study.

Semiology

In this cohort 28.5% of patients had generalized onset seizures and 68.5% of patients had focal onset seizures. Generalized tonic-clonic seizures and focal to bilateral tonic-clonic seizures were the most commonly observed seizure type. This result is consistent with the findings of previous studies in the Tibet Autonomous Region (1, 2). However, the EEG application rate for epilepsy diagnosis was 30.9% in our study, which is significantly lower than the control group in Chengdu. This may compromise the accuracy of diagnosis, in particular for seizure semiology. Though the EEG rate in the current study is higher than that in previous research conducted in the Tibetan area (1, 2), it would be beneficial to have a much higher EEG rate in future studies.

Study Limitations

This is a hospital-based cohort and a retrospective study. Children younger than 14 years old, who were typically admitted to the Pediatric Department, were not included. This admission bias and our study results may not apply to the entire population in the Ganzi region. In addition, we found that 30.9% patients underwent EEG for epilepsy diagnosis; therefore, the accuracy of seizure semiology may be reduced. Nonetheless, the present study provides useful imformation for future studies and can guide the development of strategies for managing epilepsy in the Tibetan region.

CONCLUSIONS

This study suggests that the control of endemic infectious diseases in local regions, such as cysticercosis, and hydatidosis, is important for better prevention of epilepsy. In addition, education about seizures for local primary doctors and patients will enable better management of epilepsy in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

DZ designed this study. JiaC and XW carried out this study; those two authors collected data, analyzed data, and contributed equally to this study. JiaC, YH, YD, JieC, WF, and YL helped in data collecting. SL helped analyzed results. ZZ, JP, and JM helped in EEG data analysis, JiaC wrote the draft and XW revised the final version.

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The Epidemiological Characteristics of Epilepsy in the Province of Khyber Pakhtunkhwa, Pakistan

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Previous studies have shown that Khyber Pakhtunkhwa, Pakistan has a high incidence of epilepsy and a high proportion of low socioeconomic background and high treatment gap. Considering the changes over the past 20 years little is known about the current epidemiological characteristics of epilepsy in Khyber Pakhtunkhwa, Pakistan. The current study was focused to find the impact of various contributing factors on the clinical response to anti-epileptic drugs in the KP population, Pakistan. A total of 315 participants aged 19.1 ± 8.6 years were examined. Mean age of the patients was 18 ± 8.1 year. Epilepsy was high in male patients (64.39%) and urban areas (60.1%). Mostly, 88.6% of patients were belonging to low socioeconomic status background. 42.4% patients have positive family history for epilepsy and 42.8% patients had consanguineous marriages. Middle SES class patients (OR, 2.22 [CI, 0.54–9.1]) were slightly associated with controlled response to CBZ and VPA therapy. Absence seizure (OR, 1.16 [CI, 0.59–2.3]), and Complex partial seizure (OR, 1.29 [CI, 0.58–6.3]) showed good response to CBZ therapy while, Myoclonic seizure (OR, 2.23 [CI, 0.05–8.8]) was responsive to VPA therapy. However, non-compliance (R^2 0.82, $P < 0.0001$) and nature of seizures (R^2 0.83, $P < 0.0001$) were associated with the high risk for poor response to both CBZ and VPA therapy. Epilepsy was high in male patients and in urban areas. Most patients were belonging to low socioeconomic status. Non-compliance, low socioeconomic and nature of seizures strongly predict poor clinical response of anti-epileptic drugs therapy.

Keywords: epilepsy, demographics, clinical outcome, social profile, socioeconomic status, types of seizures, carbamazepine, valproic acid

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INTRODUCTION

Epilepsy is a neurological disease, which is characterized by recurrent seizures that may occur suddenly without any provoking factors (1). Approximately 70 million people are suffering from epilepsies throughout the world. Epilepsy contributes 1% burden to global diseases while this contribution is 80% in the developing countries (2). Both developing and developed countries have different health-care priorities according to the need for primary prevention, to the recognition of seizures, and access to sustainable and appropriate therapy. Different approaches are used to properly treat epilepsy in the context of regional resources depend on the prevalence of a disease. Diversities in demographic factors such as gender (3), race (4), age (3), geographic area (5), religion, and culture (5) along with provoking factors are associated with poor responsive epilepsy.

Demographic and clinical factors have a crucial role in the management of epilepsy. False believes, low SES have a very important role in the poor management of epilepsy. Similarly, consanguineous marriages among the positive family history for epilepsy can increase the burden of epilepsy in a society. It is well-known that the incidence of epilepsy is linked to low socioeconomic status, positive family histories of epilepsy, limited access to health care system and environmental factors (6). Reports suggest that socioeconomically deprived people are more susceptible to epilepsy. The association is strongly supported by the facts that the incidence of epilepsy is high in developing countries as compared to developed countries (7). Several other studies also corroborate that socioeconomic status (SES), positive family history and poor compliance has an established association with resistant epilepsy (8–10). Health related quality of life (HRQL) is associated to proper response to AEDs and it has been reported that clinical response may vary across epileptic patients with different clinical, demographic, and socioeconomic variations (11, 12). With regard to clinical variables, seizures types and frequency have been found to be significant predictors of HRQL scores and clinical response (5, 13, 14). It has been found that psycho-social factors is also related to quality of life (QOL) in Korean epilepsy patients. Good QOL is directly related to better clinical response to AEDs and recognition of these factors will lead health professionals to develop different strategies to improve the QOL of these patients (15). Common clinical factors, seizure frequency, is closely associated with poor outcomes, QOL, and mortality (16). As these above variables are associated with epilepsy. Therefore, it has been suggested that demographic factors, gender difference, culture aspects, beliefs in different religion, geographic variations, and SES of an patients with epilepsy may also affect clinical response of a drug and will widen treatment gap. These are the factors in which interventions are very easy and treatment response can be improved which can reduce the treatment gap. Therefore, the purpose of the present study is used to examine the impact of these factors on the clinical outcomes of CBZ and VPA therapy in epileptic in Pakhtun population of Khyber Pakhtunkhwa, Pakistan. It will help us to improve the clinical response to carbamazepine and valproic acid therapy by exploring the impact of demographic and social profile of the patients during treatment.

MATERIALS AND METHODS

Study Design and Protocol

Patients with epilepsy sample size ($N = 323$) was calculated at 95% CI with SD of 8 and marginal error of 1. Keeping in view 20% drop out total patients included in the study were 315. Patients from Khyber Pakhtunkhwa, Pakistan who visited the Neurology Department of Government Lady Reading Hospital for opting treatment were included in the study on consent, assent, and surrogate assent form. The study was started in August 2014 and completed in April, 2016. The study was executed according to the CONSORT flow chart presented in **Figure 1**.

Ethics Board of the Khyber Medical University, Peshawar approved the study via no: DIR/KMU-EB/AC/000047 dated 04/07/2014. The study was conducted according to Helsinki declarations. The data was collected on a standard questionnaire designed according to the protocol of the WHO which includes all those necessary information to reduce the biases in the study.

Mean dose of carbamazepine was 452 mg/day and valproic acid 859 mg/day and was titrated for better management of epilepsy at scheduled visits.

Inclusion Criteria

Patients with epilepsy who were suitable candidate for carbamazepine and valproic acid as monotherapy or polypharmacy for first time or newly diagnosed for epilepsy were enrolled in the study. Patients with epilepsy who were willing to participate in the study after explaining the steps and the aim of the study in the context of local language were included in the study upon consent and surrogate consent form. Seizures provocative factors were controlled by proper counselling of the patients and ensure proper clinical response to CBZ and VPA as monotherapy or polypharmacy.

Exclusion Criteria

Patients with epilepsy were not included in the study who was not suitable candidate for carbamazepine and valproic acid as monotherapy or polypharmacy. Patients were also excluded from the study that was not willing to participate in the study or were suffering from some other co-morbidity. Non-compliant patients were also excluded from the study.

Assessments of Seizure Characteristics and Socioeconomic Status

Types of epilepsy were diagnosed according to guidelines of International League against Epilepsy (ILAE), witness presentation; family history; EEG report and expert opinion of concern OPD/Ward neurologists. All available information was considered in the classifications of seizures, including the medical record, interviews, EEG, and brain imaging. The SES of patients was are classified as reported by Association American Psychology report 2011 (17). The higher Socioeconomic class will have 50–100 and above, Middle class 15–49, and Low economic class will have below 15 Per capita monthly income limits (Rs.) (17).

Measurement of Seizure Control in Patients With Epilepsy

Seizures' control was recorded in the form of reduction of frequencies of seizures using standardized proforma in local language. The numbers of seizures per week were recorded at baseline and these patients were then evaluated for seizure control at 3rd and 6th month of the therapy. The patients with epilepsy compliance to the medication were checked by counting the pills remaining in the strip on scheduled visits. Drug response was determined as either freedom from seizures or reduction in

Abbreviations: AEDs, Anti-epileptic drugs; CBZ, Carbamazepine; HRQL, Health related quality of life; ILAE, International League against Epilepsy; QOL, quality of life; SES, Socioeconomic Status; VPA, Valproic Acid.

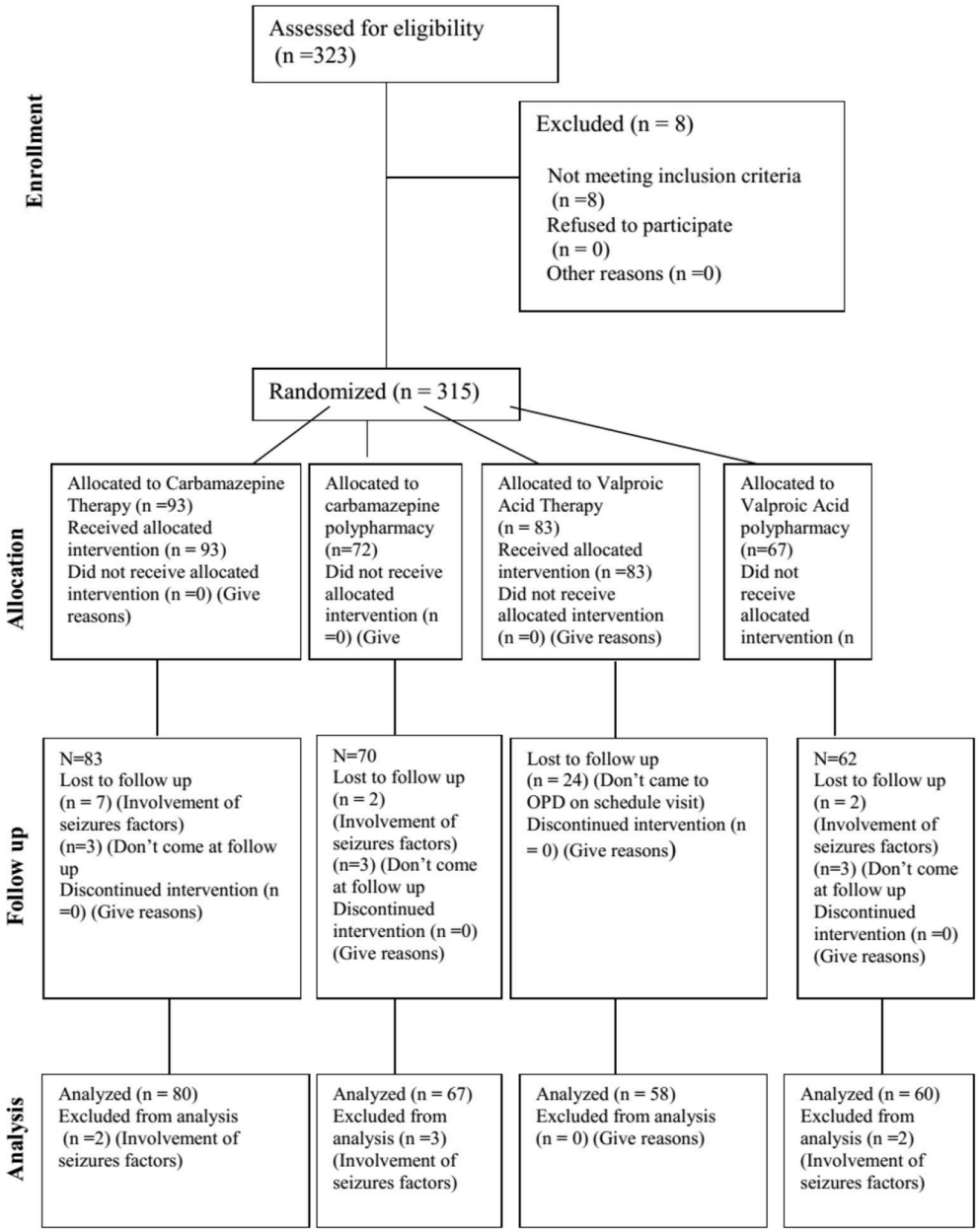

FIGURE 1 | CONSORT diagram. CONSORT diagram showing the flow of participants through each stage of a randomized trial.

number of seizure per week after initiation of carbamazepine and valproic acid therapy at 3rd and 6th month.

Statistical Analysis

The distribution of age, clinical, and demographic characteristic of epileptic patients were presented in the form of percentage. The Mean ± SD were determined for age. The expected outcome (EXP B) was determined using univariate logistic regression analysis. The prediction of clinical response with respect to all variables was determined using multivariate regression analysis by incorporating step by step variables and to determine the combined as well as individual impact of each variable on clinical outcomes of CBZ and VPA as monotherapy or polypharmacy. SPSS 20 and Stata version 12 was used for analysis.

RESULTS

Demographic Features of Epileptic Patients

Mean age of epileptic patients were 19.1 ± 8.6 years (range 1–42) (**Table 1**). The prevalence of epilepsy was higher in patients having age of 10–20 years. Epilepsy was high in male (64.39%)

TABLE 1 | Age and gender wise distribution of epilepsy in 315 epileptic patients.

Age range (years)	Total Number, *n* (%)	Mean age ± SD	Male, *n* (%)	Female, *n* (%)
1–10	47(14.9)	7.3 ± 2.5	22 (46.8)	25 (53.2)
11–20	165 (52.4)	16.1 ± 2.8	102 (61.8)	63 (38.2)
21–30	69 (22.7)	24.3 ± 2.6	45 (75.0)	11 (25.0)
31–40	31 (21.9)	33.5 ± 3.0	21 (67.7)	10 (32.3)
41–50	3 (0.95)	46.3 ± 5.1	2 (66.7)	1 (33.3)
Total	315	19.1 ± 8.6	200 (63.5)	115 (36.5)

TABLE 2 | Demographic and clinical features of epileptic patients.

Demographic data	Patients (*N* = 315), *n* (%)
Male	200 (63.5%)
Female	115 (36.5%)
Urban	181 (57.5%)
Rural	134 (42.5%)
Cousin marriages	148 (46.9%)
Non cousin marriage	167 (53.1%)
Family history Positive	135 (42.9%)
Family history Negative	180 (57.1%)
Employee	22 (6.9%)
Labor	293 (93.1%)
Know about epilepsy	239 (75.9%)
Don't Know about epilepsy	76 (24.1%)
Educated Patients (Middle grade)*	41 (13.0%)
Uneducated patients	274 (87.0%)
Low SES	261 (82.7%)
Middle SES	54 (17.3%)
1-Pre-school system (3–5 Years)	
2-Primary (Grade 1–5)	
3-Middle (Grade 6–8)	
4-High (Grade 9–10)	
5-Intermediate (Grade 11–12)	

**Grading system of educational level.*

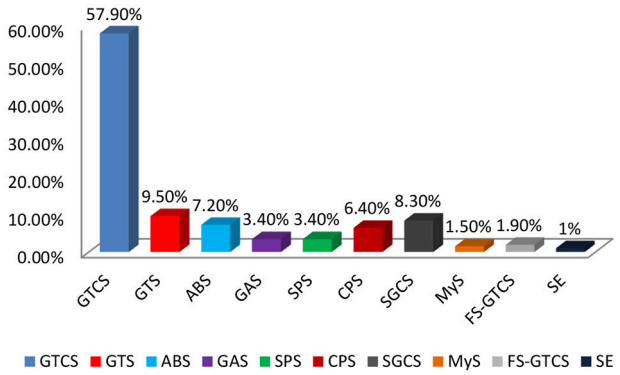

FIGURE 2 | Types of seizures in Pakhtun population.

TABLE 3 | Impact of different factors on clinical response of CBZ and VPA therapy.

Variables	Exp (B) or (OR)	CI (95%)
Gender	1.18	0.63–2.2
Area	0.67	0.36–1.2
Cousingenous marriages	0.91	0.50–1.6
Family history	0.84	0.45–1.5
Perception	0.69	0.32–1.4
Education	1.84	0.50–6.7
SES	2.22	0.54–9.1
Compliance	0.66	0.32–1.3
Generalized tonic clonic seizure	0.58	0.03–10.0
Generalized tonic seizure	0.98	0.04–20.0
Absence seizure	1.16	0.59–2.3
Generalized atonic seizures	0.81	0.02–6.8
Simple partial seizure	0.44	0.02–11.5
Complex partial seizure	1.29	0.58–6.3
Secondary generalized complex seizure	0.22	0.01–4.9
Myoclonic seizure	2.23	0.05–8.8
Febrile seizure	0.29	0.08–10.1
Status Epilepticus	0.31	0.25–1.8

The reference category is poor controlled seizure, EXP (B) mean expected value of prediction using univariate regression analysis.

than female (35.98%) patients in study population (**Table 2**). The percentage of cousin marriage and positive family history of epilepsy was (42.8%) and (42.4%) (**Table 2**). The level of education was very low in these patients. Furthermore, these patients were having low socioeconomic status (SES) (88.63%).

Phenomenology

Types of seizures were classified according to the ILAE guidelines and clinical presentation of patients with epilepsy. Generalized tonic clonic seizures was commonly observed 153 (57.9%) during this study in epileptic patients of KP (**Figure 2**). Other types of seizures were Generalized tonic seizures 25 (9.5%), Absence seizures 19 (7.2%), Generalized atonic 8 (3.4%) secondary generalized complex seizures 22 (8.3%), simple partial seizures 9 (3.4%), and complex partial seizures 17 (6.4%) were found in the target population (**Figure 2**).

Impact of Demographic and Clinical Features vs. Response of Anti-epileptic Drugs

The association of different demographic variables with clinical outcome were determined using univariate logistic regression analysis (**Table 3**). It has been found that high education level were slightly associated with controlled response (OR, 1.84 [CI, 0.50–6.7]) to CBZ and VPA as monotherapy or polypharmacy. Similarly, good SES was also associated with good response (OR, 2.22 [CI, 0.54–9.1]) to CBZ and VPA as monotherapy or polypharmacy. Absence seizure (OR, 1.16 [CI, 0.59–2.3]), Complex partial seizure (OR, 1.29 [CI, 0.58–6.3]), and Myoclonic seizure (OR, 2.23 [CI, 0.05–8.8]) showed a good response to CBZ and VPA as monotherapy or polypharmacy (**Table 3**).

Similarly, multivariate regression models were applied to demographic variables to predict clinical response of CBZ and VPA as monotherapy or polypharmacy in epileptic patients. Over all the factors added in Model 9 (R^2 0.82, $P < 0.0001$) and model 10 (R^2 0.83, $P < 0.0001$) were found to increase the risk of poor response to AEDs.

DISCUSSION

In our study the prevalence rate of epilepsies was high in male patients where most of them were belonging to urban areas. Our observations were in line to Khan et al. (18) that epilepsy was high in male population and urban areas (18). Though we found an inverse figure as reported by Mohammad et al. where epilepsy is more prevalent in female than male patients in Iran (19). We found that epilepsy was common in patients having age group of 10–20 years. These findings were in line with the reports of previous studies conducted in Pakistan and India (20–26). The percentage of consanguineous marriages and positive family history of epilepsy was high in the study population. The SES of most patients observed in our study was very low. Heaney et al. observed that low SES has an association with epilepsy because of low quality of life increased the susceptibility of an individuals to different provoking factors of epilepsy (27). Other studies also show that low SES was associated with an increased risk for epilepsy in individuals with seizures of unknown etiology (28–35). Luengo et al. reported that genetic history of patients with epilepsy have a 2.5 times higher risk for epilepsy in their coming generation (36). GTCS was common among other types of seizures in the target population which is in line with Nowshad et al. observations (18). It has been found that clinical outcome in patients with absence seizures and myoclonic seizures were good compared to other types of seizure. Poor response was also high in non-compliance patients. Regression model showed that poor compliance and nature of seizures significantly associated with poor response to CBZ and VPA as monotherapy or polypharmacy even at optimal adjusted dose of CBZ and VPA as monotherapy or polypharmacy. Thomson et al. (38) stat that compliance has a direct association with seizure response (37, 38). Dragoumi et al. (39) demonstrate that types of seizure also affect clinical outcome in epileptic patients (39). If patients show non-compliance with therapy and do not take their AEDs according to prescription then it leads to poor clinical outcome. Similarly, low SES of patient is also a hurdle in proper compliance and lead to poor clinical response. Low SES also responsible for large treatment gap. Nature of seizure is also a main factor for resistant epilepsy.

LIMITATIONS AND STRENGTH OF THE STUDY

It is a hospital based study which doesn't show the clear picture of whole society. It has an advantage that this study will provide the platform to conduct a community based study to determine the prevalence and stigmatization of epilepsy.

CONCLUSION

Male patients were having a high prevalence (64.39%) of epilepsies where 60.1% were from urban areas. Epilepsy was high in patients with age ranging 11–20 years. Positive family history of epilepsy and consanguineous marriages was the key characteristics of the epileptic patients. Non-compliance and nature of seizures strongly predict poor clinical response of Anti-epileptic drugs therapy.

AVAILABILITY OF DATA AND MATERIAL

The analyzed dataset during the current study will be provided from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

SU carried out experimental work as Ph.D. Scholar. Also prepared the 1st draft of manuscript. NA extensively revised the manuscript. He is also designed the study and wrote the research project. AK helped in diagnosis and patients follow up for their seizures control. SA helped in Clinical scoring of epilepsies. HN helped in experimental work. All authors approved the final version of manuscript.

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High Low-Density Lipoprotein Cholesterol Inversely Relates to Dementia in Community-Dwelling Older Adults: The Shanghai Aging Study

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Background: The relationship between cholesterol and cognitive function is unclear from the previous studies. This study was conducted to explore this association in older Chinese adults.

Methods: Data were from the Shanghai Aging Study, comprising 3,836 residents aged 50 years or over in an urban community. Diagnoses of dementia and mild cognitive impairment were established according to the fourth edition of diagnostic and statistical manual of mental disorders (DSM-IV) and Petersen criteria. Multivariate logistic regression models, non-matched and propensity score (PS) matched, were used to examine the association between cholesterol levels and cognitive function.

Results: There was a significantly higher proportion of participants with low levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) in the dementia group than in groups without dementia ($P < 0.05$). High LDL-C level was inversely associated with dementia, with a negative trend in the PS matched model. TC and high density lipoprotein cholesterol (HDL-C) were not significantly related to dementia in either non-matched models or PS matched models.

Conclusion: Our result indicates that high level of LDL-C is inversely associated with dementia. High level of LDL-C may be considered as a potential protective factor against cognition decline.

Keywords: low density lipoprotein cholesterol, cognitive impairment, dementia, population-based study, propensity score matching

INTRODUCTION

Dementia is a progressive brain disorder accompanied by a deterioration in memory and thinking, and often with a decrease in motivation and emotional and language problems. It has physical, mental, economic, and social effects, not only on the patients but also on their careers, their families and society at large. Worldwide, there are over 50 million prevalent dementia cases, and

nearly 10 million new cases are diagnosed per year (1). It is estimated that the existing worldwide costs of dementia are US $818 billion in 2017 and that it will become a trillion-dollar disease by 2018—equivalent to the world's 18th largest economy (2).

The brain contains 25–30% of the total body cholesterol. As one of the most essential components of neurons, cholesterol is of great importance to develop and maintain neuronal plasticity and function (3). Studies from western countries have investigated how cholesterol levels related to cognitive impairment, but have yielded inconsistent and conflicting results. In China, only a few studies have investigated the relationship between cholesterol and cognitive impairment among older community residents. The results were varied due to different study design and target population. A cross-sectional study with 597 participants in southwest China has reported that low (TC) (OR = 0.94) and (LDL-C) (OR = 0.94) were associated with mild cognitive impairment (MCI) after adjusting for age, gender and education (4). Another cross-sectional study involving 2,000 community dwellings in eight longevity areas found that higher cholesterol, including TC (OR = 0.73), LDL-C (OR = 0.82), and (HDL-C) (OR = 0.81), was associated with better cognitive function in the oldest old (5). Furthermore, an inversely U-shaped effect of TC on cognition has been observed in a multicenter study with 1,889 people aged 65 years and over from four rural counties (6).

The Shanghai Aging Study is a population-based cohort study with a design, operational procedures and diagnostic criteria similar to most cohort studies in western countries. The study is intending to examine the prevalence and incidence of dementia and MCI as well as their risk and protective factors (7). We analyzed the baseline data of this cohort to explore the association between cholesterol levels and cognitive function among older community dwellers in urban China.

METHODS

Study Population

Between January 2010 and December 2012, 3,836 residents aged ≥50 years were recruited from Jingansi community in central downtown Shanghai, China. Participants were excluded from the study if they were (1) living in nursing homes or other institutions; (2) experiencing mental deficiency or severe schizophrenia, according to their medical record or diagnoses from neurologists; or (3) having severe impairment of hearing, vision, or verbal such that could not accomplish the neuropsychological evaluation. Detailed recruitment procedures were published previously (8).

This study was approved by the Medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China (approval number: HIRB2009-195). All participants and/or their legally acceptable representatives provided signed written informed consent to participate this study.

Characteristics and Medical History

Demographic and lifestyle characteristics were collected via a face-to-face questionnaire survey. Data included age, sex, education background, and smoking habits (smoking: regular cigarette smoking more than 1 year). Participants' heights and weights were measured and were used to calculate body mass index (BMI). History of hypertension, diabetes, stroke, and coronary artery disease was collected and confirmed with participants' medical records.

Laboratory Test

A 2-ml blood sample was collected from each participant by research nurses in the morning after 12 h overnight fasting. Blood samples were sent to the central laboratory in Huashan hospital. Cholesterol profiles were measured from serum by Hitachi 7600 full automatic biochemical analyzer. TC was measured with oxidase method and LDL-C and HDL-C were measured with direct method.

Neuropsychological and Neurological Assessments

Considering different cultural backgrounds, neuropsychological tests from western countries were translated, adapted and normalized for the Chinese population. Tests applied in our study evaluated global cognition, attention, memory, language, executive function, and spatial construction function of each participant. The tests included: (1) the Mini-Mental State Examination (MMSE); (2) the Conflicting Instructions Task (Go/No Go Task); (3) the Stick Test; (4) the Modified Common Objects Sorting Test; (5) the Auditory Verbal Learning Test; (6) the Modified Fuld Object Memory Evaluation; (7) the Trail-making test A&B; (8) the Renminbi (official currency of China) Test, translated from the EURO test. Participants with at least 6 years of education were given tests 1 to 5 and 7, whereas those with <6 years of education were given tests 1 to 4 and 6 and 8 (**Figure 1**). Normative data and more details on these tests were reported elsewhere (8).

The motor responses and reflexes of participants were examined by neurologists. The Center for Epidemiologic Studies Depression and Scale (CESD) (9) was used to evaluate the depression status of participants within the previous week and a major depressive episode was defined as CESD ≥ 16. The Clinical Dementia Rating (CDR) (10) and the Lawton and Brody Activity of Daily Living (ADL) (11) were also conducted to assess the cognitive complaints and the ability to perform activities of daily living and physical self-maintenance.

Diagnoses of Cognitive Function

The consensus diagnosis of cognitive function was made by an expert panel (two neurologists, one neuropsychologist, and one neuro-epidemiologist) on the basis of all available information for each participant, including medical, neuropsychological, and neurological data and where possible computed tomography (CT) and magnetic resonance images (MRI) scans. Dementia was diagnosed according to DSM-IV criteria (12). A diagnosis of MCI, referring to Petersen's criteria (13), was considered only for subjects without dementia.

APOE Genotype Assessment

Because the APOE-ε4 variant has been found as the largest known genetic risk factor for Alzheimer's disease in a variety of

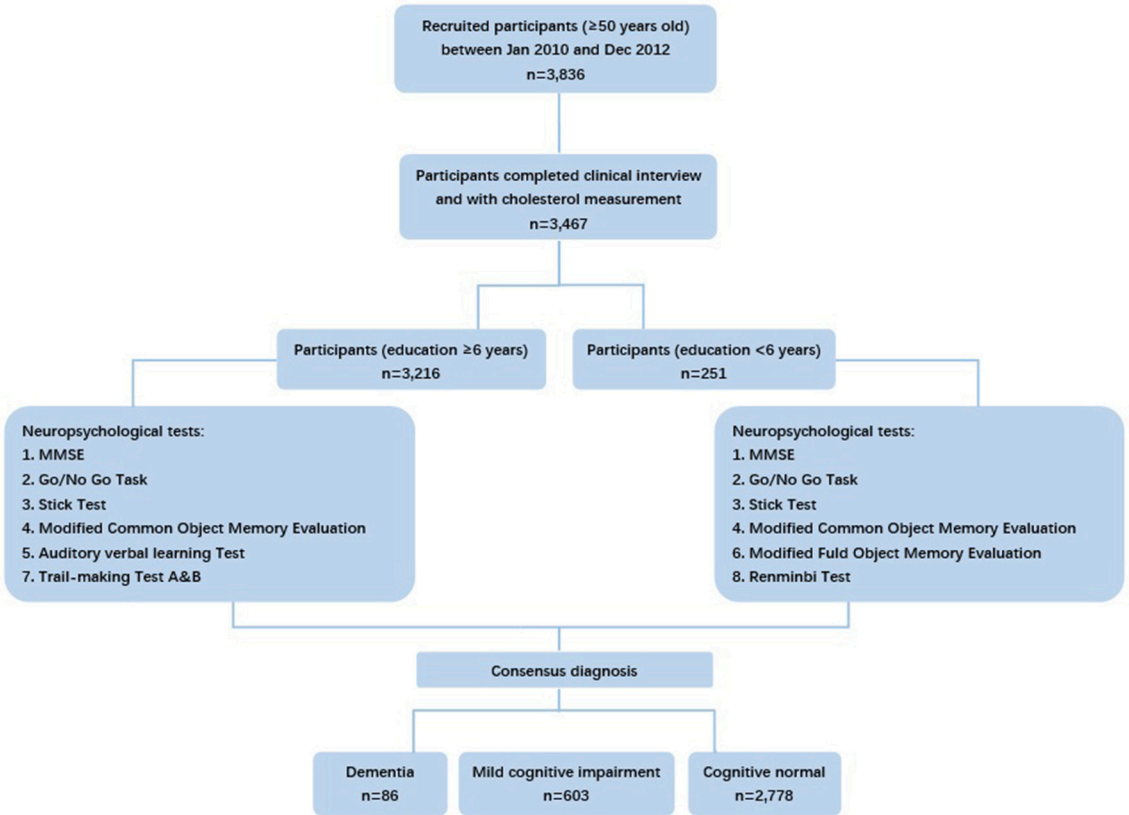

FIGURE 1 | Flowchart of participants' recruitment and deciding neuropsychological tests in our study.

ethnic groups (14), we assessed APOE genotype in our cohort. The extraction of DNA from blood or saliva samples and the assay of APOE genotyping through the TaqmanSNP method (15) were conducted in the central laboratory in Huashan hospital. APOE-ε4 positivity was defined by the occurrence of one or two ε4 alleles.

Statistical Analysis

TC, LDL-C, and HDL-C values were divided into three levels according to tertiles (5): low TC level, <4.87 mmol/L; moderate TC level, 4.87–5.72 mmol/L; high TC level, >5.72 mmol/L; low LDL-C level, <2.9 mmol/L; moderate LDL-C level, 2.9–3.7 mmol/L; high LDL-C level, >3.7 mmol/L; low HDL-C level, <1.17 mmol/L; moderate HDL-C level, 1.17–1.45 mmol/L; and high HDL-C level, >1.45 mmol/L. Differences in characteristics among groups with different cognition status (normal, MCI, or dementia) were evaluated with Kruskal–Wallis test for continuous variables and Cochran–Mantel–Haenszel statistics for categorical variables (16, 17).

Multivariate logistic regression models (non-matched models) were used to examine the association between cholesterol levels and cognition status (MCI or dementia compared with normal). TC, LDL-C, and HDL levels were included in the logistic model as dummy variables, with the low level group used as the reference to estimate the odds ratio (OR) and 95% confidence interval (CI), and with adjustment for covariates such as age, sex, years of education, BMI, depression, diabetes, stroke, hypertension, and APOE-ε4 genotype.

PS methods are being used to reduce the impact of treatment selection bias in the estimation of causal treatment effects using observational data (18). They also can be used to estimate the relationship between any non-randomized factors (19). The PS is the estimated conditional probability of assignment to a particular "treatment" given a series of vector covariates (20). In our study, PS matching was applied to reduce the bias due to non-random exposures (cholesterol levels) and potential confounders; the conditional probability of assignment to moderate levels of cholesterol was chosen as the PS. Matching was conducted in a stepwise fashion. First, we matched the PS in the low cholesterol group with those in the moderate cholesterol group, with 0.05 as a caliper (upper limit of the allowed difference in the scores). Subsequently, the scores in the high cholesterol group were matched to the effective matched pair from the first step, and the mean difference between the high cholesterol group and the other two groups was also not allowed to exceed 0.05. Finally, we obtained matched subgroups with a more balanced distribution of covariates. Multivariate logistic regression models (PS matched models) were then performed by using the PS matched subgroups in a sensitivity analysis, with adjustment of the same covariates as in non-matched models.

All analyses were conducted by SAS 9.4 (SAS Institute Inc., Cary, NC, United States). $P < 0.05$ (two-tailed) were considered statistically significant.

RESULTS

The full analysis set of this study comprised 3,467 participants who had completed diagnosis of cognition and measurement of TC, LDL-C, and HDL-C (**Figure 1**). As shown in **Table 1**, the analyzed participants were characterized by old age (mean [SD] = 69.4 [8.0] years old) and relatively high level of education (mean [SD] = 11.7 [4.0] years). Among them, 86 were diagnosed as dementia and 603 were diagnosed as MCI. The characteristics of age, education, MMSE, history of stroke, hypertension, diabetes, depression, and APOE-ε4 allele carrier status were significantly different among the normal, MCI, and dementia groups.

Significant differences in the category distributions of TC and LDL-C were found in groups with different cognition status. The lowest proportion was found in participants with dementia who had high level of TC (26.7%) and LDL-C (23.3%).

After adjusting for age, sex, years of education, APOE-ε4 genotype, BMI, depression, diabetes, hypertension and stroke, the non-matched models indicated that the OR of high LDL-C level (OR [95%CI] = 0.56[0.30, 1.04]) had an upper limit awfully close to the null threshold. A U-shaped relationship between HDL-C levels and ORs was found (P for trend = 0.0084) despite of the non-significant effect of HDL-C on dementia when the low level acted as the reference (**Table 2**). The effects of all the covariates adjusted were showed in the **Supplementary Material**.

The inverse associations were significant between high LDL-C level and dementia, whereas the associations between TC or HDL-C levels and dementia remained non-significant, according to the PS matched models (**Table 2**). In addition, the effect of LDL-C was higher than that in the non-matched

TABLE 1 | Characteristics and cholesterol profiles in 3,467 Chinese adults with different diagnoses of cognition at baseline.

	Total (*N* = 3,467)	Normal (*N* = 2,778)	MCI (*N* = 603)	Dementia (*N* = 86)	*P* value[#]
Sex, female, n (%)	1,893 (54.6)	1,511 (54.4)	331 (54.9)	51 (59.3)	0.4772
Age, year, mean (SD)	69.4 (8.0)	68.5 (7.5)	72.4 (8.7)	78.2 (7.7)	<0.0001**
BMI, mean (SD)	24.3 (3.4)	24.3 (3.4)	24.4 (3.6)	24.0 (3.9)	0.5424
Education, year, mean (SD)	11.7 (4.0)	12.2 (3.7)	10.1 (4.6)	8.0 (6.0)	<0.0001**
Smoking, n (%)	377 (10.9)	297 (10.7)	75 (12.5)	5 (5.8)	0.9500
Stroke, n (%)	377 (10.9)	275 (9.9)	87 (14.5)	15 (17.7)	0.0001**
Hypertension, n (%)	1,769 (51.2)	1,370 (49.4)	339 (56.6)	60 (70.6)	<0.0001**
Diabetes, n (%)	460 (13.3)	344 (12.4)	104 (17.4)	12 (14.1)	0.0064**
APOE-ε4 (+), n (%)	589 (17.7)	456 (17.0)	114 (20.0)	19 (22.6)	0.0349*
Depression, n (%)	599 (17.3)	439 (15.9)	135 (22.5)	25 (29.1)	<0.0001**
ADL, mean (SD)	20.7 (4.2)	20.3 (2.3)	21.1 (4.7)	32.0 (15.8)	<0.0001**
MMSE, mean (SD)	28.0 (2.7)	28.6 (1.6)	26.8 (2.7)	16.8 (5.5)	<0.0001**
TC, mmol/L, mean (SD)	5.4 (1.0)	5.4 (1.1)	5.3 (1.0)	5.2 (1.0)	0.1153
LDL-C, mmol/L, mean (SD)	3.3 (0.9)	3.3 (0.9)	3.3 (0.9)	3.2 (1.0)	0.0921
HDL-C, mmol/L, mean (SD)	1.3 (0.3)	1.3 (0.3)	1.3 (0.4)	1.4 (0.3)	0.6733
TC, category					0.0290*
Low	1,148 (33.1)	902 (32.5)	211 (35.0)	35 (40.7)	
Moderate	1,169 (33.7)	935 (33.7)	206 (34.2)	28 (32.6)	
High	1,150 (33.2)	941 (33.9)	186 (30.9)	23 (26.7)	
LDL-C, category					0.0221*
low	1,073 (31.0)	843 (30.4)	193 (32.0)	37 (43.0)	
Moderate	1,307 (37.7)	1,047 (37.7)	231 (38.3)	29 (33.7)	
High	1,083 (31.3)	884 (31.9)	179 (29.7)	20 (23.3)	
HDL-C, category					0.5419
Low	1,148 (33.2)	918 (33.1)	203 (33.7)	27 (31.4)	
Moderate	1,175 (33.9)	951 (34.3)	199 (33.0)	25 (29.1)	
High	1,140 (32.9)	905 (32.6)	201 (33.3)	34 (39.5)	

[#]*Comparison among groups with different diagnoses of cognition.*

**P-value < 0.05, ***P-value < 0.01.*

MCI, mild cognition impairment; BMI, body mass index; MMSE, Mini-Mental State Examination; APOE-ε4 (+), ApoE-ε4 allele positive; ADL, Activities of Daily Living; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

TC: low, <4.87 mmol/L; moderate, 4.87–5.72 mmol/L; high, >5.72 mmol/L.

LDL-C: low, <2.9 mmol/L; moderate, 2.9–3.7 mmol/L; high, >3.7 mmol/L.

HDL-C: low, <1.17 mmol/L; moderate, 1.17–1.45 mmol/L; high, >1.45 mmol/L.

TABLE 2 | Odds ratios for TC, LDL-C and HDL-C among participants with dementia vs. normal, and with mild cognitive impairment vs. normal, by non-matched and PS matched models.

	Non-matched Models						PS Matched Models					
	MCI vs. Normal			Dementia vs. Normal			MCI vs. Normal			Dementia vs. Normal		
	n	OR (95%CI)	P for trend	*n*	OR (95%CI)	P for trend	*n*	OR (95%CI)	P for trend	*n*	OR (95%CI)	P for trend
TC			0.6118			0.2349			0.7690			0.1290
Low	1,063	1.00 (reference)		899	1.00 (reference)		720	1.00 (reference)		612	1.00 (reference)	
Moderate	1,085	1.00 (0.79, 1.26)		919	0.76 (0.42, 1.35)		730	1.06 (0.80, 1.41)		610	0.76 (0.38, 1.54)	
High	1,076	0.95 (0.74, 1.21)		923	0.69 (0.37, 1.27)		728	0.96 (0.73, 1.28)		615	0.56 (0.27, 1.19)	
LDL-C			0.3684			0.5047			0.9439			0.0405*
Low	991	1.00 (reference)		845	1.00 (reference)		815	1.00 (reference)		704	1.00 (reference)	
Moderate	1,215	1.02 (0.81, 1.28)		1,026	0.67 (0.39, 1.18)		825	1.00 (0.77, 1.31)		699	0.61 (0.32, 1.15)	
High	1,018	0.99 (0.77, 1.26)		870	0.56 (0.30, 1.04)		830	0.99 (0.76, 1.30)		706	0.50 (0.26, 0.98)	
HDL-C			0.2196			0.0084**			0.7776			0.5566
Low	1,070	1.00 (reference)		909	1.00 (reference)		666	1.00 (reference)		575	1.00 (reference)	
Moderate	1,106	1.06 (0.84, 1.34)		938	0.89 (0.47, 1.66)		678	1.14 (0.84, 1.53)		574	0.81 (0.36, 1.82)	
High	1,048	1.06 (0.82, 1.36)		894	1.18 (0.64, 2.18)		661	1.05 (0.78, 1.43)		572	1.21 (0.59, 2.47)	

Non-matched models and PS matched models adjusted for age, sex, years of education, ApoE-ε4 allele carrier status, BMI, depression, diabetes mellitus, hypertension and stroke.
**P-value < 0.05, **P-value < 0.01.*
TC: low, <4.87 mmol/L; moderate, 4.87–5.72 mmol/L; high, >5.72 mmol/L.
LDL-C: low, <2.9 mmol/L; moderate, 2.9–3.7 mmol/L; high, >3.7 mmol/L.
HDL-C: low, <1.17 mmol/L; moderate, 1.17–1.45 mmol/L; high, >1.45 mmol/L.

model. Compared with those with low level, participants with high level of LDL-C were less likely to have dementia (OR [95%CI] = 0.50[0.26, 0.98]) and the OR reduced with the increasing levels (P for trend = 0.0405).

DISCUSSION

In this community-based cross-sectional study, high level of LDL-C was found to be inversely associated with dementia in older Chinese adults, after controlling for demographic characteristics, health behavior, mood assessment, and the medical history of participants.

Our findings are consistent with those from several prior studies. Higher LDL-C (OR [95%CI] = 0.82[0.70, 0.96]) was reported to be significantly related with higher MMSE scores among the oldest old (aged 80+years) in a community-based cross-sectional study with 2,000 subjects from eight longevity areas in China, after adjusting for age, gender, residence, marital status, education level, current alcohol drinking habits, current cigarette smoking practices, sleep quality, anemia, central obesity, hypertension, diabetes, and chronic kidney disease (5). Another cross-sectional study in South Korea did not find a significant association between (TC) levels (non-fasting) and cognition function in Alzheimer's disease groups (21). Two additional cross-sectional studies in Chinese population also reported a non-significant relationship (6, 22). However, there are also some studies with different findings. For example, elevated level of TC (≥225.01 mg/dl: OR [95%CI] = 1.77 [1.03, 3.04]) was reported to be a risk factor for vascular dementia in a cross-sectional analysis among 2,820 Medicare recipients aged 65+ years in New York (23). Moreover, higher LDL-C level was found to be associated with higher amyloid deposition in a medical center-based study with 74 elderly subjects aged 78 years on average (24).

Elevated HDL-C was found to be negatively associated with cognitive impairment (lower HDL-C: OR [95%CI] = 1.45[1.12, 1.88]) in the Korean Urban Rural Elderly (KURE) study, which involved 3,514 adults aged 65+ years (25). In the Maine-Syracuse study with 540 participants aged 60+ years and without dementia and stroke, a positive relationship between HDL-C and cognitive performance was reported (MMSE: $\beta = 0.195$, $P = 0.006$) (26). The PAQUID study, involving 334 French elderly subjects aged 73+ years, also had a similar finding (higher HDL-C: OR [95%CI] =0.10[0.02, 0.53]) (27). A study among 130 Australian women with mean age of 62.5 years found a much earlier positive effect of HDL-C (non-fasting) on verbal memory (28). Another study in the Czech Republic, involving 141 adults (MMSE score≥24, 69 years of age on average, 47% female, 14.4 years of education on average) found an association between HDL-C and better composite cognitive scores ($\beta = 0.30$, $P = 0.026$), only among women (29). Our study, however, did not find a significant association between HDL-C and cognitive status.

Although the exact biological mechanism of LDL-C's potential protective effect is still unknown, we conjecture that one possibility is that high LDL-C might indicate a good nutritional status or health condition. Lower cholesterol has been found to be associated with a higher mortality in the elderly (30, 31), and it may accompany malnutrition, chronic diseases and cancer (32, 33), which in turn may positively associate with cognitive decline (34). On the other hand, because cholesterol is a major component of the brain, it is possible that decreasing cholesterol

levels in the elderly is associated with cerebral atrophy, a typical anatomic syndrome of dementia (3). Another speculation is that high LDL-C could reduce neurons' impairments or facilitate compensatory repair of injured neurons (35). The inhibitions of dendrite outgrowth (36) and synaptogenesis (37), and the acceleration of neurodegeneration (38) have been observed when neurons was a short of cellular cholesterol or cholesterol supply. Besides, cholesterol plays an important role in the synthesis, transportation and metabolism of steroid hormones as well as lipid-soluble vitamins, both of which have an impact on synaptic integrity and neurotransmission (37, 39, 40). Apart from the reasons mentioned above, there is another hypothesis about selective survival: participants aged 70+ are more likely to be resistant to the adverse effects of high LDL-C or other cerebrovascular risk factors (41). For example, oldest-old individuals were found to show more variability in cognitive function (42) and to be less apt to age-related cognitive decline (43). At the same time, these participants may also be less susceptible to the benefit of high HDL-C. Further, the protective effect of HDL-C is inconsistent. Indeed, some genetic mechanisms raising plasma HDL-C did not lower risk of myocardial infraction (44) and even the Tromsø study reported that high HDL-C could increase the future risk of venous thromboembolism in female subjects (45).

There might be a possibility of a reversal causality of lipid level and dementia. Participants with dementia may be more likely to have an eating disorder, be malnourished and thus probably accompany with reduction of cholesterol level. However, the cross-sectional study design limited our ability to explore the causal effects. Further prospective studies are needed to provide the evidence to the causality. The second limitation in our study is that we could not discriminate the vascular dementia and Alzheimer's disease because not every participant's MRI was available at baseline. Third, the "snapshot" lipid profile measurements might not be good representative of the actual lipid levels. Fourth, compared with other studies in China, we found that the distribution of cholesterol data and the cut-off values of cholesterol are different with those in the previous Chinese studies, due to the differences in demographic characteristics, regions and socioeconomic status. To be specific, the population of the study by Yue-Bin et al. was in rural areas and characterized by older age (mean age = 85.8 years) and lower education; however, our population was in a high-income city, Shanghai, and characterized by relatively younger age (mean age = 69.4 years), higher education and better economic status. In this regard, the cut-off values in different studies might be less comparable. Further multi-centered population-based studies with larger sample size are needed to verify the U-shape curve of lipid profile. Finally, our findings may not be largely generalizable because our population was characterized by relatively higher education and better economic status than those found in other areas of China; conversely, our findings may be more comparable with that in western studies.

CONCLUSION

Our data indicate that high level of LDL-C is inversely associated with dementia in older Chinese adults. High level of LDL-C may be considered as a potential protective factor against cognitive decline. Further long-term prospective studies with a larger sample size and accurate lipid measurement should be carried out to verify this association and to explore underlying pathological mechanisms.

AUTHOR CONTRIBUTIONS

This work was conceptualized by ZH and DD and all approved the protocol. Data collection was done by DD, QZ, QG, XL, and LZ. Statistical analysis was undertaken by FZ, WD, FW and JL. FZ, WD, and DD prepared the manuscript. WD and DD are the guarantors of this paper.

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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.2018.00952/full#supplementary-material

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The Gaps Between Current Management of Intracerebral Hemorrhage and Evidence-Based Practice Guidelines in Beijing, China

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Background: The leading cause of death in China is stroke, a condition that also contributes heavily to the disease burden. Nontraumatic intracerebral hemorrhage (ICH) is the second most common cause of stroke. Compared to Western countries, in China the proportion of ICH is significantly higher. Standardized treatment based on evidence-based medicine can help reduce ICH's burden. In the present study we aimed to explore the agreement between the management strategies during ICH's acute phase and Class I recommendations in current international practice guidelines in Beijing (China), and to elucidate the reasons underlying any inconsistencies found.

Method: We retrospectively collected in-hospital data from 1,355 ICH patients from 15 hospitals in Beijing between January and December 2012. Furthermore, a total of 75 standardized questionnaires focusing on ICH's clinical management were distributed to 15 cooperative hospitals. Each hospital randomly selected five doctors responsible for treating ICH patients to complete the questionnaires.

Results: Numerous approaches were in line with Class I recommendations, as follows: upon admission, all patients underwent radiographic examination, about 93% of the survivors received health education and 84.5% of those diagnosed with hypertension were prescribed antihypertensive treatment at discharge, in-hospital antiepileptic drugs were administered to 91.8% of the patients presenting with seizures, and continuous monitoring was performed for 88% of the patients with hyperglycemia on admission. However, several aspects were inconsistent with the guidelines, as follows: only 14.2% of the patients were initially managed in the neurological intensive care unit and 22.3% of the bedridden patients received preventive treatment for deep vein thrombosis (DVT) within 48 h after onset. The questionnaire results showed that imaging examination, blood glucose monitoring, and secondary prevention of ICH were useful to more clinicians. However, the opposite occurred for the neurological intensive care unit requirement. Regarding the guidelines' recognition, no significant differences among the 3 education subgroups were observed ($p > 0.05$).

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Conclusions: Doctors have recognized most of ICH's evidence-based practice guidelines. However, there are still large gaps between the management of ICH and the evidence-based practice guidelines in Beijing (China). Retraining doctors is required, including focusing on preventing DVT providing a value from the National Institutes of Health Stroke Scale and Glasgow Coma Scalescores at the time of admission.

Keywords: intracerebral hemorrhage, management strategies, international practice guidelines, gap, questionnaire

INTRODUCTION

In most Western countries, after coronary heart disease and cancer, stroke represents the third most common cause of death (1). However, it has been the leading cause of death in recent years in China (2). Nontraumatic intracerebral hemorrhage (ICH) is the second most common cause of stroke, carrying a higher risk of mortality and disability (3, 4). An earlier study has shown through a meta-analysis of 36 trials that the median case fatality at 1 month was 40%, and the long-term functional independence rate was only 12–39%. An improvement over time was not observed for either parameter (5). In China, 17–55% of strokes are caused by ICH (6, 7), which is a higher proportion compared to that in Western countries (8, 9). Standardized treatment based on evidence-based medicine can help reduce ICH's disease burden. To date, there are only two studies available on ICH's current management in China (10, 11). However, such studies have not focused on the consistency between clinical practice in ICH's management and the recommendations in the current evidence-based international practice guidelines.

The clinical practice guide is defined as the best guidance and is obtained from a systematic synthesis of the evidence generated and an evaluation of the pros and cons of the various options for intervention. In such a guide, a level I recommendation implies evidence that supports and/or agrees that an operation or treatment is useful and effective. In the present study, we systematically examined the current management and functional outcome of ICH patients in Beijing. Additionally, we focused on assessing the consistency between clinical management of the acute phase of ICHand the guidelines for the management of spontaneous ICH from the American Heart Association/American Stroke Association in 2010. Furthermore, we analyzed the underlying reasons of any inconsistencies found.

Abbreviations: BMI, body mass index; CT, computed tomography; CTA, CT angiography; CTV, CT venography; DVT, deep venous thrombosis; EEG, electroencephalogram; ES, elastic stockings; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; IPC, intermittent pneumatic compression; IQR, interquartile range; IVH, intraventricular hemorrhage; MR, magnetic resonance; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; Neuro-ICU, neurological intensive care unit; NIHSS, National Institutes of Health Stroke Scale; PCCs, prothrombin complex concentrates; PE, pulmonary embolism; rFVIIa, recombinant factor VIIa.

METHODS

Study Design

We retrospectively collected in-hospital data of ICH patients from 15 hospitals in Beijing between January and December 2012. The hospitals were selected as follows. Firstly, the hospitals were classified as grade I (community hospitals with only the most basic facilities and very limited inpatient capacity), grade II (hospitals with at least 100 inpatient beds providing acute medical care and preventative care services to populations of at least 100,000), and grade III hospitals (major tertiary referral centers in the provincial capitals and major cities) in China. Since grade I hospitals are unable to treat ICH patients, they were not included in the study. Secondly, the Public Health Information Center has registered all medical institutions in Beijing, and there are 121 hospitals that can treat patients with ICH, including 71 grade II and 50 grade III hospitals. Thirdly, we divided 121 hospitals into groups according to geographical location, that is, their districts and counties. Lastly, one hospital was randomly selected in each group and the hospital agreed to participate in the investigation. As a result, we included eight grade II and seven grade III hospitals. Patients were traced from the discharge lists with an ICH diagnosis. We retrospectively investigated the clinical data and treatment information.

Additionally, a questionnaire for doctors was developed and focused on the clinical management of ICH, referring to guidelines for the management of spontaneous ICH and the hospital facilities, including hospital imaging equipment, related treatment drug stocks and ward conditions, etc. A total of 75 standardized questionnaires were distributed to 15 cooperative hospitals. Each hospital randomly selected five doctors responsible for treating ICH patients to complete the questionnaires. All surveys on ICH patients and doctors were completed by March 2014.

Patient Eligibility

Following the World Health Organization criteria (12), diagnosis of ICH was performed by using computed tomography (CT) or magnetic resonance (MR) imaging. ICH patients were eligible for the study if they met the following criteria: (1) diagnosis of spontaneous ICH; (2) age $\geq$18 years; and (3) presentation within 7 days from onset of symptoms. We excluded from the study any ICH case secondary to trauma.

Clinical Data

The demographic and clinical variables were are follows: sex, age, body mass index, alcohol, and tobacco use as well as history of

hypertension, diabetes mellitus, hyperlipidemia, stroke, coronary heart disease, or medications (antihypertensive, antiplatelet, and anticoagulation agents). Stroke severity upon admission was evaluated using the Glasgow Coma Scale (GCS) and the National Institutes of Health Stroke Scale (NIHSS).

The enrolled hospitals utilized the following diagnostic and management approaches: routine laboratory tests, neuroimaging, intravenous/oral medications, supportive care, and surgery. Additionally, we recorded the length of hospital stay, the modified Rankin Scale score, health guidance at discharge, death, and the discharge destination. A poor clinical outcome was defined as modified Rankin Scale >2 at discharge.

Finally, we recorded whether there were in-hospital complications (e.g., pneumonia, deep venous thrombosis [DVT], recurrent stroke, urinary tract infection, sepsis, pulmonary embolism [PE], coronary event, seizure, and fall with injury) or any other clinically significant events responsible for prolonging the hospital stay.

Radiological Data

We recorded the presence or absence of intraventricular extension, the localization of hematomas and the hematomas' volume. The latter was recorded based on the ABC/2 method, in which A is the greatest diameter on the largest hemorrhage slice; B is the diameter perpendicular to A; and C is the approximate number of axial slices with hemorrhage multiplied by the slice thickness (13). The hematomas' localization was subclassified as follows: basal ganglia, lobar, thalamus (supratentorial), cerebellum, brainstem (infratentorial), or intraventricular.

Doctor Questionnaire Data

There were three parts to the doctor's questionnaire. The first part involved the participants' demographic variables. The second part involved information of the hospitals they visited. The third part involved investigating factors associated with ICH management. The item pool for the questionnaire was generated from Class I recommendations of guidelines for the management of spontaneous ICH from the American Heart Association/American Stroke Association in 2010. The third part of the questionnaire required a specific rating on a four-point scale. Specifically, this was based on the clinicians' assessment of the need for the items in the questionnaire: (1) no reason to be done; (2) could be done or not; (3) should be done; and (4) must be done. Additionally, a final open question was included. With the latter, clinicians were asked to explain the reason behind the choice of an item that should be done or must be done. We calculated the scores by summing the ratings of all participants for each item.

Quality Control and Data Collection

All sub-centers received the centrally designed standardized paper-based case report form. Physicians responsible for the sub-centers were trained centrally by the task group. Once trained, the physicians were then responsible for training the first-level monitors at the sub-centers, following a uniform protocol. During the course of the study, 20% of the case report forms were randomly selected by the independent clinical research organization and were compared to the original case information in order to verify data authenticity. A team of on-site staff supervised the administration of the questionnaires in each sub-center. The participants independently completed the questionnaire after having received instructions by a researcher. Additionally, the researcher supervised the completed questionnaire to ensure that all questions had been answered. Completeness and logical consistency were evaluated in all the data submitted to the task group. Finally, the task group utilized double entry for the data.

Statistical Methods

Statistical analyses were performed using the statistical package version 19.0 (SPSS, Inc., Chicago, IL, United States). Continuous variables were summarized as median (interquartile range) or mean (SD). Categorical variables were presented as percentages. To compare the scale scores, we used the following tests: one-way analysis of variance; the Mann–Whitney *U*-test; and the Kruskal–Wallis *H*-test. All tests were two-tailed, and statistical significance was given to $p < 0.05$.

RESULTS

Following a review of the discharge lists, 1,442 patients were observed to have a diagnosis of spontaneous ICH. Of these, 87 patients were excluded from this study. The reasons for the exclusion were as follows: (1) two patients were <18 years of age; (2) 36 patients were hospitalized 7 days after the onset; and (3) 49 patients were missing data. The final statistical analysis included the remaining 1,355 patients. **Table 1** describes the demographics and clinical characteristics of ICH patients. The median age was 60.7 years, and 64.1% of the patients were men. The proportion of all ICH patients with a history of hypertension was 68.9%. The frequency of bleeding sites for all ICH patients was as follows: 46.4% basal ganglia; 20.1%, lobar; 17.8%, thalamus, 6.3%, brainstem; 6%, cerebellum; and 3.4% intraventricular hemorrhage.

Table 2 shows that 689 patients were transported to the hospital by ambulance, and the assessment proportions of the NIHSS and GCS scores upon admission were only 8.9 and 15.3%, respectively. A total of 194 patients (14.3%) received cerebral vascular imaging (e.g., CTA/MRA/CTV/MRV) and the following secondary causes were identified: tumor, arteriovenous malformations, aneurysms, cavernous hemangioma, and moyamoya disease in 57 cases. A total of 1,129 patients (83.3%) underwent imaging reexaminations at the hospital. Additionally, of a total of 28 patients with ICH caused by coagulopathy, 19 (67.9%) received one or more reversal treatments with platelets, vitamin K, fresh-frozen plasma (FFP), or prothromb in complex concentrates (PCCs). Among 991 patients who were bedridden within 48 h from onset, 221 (22.3%) received preventive DVT treatment. Specifically, seven patients were simultaneously managed by intermittent pneumatic compression (IPC) and elastic stockings (ES), while 186 and 28 patients were managed with IPC and ES, respectively.

Only 193 patients (14.2%) were initially treated in the neurological intensive care unit (Neuro-ICU). The remaining

TABLE 1 | Characteristics of ICH patients*.

	All $N = 1355$(%)
Age, years, mean (SD)	60.7(13.6)
Male	869 (64.1)
Living alone	44 (3.2)
EDUCATION	
Elementary or below	429 (31.7)
Middle school	321 (23.7)
High school or above	605 (44.6)
DISEASE HISTORY	
Hypertension	933 (68.9)
Diabetes mellitus	186 (13.7)
Hyperlipidaemia	52 (3.8)
Stroke	362 (26.7)
Atrial fibrillation	145 (10.7)
Coronary artery disease	113 (8.3)
Current smoker	323 (23.8)
Current heavy drinker§	63 (4.6)
Overweight‖	869 (64.1)
MEDICATION HISTORY	
Antihypertensive therapy	470 (34.7)
Antiplatelet therapy	90 (6.6)
Warfarin	18 (1.3)
Lipid-lowering therapy	21 (1.5)
Hypoglycaemic therapy	117 (8.6)
CLINICAL FEATURES	
Time from symptom onset to hospital presentation <5 h	744 (54.9)
Blood pressure, mmHg, median (IQR)	
Systolic blood pressure	172 (167–176)
Diastolic blood pressure	95 (85–105)
Laboratory, median (IQR)	
Hemoglobin, g/DL	140 (134–150)
White cell count, 10^9/L	8.1 (6.1–9.4)
Platelets, 10^9/L	209 (177–302)
INR	0.9 (0.7–1.3)
Serum glucose, mmol/L	7.9(5.7–11.2)
Imaging characteristics	
Haematoma location	
Basal ganglia	629 (46.4)
Lobar	272 (20.1)
Thalamus	241 (17.8)
Brain stem	86 (6.3)
Cerebellum	81 (6)
IVH	46 (3.4)
Haematoma volume (mL)‡	
Supratentorial	
<30	868 (66.3)
30–60	231 (17.6)
>60	43 (3.3)
Infratentorial	
<10	123 (9.4)
10–20	34 (2.6)
>20	10 (0.8)
Intraventricular extension	560 (42.9)

*IQR, interquartile range; INR, international normalized ratio; IVH, intraventricular hemorrhage; *Values are reported as mean ± SD, median (IQR), or number (percentage) of subjects.*

§ ≥4 drinks on any single day prior to stroke onset (a standard drink was defined as 12 fl oz of regular beer, 5 fl oz of table wine, or a 1.5–fl oz shot of 80-proof spirits).

‖ Defined as body mass index (BMI) ≥24.

‡ 46 patients with IVH were excluded.

patients were admitted to the neurology and neurosurgical wards. Of the 343 patients exhibiting hyperglycemia upon admission, 88% were continuously monitored and 77.8% received hypoglycemic therapy, mostly as insulin. Sixty-one patients (4.5%) presented with clinical seizures or electroencephalography (EEG) seizures. Of these, 56 patients (91.8%) received antiepileptic drugs during hospitalization. Additionally, 95 cases (7.0%) received a prophylactic antiepileptic treatment. EEG and bedside EEG were used in 22 (1.6%) and 12 (0.9%) patients, respectively. A total of 22 patients had a cerebellar hematoma with indications for surgery. Of these, 11 patients (50%) received surgical intervention; six cases underwent combined hematoma evacuation with decompressive craniectomy/shunt insertion, four cases underwent shunt insertion alone, and one underwent decompressive craniectomy alone. The in-hospital mortality rate was 24.5% (332/1355). Among the 1,023 survivors, 594 patients (Modified Rankin Scale 3–5) were disabled/dependent at discharge. Approximately 93.0% of the survivors received health education and 84.5% of those diagnosed with hypertension were prescribed antihypertensive treatment at discharge.

Here we summarize the infrastructures of 15 hospitals. All hospitals were usually equipped with CT, MR imaging (MRI), and EEG, and had platelets, FFP, and IPC available. Only nine hospitals (60.0%) had the emergent green channel for ICH. Hospitals rarely had PCCs and recombinant factor VIIa availability (**Table 3**). As shown in **Table 4**, the 75 doctor questionnaire respondents mostly had a master's degree, and the proportion of those with both a master's and doctoral degree was 76.0% of all respondents. **Table 5** shows that, regarding the guidelines, most clinicians agreed with the utility of examining patients with imaging and utilizing antihypertensive therapy as a preventive for recurrent ICH. However, most clinicians did not consider Neuro-ICU management as a requirement in ICH's acute phase.

No significant difference was observed by analysis of variance among the three education groups ($p > 0.05$; **Table 6**). Additionally, the Mann–Whitney *U*-test found no significant differences among the two department groups ($p > 0.05$). Finally, we did not observe significant differences among the three title groups by the Kruskal–Wallis *H*-test ($p > 0.05$).

DISCUSSION

Previously reported national multicenter studies focused exclusively on a few sub-centers from Beijing (10) or a disproportionate number of grade II and III hospitals (11). Such evaluations could not truly reflect the status of ICH management in Beijing. Furthermore, in these rigorously designed prospective studies, sub-centers conducted research based on uniform case report forms and flowcharts. This resulted in biases and overestimation of the patterns of care. On the contrary, in the present study, only 9 and 15% patients were evaluated with NIHSS and GCS scores, respectively, on admission by doctors. These observations were far from the lowest proportions reported in other studies (10, 11). Similarly to community residents, EMS was called by 689 (51%) patients following the

TABLE 2 | In-hospital management and outcomes of ICH patients.

	Actual treatments number of cases	Should be taken number of cases by guideline/All Number	%
Transported to hospital by ambulance	689	1,355	50.8
Assessment NIHSS score on admission	121	1,355	8.9
Assessment GCS score on admission	208	1,355	15.3
NEUROIMAGING ASSESSMENT			
CTA/MRA/CTV/MRV	194	1,355	14.3
Review of neuroimaging (CT/MRI)	1,129	1,355	83.3
HEMOSTASIS/ANTIPLATELET TREATMENT			
Coagulopathy[§]	28	-	-
Reversal therapy by one or more of platelet, vitamin K, FFP, and PCCs	19	28	67.9
DVT PROPHYLAXIS			
Bedridden within 48 h after onset	991	-	-
One or more of IPC and ES	221	991	22.3
General monitoring			
Treated at the Neuro-ICU	193	1,355	14.2
Treated at the Stroke unit	66	-	-
Treated at the Neurology ward	458	-	-
Treated at the Neurosurgery ward	473	-	-
MANAGEMENT OF GLUCOSE			
Random blood glucose ≥11.1 mmol/L on admission	343		
Glucose monitoring within 24 h of onset	302 (22.3)	343	88.0
Received hypoglycemic therapy mainly with insulin	267 (19.7)	343	77.8
MANAGEMENT OF SEIZURES			
Clinical seizures or electroencephalography seizures	61	-	-
Patients presented with seizures received antiepileptic treatment	56	61	91.8
Patients presented without seizures received prophylactic antiepileptic treatment	95	-	-
NEUROSURGICAL INTERVENTION FOR CEREBELLUM HEMATOMA			
Indications for surgery	22	-	-
Received surgery	11	22	50.0
OUTCOME AT DISCHARGE (AS MEASURED BY THE MODIFIED RANKIN SCALE)			
0–2	429	1,355	31.7
3–5	594	1,355	43.8
6	332	1,355	24.5
PREVENTION OF RECURRENT ICH FOR SURVIVORS AFTER DISCHARGE			
Health education	950	1,023	92.9
Antihypertensive treatment	595	704	84.5

NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Score; CTA, CT angiography; CTV, CT venography; MRA, magnetic resonance angiography; MRV, magnetic resonance venography; CT, computerized tomography; MRI, magnetic resonance imaging; FFP, fresh frozen plasma; PCC, prothrombin complex concentrates; DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; ES, elastic stockings; Neuro-ICU, neurological intensive care unit.

[§] *Defined as platelet ≤70*10^9/L or international normalized ration ≥2.0.*

onset of symptoms (14). Nevertheless, we believe that our results are valid and may be more representative of actual realistic scenarios. Additionally, in this study, the elaborate questionnaire was of aid in revealing the underlying reasons that led to the inconsistencies between current management in the acute phase of ICH and evidence-based guidelines.

The Class I recommendations in the guidelines include the following: pre-hospital transfer, emergency diagnosis and assessment, medical treatment, inpatient management and prevention of secondary brain injury, procedures of clot removal, prevention of recurrent ICH, etc. (15). As for emergency diagnosis and assessment, brain imaging is the gold standard for diagnosing ICH because clinical presentation alone is unable to differentiate hemorrhagic from ischemic stroke (16–20). In the present study, we implemented a rapid neuroimaging assessment. As a consequence, none of patients were excluded due to lack of CT/MRI. This approach was in line with the current practice guidelines. Additionally, 14% of the patients underwent cerebral vascular imaging. The results obtained from the doctor's questionnaires demonstrated that all hospitals were generally equipped with both CT and MRI. Clinicians agreed on the utility of these diagnostic modalities for ICH's diagnosis. The frequent

TABLE 3 | Characteristics of cooperative hospital related to ICH management*.

Variable	All $N = 15$(%)
Emergent green channel for ICH	9 (60)
Neuro-ICU	10 (66.7)
EQUIPMENT/PREPARATION	
CT	15 (100)
MRI	15 (100)
Platelets	15 (100)
FFP	14 (93.3)
PCCs	3 (20)
rFVIIa	1 (6.7)
ES	12 (80)
IPC	14 (93.3)
EEG	15 (100)
Bedside EEG	8 (53.3)

ICH, intracerebral hemorrhage; Neuro-ICU, neurological intensive care unit; CT, computerized tomography; MRI, magnetic resonance imaging; FFP, fresh frozen plasma; PCCs, prothrombin complex concentrates; rFVIIa, recombinant activated human coagulation factor VII; IPC, intermittent pneumatic compression; ES, elastic stockings; EEG, electroencephalogram.

**Values are reported as number (percentage) of subjects.*

TABLE 4 | Characteristics of doctor questionnaire respondents*.

	All $N = 75$
SEX	
Male	40 (53.3)
AGE (YEARS)	
20–40	59 (78.7)
41–60	16 (21.3)
HIGHEST LEVEL OF EDUCATION	
Graduate	18 (24)
Master	43 (57.3)
Doctor	14 (18.7)
DEPARTMENTS	
Neurology	45 (60)
Neurosurgery	30 (40)
PROFESSIONAL TITLE	
Junior	26 (34.7)
Intermediate	27 (36)
Senior	22 (29.3)

**Values are reported as number (percentage) of subjects.*

use of CT/MR angiogram supported the high reported interest in rapidly identifying ICH's etiology. Unfortunately, we observed that the proportion of CTA/MRA examinations was very low. Therefore, this finding indicates that strengthening the doctors' education on the use of CTA/MRA is needed.

The guidelines recommended rapid correction of severe coagulopathy. In the present study, approximately 68% of the patients with thrombocytopenia or coagulopathy upon admission received reversal treatment. The questionnaires' results demonstrated that over 95% of clinicians agreed that correction should or must be done. However, the clinicians found that limited care and "do not resuscitate" orders were a common reality. As a consequence, the latter measures represented a limitation to the standard scheme's application. Additionally, while previous studies have shown that PCC administration was optimal for rapid coagulopathy reversal (21), in the present study, FFP and vitamin K were used with a higher frequency. Such a discrepancy could be due to two reasons. First, the clinicians were unfamiliar with the use of PCCs and management of PCCs' complications. Second, only a few hospitals in Beijing had PCCs available, as opposed to FFP and vitamin K, which were generally more available.

Previous studies found that the combination of ES and IPC was associated with a reduced risk of asymptomatic DVT compared to ES alone. Furthermore, ES alone was insufficient to prevent DVT (22, 23). In the present study, only 22% of the bedridden patients received preventive DVT treatment within 48 h of onset. Such a finding was extremely inconsistent with the guidelines. Additionally, none of the cases in the ES combined with the IPC group were complicated with DVT. However, in this study eight cases of DVT were observed in the ES or IPC alone groups. Such an observation suggests that ES or IPC alone did not represent an appropriate preventive measure. The questionnaires' results demonstrated that over 95% of the clinicians agreed with DVT prevention, but exclusively for bedridden patients within 48 h from onset. However, a considerable number of clinicians preferred intermittent alternative means to ES or IPC for DVT prevention (e.g., extremity massage). This may represent one of the reasons underlying the poor outcomes.

In a previous study, Diringer et al. observed an increase of the in-hospital mortality rate in ICH patients who were not managed in the Neuro-ICU, finding a lower mortality rate in those patients who were under the full-time care of an intensive care unit (24). In the present study, only 14% of the patients were initially managed in the Neuro-ICU. Such a percentage was extremely inconsistent with the guidelines. The questionnaire's responses showed that only 60% of the clinicians agreed that Neuro-ICU management should or must be done. The remaining clinicians believed that Neuro-ICU management for ICH patients depended on their severity and clinical course (e.g., in the case of a hematoma enlargement). Additionally, it is of note that only a handful of tertiary hospitals in Beijing have an independent Neuro-ICU. Such ward conditions may offer insufficient space for the accommodation of all ICH patients. Finally, the high cost involved in Neuro-ICU management may also represent a potential barrier.

It has been demonstrated that high blood glucose upon admission predicts an increased risk of mortality and poor outcome in ICH patients with and without diabetes (25–27). Of note, studies with tight glucose control on ICH patients have shown contradictory results (28–32). To date, the optimal management of hyperglycemia in ICH and the target glucose remain unclarified. In the present study, the vast majority of patients with hyperglycemia on admission received continuous monitoring and hypoglycemic therapy. This approach was highly consistent with the guidelines. This might be due to the fact that

TABLE 5 | Results of the 10-item questionnaire to assess the perceived as important of the AHA guideline recommendations*.

Abbreviated item-label§	All $N = 75$ (%)			
	A	B	C	D
Rapid neuroimaging assessment	0	0	4 (5.3)	71 (94.7)
Rapid hemostasis/antiplatelet treatment for deficiency	1 (1.3)	1 (1.3)	29 (38.7)	44 (58.7)
Rapid correction of coagulopathy	0	0	16 (21.3)	59 (78.7)
Deep vein thrombosis prophylaxis	0	3 (4.0)	29 (38.7)	43 (57.3)
Treatment in Neuro-ICU	1 (1.3)	28 (37.3)	11 (14.7)	35 (46.7)
Glucose monitoring and normoglycemia	0	1 (1.3)	14 (18.7)	60 (80)
Antiepileptic therapy for clinical seizures	3 (4.0)	3 (4.0)	12 (16)	57 (76)
Antiepileptic therapy for electrographic seizures	1 (1.3)	6 (8)	19 (25.4)	49 (65.3)
Neurosurgery for severe cerebellum hematoma	0	0	21 (28)	54 (72)
Antihypertensive treatment for prevention of recurrent ICH	0	0	1 (1.3)	74 (98.7)

A, represents no reason to be done; B, represents could be done or not; C, represents should be done; D, represents must be done.
**Values are reported as number (percentage) of subjects.*
§represents the question: should the following items be conducted for ICH patients?

TABLE 6 | Subgroup analyses comparing total scores of participants for each item.

	Scores	Test Value	*P*
HIGHEST LEVEL OF EDUCATION, MEAN ± *SD*			
Graduate ($n = 18$)	32.6 ± 2.9		
Master ($n = 43$)	33.1 ± 2.3	0.49	0.61
Doctor ($n = 14$)	33.4 ± 2.7		
DEPARTMENTS, MEDIAN (IQR)			
Neurology ($n = 45$)	35 (34–39)	−1.690	0.091
Neurosurgery ($n = 30$)	39 (36–40)		
PROFESSIONAL TITLE, MEDIAN (IQR)			
Junior ($n = 26$)	33 (31–34)		
Intermediate ($n = 27$)	34 (32–36)	3.36	0.187
Senior ($n = 22$)	34 (31.5–35)		

IQR, interquartile range.

the implementation of measures was relatively easy. As shown in the questionnaires, 99% of the clinicians unanimously agreed that hyperglycemic management should or must be done.

It has been shown that the incidence of seizures post-ICH varies widely, from <10% to >20% (33–36). Numerous seizures were detected exclusively by EEG monitoring. Earlier studies have demonstrated that exclusively clinical seizures or EEG seizures in patients with a change in mental status should be treated with antiepileptic drugs (37, 38). In the present study, most of the patients that presented with seizures received antiepileptic drugs during their hospital stay. Additionally, prophylactic antiepileptic treatment was administered to patients receiving surgical intervention. The questionnaire's results showed that >90% of the clinicians agreed that antiepileptic drugs should or must be administered in the event of seizures. Of note, prophylactic antiepileptic therapy has been shown to be harmful for ICH patients (37, 38). However, its universal application in surgical patients suggests that on this matter, neurosurgeons in Beijing might prefer habitual practices rather than rely on the guidelines. Our findings show that epilepsy is diagnosed in <5% of patients, perhaps because of the low use of EEG and bedside EEG.

Current guidelines recommend that patients with cerebellar hemorrhage, who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction, should undergo surgical removal of the hemorrhage as soon as possible. However, none of these recommendations are based on prospective clinical trials with clearly defined selection criteria (39–42). In the present study, surgical intervention was performed on 50% of the patients with indications for surgery. This might due to the higher ratio of hematoma without IVE and mild compression of the fourth ventricle in this patient group. The questionnaire's results showed that 100% of the clinicians agreed that surgery should or must be indicated in these cases. However, the optimal timing for surgery remained controversial because perihematomal edema fluctuated over time.

Following ICH's acute phase, the large randomized PROGRESS trial found that blood pressure reduction was

beneficial in the prevention of future vascular events (43). The effect was particularly strong for ICH's secondary prevention; an average systolic blood pressure reduction of 12 mmHg decreased the risk of recurrent ICH by up to 76% (44). In this study, most of the survivors received health education. This was especially true for patients with hypertension who continued to receive antihypertensive treatment post-discharge. The questionnaire's results showed that 100% of the clinicians agreed that antihypertensive treatment should or must be prescribed. However, in reality, care was generally limited, especially for patients with a poor clinical outcome.

Our study has some limitations that deserve comments. First, our study may be affected by selection bias because this hospital-based study emphasized moderate-to-severe strokes that required admission, while rapidly fatal or very mild strokes may not have been directly admitted into the hospital. Second, as the Chinese capital, Beijing has relatively better medical resources than most other parts of the country, so we assume that there is a huge gap in other areas. Third, this study was a cross-sectional study that lacked follow-up information. Therefore, the association between management patterns and long-term functional outcomes post-ICH was not evaluated. Besides, the patient's treatment information occurred in 2012 and the doctors were questioned in early 2014. There was indeed a lag of more than 1 year between the two parts of the surveys. Fourth, our study focused on exploring if clinical practices in Beijing conformed to Class I recommendations in the guidelines for ICH management. Additionally, there were largely low-level recommendations that we did not assess, such as the following: temperature management, intracranial pressure monitoring and treatment, surgical intervention for supratentorial hematoma, etc. Last, in this study, the assessment proportion of the NIHSS and GCS scores on admission was so low that the existing data do not represent the stroke's severity.

In summary, while most of the evidence-based practice guidelines of ICH have been recognized by doctors, there are still large gaps between current ICH managements and evidence-based practice guidelines in Beijing, China. Therefore, strengthening doctors' education and aiding the development of management strategies to improve ICH care are needed. With its massive population undergoing rapid aging and other demographic transitions, China faces an increasingly heavy burden of stroke across a variety of healthcare settings. The health status of Beijing is likely a microcosm of that of China. Therefore, having a better understanding of current management strategies can help to develop and improve the healthcare process for patients with ICH in China.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of Tiantan Hospital Affiliated to Capital Medical University of China (IRB No: KY2014-044-03). The acquisition of informed consent was exempted because patients' identification was not uncovered, and there was no intervention such as drug therapy in this retrospective analysis.

AUTHOR CONTRIBUTIONS

DL, HS, and WW conceived and designed the experiments. DL, HS, XR, and DS performed the experiments. DL, HS, YL, LT, and JF collected and analyzed the data. DL and HS wrote the manuscript. XG, BJ, and WW revised the manuscript.

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Association Between HLA Genotype and Cutaneous Adverse Reactions to Antiepileptic Drugs Among Epilepsy Patients in Northwest China

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This study aimed to investigate the association between HLA genotypes and antiepileptic drug-induced cutaneous adverse reactions (AEDs-cADRs) among patients with epilepsy in Ningxia Hui Autonomous Region of Northwest China. Fifteen patients with AEDs-cADRs and 30 matched AEDs tolerant controls from anested case-control study were tested the HLA-A, HLA-B, and HLA-DRB1 genotype using the polymerase chain reaction sequence-based typing (PCR-SBT). Significant difference was not observed between AEDs-cADRs and AEDs tolerant groups in terms of HLA-A, HLA-B, and HLA-DRB1 genotype frequencies. Future studies using larger cohorts are needed to verify this observation.

Keywords: antiepileptic drugs, Chinese, epilepsy, HLA genotype, cutaneous adverse reaction

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INTRODUCTION

Cutaneous adverse drug reactions (cADRs) are common adverse reactions observed in patients using antiepileptic drugs (AEDs). Studies have demonstrated that the incidence of AEDs-cADRs was about 3.61%. Also, cADRs are relatively common with the use of aromatic antiepileptic drugs (AAEDs), including carbamazepine (CBZ), phenytoin (PHT), lamotrigine (LTG), and phenobarbital (PB) (1). They manifest as ordinary maculopapular eruption (MPE), eventually leading to serious life-threatening conditions such as hypersensitivity syndrome (HSS), Steven-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN). AEDs-cADRs often lead to drug discontinuation in patients with epilepsy, resulting in the inability to control seizures. A 40% mortality rate has been reported in patients with severe cADRs (2).

Since 2004, a number of studies have suggested a strong association of HLA genotype with the occurrence of AEDs-cADRs. However, this association differs between different races and areas (3–5). In China, the majority of studies have been carried out in southern Chinese Han population (6–8). Since the seventh century, central Asians, Arabs, and Persians have migrated to China and settled to gradually form the Hui ethnicity. Some studies have suggested genetic differences between the Hui and the Han (9). Ningxia, located in Northwest China, has the largest Hui population in China. Therefore, Ningxia is an ideal state to study regional and ethnic differences. A nested case-control study was conducted in patients who were AEDs-cADRs and AEDs tolerant to determine the association between HLA genotypes and patients with AEDs-cADRs in Ningxia.

MATERIALS AND METHODS

Study Participants

Study participants were patients diagnosed with epilepsy by the Department of Neurology in Ningxia Medical University General Hospital. The inclusion criteria were as follows: ① Ningxia resident with no history of marriages with other ethnic groups for more than three generations; ② Clear indications for AEDs treatment; ③ Have not been administered oral AEDs, and potential adverse drug reactions declared in patients or their guardians, after which signed informed consents were obtained; and ④ The initial dose and increasing dose of AEDs determined according to the "Pharmacopeia of People's Republic of China" (2010 edition). The exclusion criteria were as follows: ① Having a history of alcohol-related epilepsy; ② Having a treatable cause (such as metabolic disorders, poisoning, and infection); ③ With progressive brain or central nervous system diseases, such as encephalitis, tumors, or degenerative diseases; ④ Suffering from other diseases and the emergence of allergy during the follow-up period; and ⑤ Having to discontinue or substitute medications and not completing 12 weeks of prescribed oral AEDs.

Four hundred and fifteen patients were followed up bi-weekly for 12 weeks after initiating oral AEDs. The initial dosage of PHT, LTG, CBZ, and valproate (VPA) was 200, 500, 12.5, 100 mg/d, and 5 mg/kg/d, respectively. They were examined for symptoms and signs of cADRs in an epileptic clinic every 2 weeks. AEDs tolerance was defined as patients who were able to tolerate AEDs without cADRs manifestation. If cADRs manifested, the AEDs were discontinued immediately and a dermatologist was consulted to diagnose and treat the patients (**Figure 1**).

Two attending or one chief physician from the Department of Dermatology examined the patients. The criteria for the diagnosis and classification of cADRs were as follows: ① MPE: a rash, not involving the mucosa, no organ or system damage, and resolved after 1–2 weeks; ② HSS: in addition to skin rash, numerous viscera involvement with systemic manifestations, such as fever, arthralgia, eosinophilia, and lymphadenopathy; ③ SJS: the occurrence of skin exfoliation, involving a range of no $<$10% of the body area, with or without other organ or system damage; ④ TEN: the presence of skin exfoliation, involving more than 30% of the body area, with or without other organ or system damage; and ⑤ SJS/TEN: the presence of skin exfoliation, involving a range of 10–30% of the total body area. The patients were treated for skin damage based on the severity as determined by a dermatologist after cADRs diagnosis was confirmed. These patients were assigned to the AEDs-cADRs group.

Nested case-control design is the most common way to reduce the costs of exposure assessment in prospective epidemiological studies. They can also reduce the sample size through matching (10). In this study, 15 patients with epilepsy who developed cADRs were defined as the AEDs-cADRs group. For each patient with AEDs-cADRs, two patients with AEDs tolerance were selected and matched by AEDs, gender, age (±3 years), and ethnicity.

Clinical Data Collection

A unified AEDs-cADRs epidemiological questionnaire, including demographics, underlying diseases, medication history, allergies, and seizure history, was used. The occurrence of cADRs during the 12 weeks was recorded, including the date of cADRs manifestation and other clinical manifestations involving the mucosa and subtypes.

Ethics Statement

The General Hospital of Ningxia Medical University Ethics Committee approved the study. Also, the study was performed in compliance with the Helsinki Declaration. Access to the patient information database was granted by the General Hospital of Ningxia Medical University and approved by the ethics committee following study review. All enrolled patients agreed to have their data published and signed a written informed consent form.

HLA-A, HLA-B, and HLA-DRB1 Genotyping

Peripheral venous blood (3 mL) from each participant was collected in anticoagulant tubes. An extraction kit (Beijing

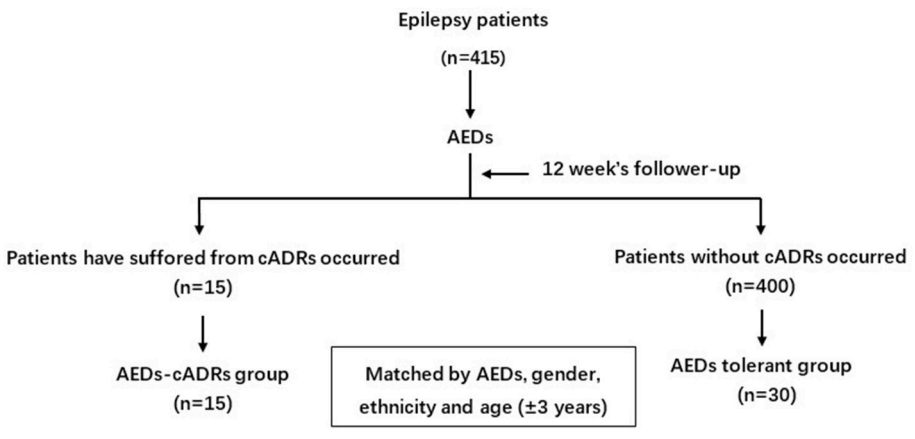

FIGURE 1 | Flow chart of the nested case-control study.

TABLE 1 | The characteristics of AEDs-cADRs group.

AEDs-cADRs group	Gender	Age (years)	Ethnicity	Address (city)	Allergy history	Type of AEDs	Daily dose	Time of occurrence	Type of cARDs
C01	M	19	Han	Zhongning	No	PHT	300 mg	After 6 m	MPE
C02	M	14	Han	Shizuishan	No	LEV	1250 mg	After 5 d	MPE
C03	F	20	Han	Yinchuan	No	CBZ	100 mg	After 6 d	MPE
C04	M	41	Han	Yinchuan	No	CBZ	200 mg	After 43 d	MPE
C05	F	25	Han	ShiZuiShan	No	LTG	6.25 mg	After 5 d	MPE
C06	F	31	Hui	Yinchuan	YES	LTG	50 mg	After 7 d	MPE
C07	M	14	Han	ShiZuiShan	No	LEV	500 mg	After 1 m	MPE
C08	M	27	Han	ShiZuiShan	No	LTG	12.5 mg	After 2 m	MPE
C09	F	41	Hui	Pengyang	No	LTG	25 mg	After 1 m	HSS
C10	M	55	Han	Yinchuan	No	LTG	25 mg	After 2 m	MPE
C11	M	40	Hui	Yongning	No	LTG	50 mg	After 15 d	MPE
C12	M	22	Han	Jingyuan	No	LTG	25 mg	After 13 d	MPE
C13	M	60	Han	ZhongNing	No	VPA	400 mg	After 1 d	MPE
C14	F	16	Han	Guyuan	No	LTG	12.5 mg	After 10 d	MPE
C15	M	55	Han	Yinchuan	No	LTG	25 mg	After 5 d	MPE

TABLE 2 | The characteristics of AEDs tolerant group.

AEDs tolerant group	Gender	Age (years)	Ethnicity	Address (city)	Type of AEDs	AEDs tolerance group	Address (city)	Gender	Age (years)	Ethnicity	Type of AEDs
M01	M	24	Han	Qingtongxia	PHT	M16	Yongning	M	26	Han	LTG
M02	M	24	Han	Yongning	PHT	M17	Yongning	F	25	Hui	LTG
M03	M	17	Han	Jingyuan	LEV	M18	Yongning	F	25	Hui	LTG
M04	M	24	Han	Yanchi	LEV	M19	Yinchuan	M	30	Han	LTG
M05	F	27	Han	Helan	CBZ	M20	Yinchuan	M	65	Han	LTG
M06	F	25	Han	Zhongwei	CBZ	M21	Helan	M	35	Han	LTG
M07	M	45	Han	Wuzhong	CBZ	M22	Helan	M	36	Han	LTG
M08	M	39	Han	Zhongning	CBZ	M23	Shizuishan	M	17	Han	LTG
M09	F	17	Han	Yingchuan	LTG	M24	Zhongwei	M	28	Han	LTG
M10	F	22	Han	Yongning	LTG	M25	Zhongwei	M	32	Han	VPA
M11	F	27	Hui	Yongning	LTG	M26	Yinchuan	M	12	Han	VPA
M12	F	20	Hui	Yanchi	LTG	M27	Qingtongxia	F	20	Han	LTG
M13	F	23	Han	Yinchuan	LEV	M28	Helan	F	44	Han	LTG
M14	M	21	Han	Yinchuan	LEV	M29	Helan	M	23	Han	LTG
M15	M	35	Han	Helan	LTG	M30	Zhongning	M	30	Han	LTG

Tiangen Biotech Company, China) was used to extract genomic DNA from whole blood according to the manufacturer's protocols. HLA genotype was performed using PCR-SBT at the Beijing Boao Crystal Biotechnology Company, China. The following procedural steps were adopted: ① amplification of HLA-A, HLA-B, and HLA-DRB1 loci; ② purification and detection of the amplified products; and ③ HLA genotyping sequencing using a 3730XL ABI detector.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation (SD) and categorical variables as frequencies (%). The Pearson chi-squared test was used to compare categorical variables and the Student *t*-test to compare continuous variables. Differences in HLA genotype frequency between the groups were analyzed using the Fisher's exact test. Risk association between HLA alleles and AEDs-cADRs were presented as odds ratios (OR) and 95% confidence intervals (CI). *P*-values and 95% CIs were estimated using two-tailed tests. Data were analyzed using SPSS13.0 software.

RESULTS

Characteristics of the Study Participants

The age of the 15 patients with AEDs-cARDs ranged from 14 to 60 years old,with an average age of 39.2 ± 15.4 years old. These included 10 male patients and 5 female patients with a ratio of 2:1. Twelve patients were of Han ethnicity and three of Hui ethnicity. Ten patients were with generalized epileptic seizures and five were with partial epileptic seizures. One patient

TABLE 3 | Genotypes of HLA-A, HLA-B, and HLA-DRB1 in AEDs-cADRs group.

AEDs-cADRs group	Type of AEDs	Type of cADRs	HLA sub-type					
			HLA-A*		HLA-B*		HLA-DRB1*	
C01	PHT	MPE	3201	3303	3501	4403	0405	0803
C02	LEV	MPE	0207	3201	4601	5201	0901	1202
C03	CBZ	MPE	1101	2402	1505	5101	0803	1210
C04	CBZ	MPE	0201	2402	1518	5101	1101	1454
C05	LTG	MPE	0201	0207	1501	4801	0405	1405
C06	LTG	MPE	0203	0207	4601	5801	0301	1454
C07	LEV	MPE	0206	1101	1518	3501	0401	1501
C08	LTG	MPE	0206	3303	4403	5101	1302	1454
C09	LTG	HSS	2402	3101	2705	5101	0101	0701
C10	LTG	MPE	0201	2402	1302	1501	0701	1501
C11	LTG	MPE	0101	0206	1301	5701	0401	0901
C12	LTG	MPE	2901	3101	0705	5101	0803	1202
C13	VPA	MPE	3101	3303	4006	5102	1101	1101
C14	LTG	MPE	0207	1101	3501	4002	0901	1202
C15	LTG	MPE	0207	3001	1302	5101	0701	1201

In the HLA naming protocol,"" separates the HLA locus (A, B and DRB1) from the serotype (32, 33 and 35), eg. HLA-A* 3201.*

TABLE 4 | Genotypes of HLA-A, HLA-B, and HLA-DRB1 in AEDs tolerant group.

AEDs tolerant group	Type of AEDs	HLA sub-type					
		HLA-A*		HLA-B*		HLA-DRB1*	
M01	PHT	1101	2601	0801	4001	0301	0405
M02	PHT	1101	1101	3503	5102	1101	1123
M03	LEV	1101	2402	0702	5401	0405	1501
M04	LEV	1101	1101	0702	4001	0101	0901
M05	CBZ	0201	0201	4003	6701	1302	1405
M06	CBZ	1101	3303	5201	5801	0301	0803
M07	CBZ	0302	1101	0801	1502	0301	1202
M08	CBZ	0201	3303	1501	5001	0701	1101
M09	LTG	0207	1101	0702	5101	0901	1501
M10	LTG	0201	3004	5801	5801	0410	1454
M11	LTG	1101	3001	1302	5201	0701	1502
M12	LTG	0201	3303	1301	5801	0301	1202
M13	LEV	0201	0301	3502	4101	0101	0301
M14	LEV	0101	3001	1302	3503	1103	1301
M15	LTG	0101	0201	4002	4601	1101	1202
M16	LTG	0101	0101	4001	4001	1454	1454
M17	LTG	2402	2402	3802	5101	1201	1312
M18	LTG	2402	3001	3503	5401	1101	1501
M19	LTG	0203	3303	1801	5502	1104	1602
M20	LTG	0301	3303	5201	5801	0301	1502
M21	LTG	0201	2402	1501	5101	0901	1001
M22	LTG	1101	3101	0702	4001	0101	0901
M23	LTG	0201	2601	4006	4006	0803	0901
M24	LTG	3001	3101	1302	5101	0701	1454
M25	VPA	0201	0201	4006	4601	0901	1210
M26	VPA	0201	2601	1301	5701	0701	1202
M27	LTG	0201	2402	4801	5502	0901	1405
M28	LTG	0207	2402	4006	4601	0901	0901
M29	LTG	0207	1101	4601	5502	0803	1202
M30	LTG	0207	3101	4601	5101	1202	1454

In the HLA naming protocol,"" separates the HLA locus (A, B and DRB1) from the serotype (32, 33 and 35), eg. HLA-A* 3201.*

had a pollen allergy history. One patient received PHT that induced cADRs, two patients received CBZ, two received LEV, one received VPA, and nine received LTG. Moreover, there were 14 patients with MPE and one Hui female patient with HSS who accepted treatment after onset. Further, five patients had cADRs after taking the initial dose of AEDs, of which one patient received CBZ, one received LEV, and three received LTG. The average time from patients taking AEDs to the occurrence of cADRs was 93.4 ± 70 days, with the longest latency period being 6 months and the shortest being 1 day (**Table 1**).

The age of the 30 AEDs tolerant patients ranged from 12 to 65 years old, with an average age of 31.7 ± 12.4 years old. These included 19 male patients and 11 female patients at a ratio of 1.7:1. Further, 26 patients were of Han ethnicity and 4 were of Hui ethnicity. Twenty-three had generalized seizures, and seven had partial seizures. Moreover, two received PHT, four received LEV, four received CBZ, two received VPA, and eighteen received LTG (**Table 2**).

Genotypes of HLA-A, HLA-B, and HLA-DRB1

In the AEDs-cADRs group, the number of HLA-A, HLA-B, and HLA-DRB1 genotypes detected was 12, 18, and 15, respectively. Higher distribution frequencies of HLA-A genotype were A*0207 (16.67%) and A*2402 (13.33%). The highest distribution frequency of HLA-B genotype was B*5101 (20%). The distribution frequency of A*0201, A*0206, A*3101, A*3303, B*3501, DRB1*0701, DRB1*0803, DRB1*0901, DRB1*1101, DRB1*1202, and DRB1*1454 was 10% (**Table 3**).

In the AEDs tolerant group, the number of HLA-A, HLA-B, and HLA-DRB1 genotypes detected was 13, 26, and 23, respectively. Higher distribution frequencies of the HLA-A genotype were A*0201 (21.67%) and A*1101 (20%). The distribution frequency of the HLA-B genotype was lower than 10%. Higher distribution frequency of the HLA-DRB1 genotype was DRB1*0901 (15%), followed by DRB1*0301(10%) and DRB1*1202 (10%) (**Table 4**).

Association Between HLA-A, HLA-B, and HLA-DRB1 Genotypes and AEDs-cADRs, LTG-cADRs, and AAEDs-cADRs

As shown in **Table 5**, OR values of 15 HLA genotypes were >1. No significant differences in HLA genotype frequencies were observed between the AEDs-cADRs and AEDs tolerant group ($P > 0.05$).

HLA genotyping in 9 patients with LTG-cADRs identified a total of 11 HLA-A types, 13 HLA-B types, and 13 HLA-DRB1 types. In 18 patients of LTG tolerant group, 12 HLA-A types,

TABLE 5 | Association between HLA-A, HLA-B, HLA-DRB1, and AEDs-cADRs.

HLA type	Frequency		OR(95%CI)	*P*-value
	AEDs-cADRs group ($2n = 30$)	AEDs tolerant group ($2n = 60$)		
A*0203	1/30 (3.3%)	1/60 (1.7%)	2.034 (0.12∼33.70)	1.00
A*0207	5/30 (16.7%)	4/60 (6.7%)	2.800 (0.69∼11.32)	0.15
A*2402	4/30 (13.3%)	7/60 (11.7%)	1.165 (0.31∼4.34)	1.00
A*3101	3/30 (10.0%)	3/60 (5.0%)	2.111 (0.40∼11.15)	1.00
A*3303	3/30 (10.0%)	5/60 (8.3%)	1.222 (0.27∼5.50)	1.00
B*1501	2/30 (6.7%)	2/60 (3.3%)	2.071 (0.28∼15.48)	0.60
B*1502	0/30 (0.0%)	1/60 (1.7%)	1.017 (0.98∼1.05)	1.00
B*4002	1/30 (3.3%)	1/60 (1.7%)	2.034 (0.12∼33.70)	1.00
B*4801	1/30 (3.3%)	1/60 (1.7%)	2.034 (0.12∼33.70)	1.00
B*5102	1/30 (3.3%)	1/60 (1.7%)	2.034 (0.12∼33.70)	1.00
DRB1*0405	2/30 (6.7%)	2/60 (3.3%)	2.071 (0.28∼15.48)	0.60
DRB1*0803	3/30 (10.0%)	3/60 (5.0%)	2.111 (0.40∼11.15)	0.40
DRB1*1201	1/30 (3.3%)	1/60 (1.7%)	2.034 (0.12∼33.70)	1.00
DRB1*1210	1/30 (3.3%)	1/60 (1.7%)	2.034 (0.12∼33.70)	1.00
DRB1*1302	1/30 (3.3%)	1/60 (1.7%)	2.034 (0.12∼33.70)	1.00

TABLE 6 | Association between HLA-A, HLA-B, HLA-DRB1, and LTG-cADRs.

HLA type	Frequency		OR(95%CI)	*P*-value
	LTG-cADRs group ($2n = 18$)	LTG tolerant group ($2n = 36$)		
A*0206	4/18 (22.2%)	4/36 (11.1%)	2.28 (0.50∼10.5)	0.29
A*2402	2/18 (11.1%)	2/36 (5.6%)	2.12 (0.27∼16.5)	0.48
A*3101	2/18 (11.1%)	2/36 (5.6%)	2.12 (0.27∼16.5)	0.48
B*5101	4/18 (22.2%)	2/36 (5.6%)	4.85 (0.80∼29.6)	0.76
DRB1*3303	3/18 (16.7%)	2/36 (5.6%)	3.40 (0.51∼22.5)	0.19

17 HLA-B types, and 17 HLA-DRB1 types were identified. OR values of 5 HLA genotypes were >1. No significant differences in HLA genotype frequency were found between the LTG-cADRs and LTGtolerant group ($P > 0.05$) (**Table 6**).

HLA genotyping in 12 patients with AAEDs-cADRs identified a total of 12 HLA-A types, 15 HLA-B types, and 15 HLA-DRB1 types. In 24 patients of AAEDs tolerant group, 13 HLA-A types, 23 HLA-B types, and 20 HLA-DRB1 types were identified. The OR values of 13 HLA genotypes were >1. No significant difference in HLA genotype frequency was observed between AAEDs-cADRs and AAEDs tolerant group ($P > 0.05$) (**Table 7**).

DISCUSSION

The occurrence of AEDs-cADRs in patients with epilepsy may be influenced by gender, age, initial AEDs dosage, incremental AEDs dosage, and adding rate, with or without a history of allergies, monotherapy or polytherapy, functional status of the liver and kidney, and genetic factors (11). Chung and colleagues reported that HLA-B*1502 was strongly correlated with CBZ-SJS/TEN in Taiwan Han populations (4). This result was later supported by others (3), especially for serious cADRs, with HLA susceptibility genes being the most important factor.

Different AEDs induce different cADR symptoms. In a large-scale study on 3,793 patients with epilepsy taking AEDs, the overall incidence rate of AEDs-cADRs reached 3.61%. The incidence rates of AEDs induced by cADRs were as follows: LTG (11.11%), OXC (8.92%), CBZ (3.80%), PHT (1.98%), PB (0.42%), VPA (0.57%), and LEV (1.65%) (1). About 88.41% of cADRs were induced by AAEDs of CBZ (47.56%), LTG (17.07%), OXC (9.15%), PHT(9.15%), and PB(5.49%) (12). These results suggested that AAEDs were more likely to induce cADRs in clinical practice compared with other types of AEDs. In the present study, 80% of patients with AEDs-cADRs were AAEDs-cADRs (12/15). Of these, LTG-cADRs was the most common (9/15).

Correlation studies on HLA genotypes and AEDs-cADRs have been conducted in mainland China (6–8), Taiwan (4), Hong Kong (13), Southeast Asia (14–16), Japan (17), Korea (18), Europe (19), North America (20), and other regions. The reported correlations between HLA genotypes and AEDs-cADRs have the following characteristics: ① Susceptible genes associated with AEDs-cADRs may be different among different races. For example, HLA-B*1502 is the susceptible gene for AEDs-SJS/TEN in Han Chinese and Southeast Asians. However, in Japan, Europe, and other parts of the world, the susceptible gene for CBZ-cADRs is HLA-A*3101. ② In the Han population in Southeast Asia, HLA-B*1502 may have a susceptibility to aromatic AEDs-SJS/TEN. ③ The incidence rate of AEDs-cADRs is relevant to the distribution rate of HLA-B*1502 alleles among different races. The higher the distribution rate of HLA-B*1502 in the race, the higher the incidence rates for AEDs-cADRs.

Ningxia, located in Northwest China, is an agglomeration of Hui ethnicities that are unlike the southern Han Chinese population genetically. Whether any HLA susceptibility genes are responsible for the occurrence of AEDs-cADRs among the northwestern population in China is not known. Therefore, the distribution rate of HLA genotypes was compared in the following groups: all patients in the AEDs-cADRs group vs. patients in the AEDs tolerant group, AAEDs-cADRs group vs. AAEDs tolerant group, and LTG-cADRs group vs. LTGtolerant group. The results suggested that the HLA-A, HLA-B, and HLA-DRB1 genotype distribution frequencies were not statistically significantly different between the two groups.

The present study had some limitations that might have impacted the outcome. First, selecting a large number of patients with AEDs-cADRs was difficult. Nine patients with LTG-cADRs were enrolled in this study. However, only one patient with CBZ-cADRs, one patient with PHT-cADRs, two patients with CBZ-cADRs, two patients with LEV-cADRs, and one patient with VPA-cADRs. Future studies focusing

TABLE 7 | Association between HLA-A, HLA-B, HLA-DRB1, and AAEDs-cADRs.

HLA type	Frequency		OR(95%CI)	*P*-value
	AAEDs-cADRs group ($2n = 24$)	AAEDs tolerant group ($2n = 48$)		
A*0203	1/24 (4.2%)	1/48 (2.1%)	2.043 (0.12∼34.16)	1.00
A*0207	4/24 (16.7%)	4/48 (8.3%)	2.00 (0.50∼9.70)	0.42
B*1302	2/24 (8.3%)	2/48 (4.2%)	2.091 (0.28∼15.83)	0.60
B*1501	2/24 (8.3%)	2/48 (4.2%)	2.091 (0.28∼15.83)	0.60
B*4002	1/24 (4.2%)	1/48 (2.1%)	2.043 (0.12∼34.16)	1.00
B*4801	1/24 (4.2%)	1/48 (2.1%)	2.043 (0.12∼34.16)	1.00
B*5101	6/24 (25.0%)	5/48 (10.4%)	2.87 (0.77∼10.60)	0.16
DRB1*0101	1/24 (4.2%)	1/48 (2.1%)	2.043 (0.12∼34.16)	1.00
DRB1*0405	2/24 (8.3%)	1/48 (2.1%)	4.273 (0.37∼49.68)	0.25
DRB1*0701	3/24 (12.5%)	3/48 (6.3%)	2.143 (0.40∼11.15)	0.39
DRB1*0803	3/24 (12.5%)	3/48 (6.3%)	2.143 (0.40∼11.15)	0.39
DRB1*1201	1/24 (4.2%)	1/48 (2.1%)	2.043 (0.12∼34.16)	1.00
DRB1*1302	1/24 (4.2%)	1/48 (2.1%)	2.043 (0.12∼34.16)	1.00

on large-sample populations with similar epilepsy and AEDs should be conducted. Second, the study did not adjust for age, gender, and other possible confounding variables during statistical analysis due to the small sample size. This might have had a minor impact on the results because the patients and controls were matched using a nested case–control design.

CONCLUSIONS

The presentstudy did not find a significant association between any HLA genotypes and AEDs-cADRs in patients with epilepsy in Northwest China. Future studies using larger cohorts are needed to verify this observation.

AUTHOR CONTRIBUTIONS

QZ conceived this study. XW, LC, XL, and XX recruited patient samples and collected clinical data. Beijing Boao Crystal Biotechnology Company Completed HLA Genotyping. XW provided statistical analyses of the patient data and laboratory analyses.

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Determinants of Developing Stroke Among Low-Income, Rural Residents: A 27-Year Population-Based, Prospective Cohort Study in Northern China

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Although strokes are the leading cause of death and disability in many countries, China still lacks long-term monitoring data on stroke incidence and risk factors. This study explored stroke risk factors in a low-income, rural population in China. The study population was derived from the Tianjin Brain Study, a population-based stroke monitoring study that began in 1985. This study documented the demographic characteristics, past medical histories, and personal lifestyles of the study participants. In addition, physical examinations, including measurements of blood pressure (BP), height, and weight, were performed. Hazard ratios (HRs) were estimated for the risk factors for all subtypes of stroke using multivariate Cox regression analyses. During the study with mean following-up time of 23.16 years, 3906 individuals were recruited at baseline, and during 27 years of follow-up, 638 strokes were documented. The multivariate Cox regression analyses revealed a positive correlation between age and stroke incidence. Limited education was associated with a 1.9-fold increase in stroke risk (lowest vs. highest education level). Stroke risk was higher among former smokers than among current smokers (HR, 1.8 vs. 1.6; both, $P < 0.05$). Moreover, stroke risk was significantly associated with sex (HR, 1.8), former alcohol drinking (HR, 2.7), baseline hypertension (HR, 3.1), and overweight (HR, 1.3). In conclusion, this study identified uncontrollable (sex and age) and controllable (education, smoking, alcohol drinking, hypertension, and overweight) risk factors for stroke in a low-income, rural population in China. Therefore, it is critical to control BP and weight effectively, advocate cessation of smoking/alcohol drinking, and enhance the education level in this population to prevent increase in the burden of stroke in China.

Keywords: stroke, risk factors, epidemiology, population-based study, cohort study

INTRODUCTION

Cerebrovascular disease is one of the leading causes of death and disability worldwide (1, 2). Stroke, a type of cerebrovascular disease, has been reported by the World Health Organization as the leading cause of disability among adults and the second leading cause of death worldwide (3). Overall, 71% of stroke-related deaths and 78% of disability-adjusted life loss occurred in low- and middle-income countries (4). In China, strokes account for 21.6% of total male mortality and 20.8% of total female mortality. Thus, strokes remain a major health problem in China (5).

Over the past two decades, China has experienced rapid health and sociodemographic changes that have affected the prevalence of common risk factors for stroke (6, 7). Although developed countries have shown a significant downward trend in stroke incidence through effective control of risk factors (8–10), China still lacks long-term monitoring data on stroke incidence and risk factors, especially among rural residents with low income and poor access to education. Therefore, this study aimed to explore the risk factors for developing stroke among the low-income, rural population in northern China.

MATERIALS AND METHODS

Study Population and Sample Process

This is a population-based cohort study, which has conducted since 1991 in rural Tianjin, China. The study population has been described previously (11–14). Briefly, it included 14,936 people in 1991, 95% of whom were low-income farmers living in 18 administrative villages. The main source of income was cereal crop production, and the per capita incomes were <100 USD in 1990 and <1000 USD in 2010 (15).

The sampling method used in this cohort study has also been reported previously (16). In short, all residents living in the 18 administrative villages were recruited into the study. The villages were divided into three geographic regions (east, south, and north), and two villages were randomly selected from each region. Using a stratified cluster sampling approach, we selected all residents (≥15 years old) from the six villages who had no histories of ischemic heart disease (such as coronary heart disease or myocardial infarction) or stroke as participants of the survey. For this analysis, only participants aged ≥18 years were included.

This study was carried out in accordance with the recommendations of the Study involving human subjects, committee of Tianjin Medical University General Hospital. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of Tianjin Medical University General Hospital.

Baseline Information

All information regarding demographic characteristics (including sex, age, and education level), past medical histories (including hypertension, diabetes mellitus [DM], stroke, and cardiovascular disease), and personal lifestyles (including smoking and alcohol drinking) was collected by trained local researchers through face-to-face interviews. Physical examinations, which included measurements of blood pressure (BP), height, and weight, were conducted during the interview.

Measurement Methods

The BP measurement methods are described previously (16). Briefly, standardized BP measurements were performed using a mercury sphygmomanometer, with the cuff adjusted to each patient's arm circumference. BP was measured by placing the cuff on the arm, at the level of the heart. If the difference between two systolic BP (SBP) readings was <10 mmHg and/or the difference between two diastolic BP (DBP) readings was <5 mmHg, the average of the two measurements was recorded, with the latter measurement taken after the patient had rested for 5 min in the supine position. If the differences between the two readings were outside of the indicated ranges, or the BP reached the criterion for hypertension, another two readings were obtained after an additional 20 min of resting. Hypertension was categorized into four types: normal BP, isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), and systolic-diastolic hypertension (SDH).

Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters), and categorized as follows: normal (<24 kg/m^2), overweight (24–27.9 kg/m^2), and obese (≥28 kg/m^2) (17).

Case Definition

The stroke monitoring details and protocol used to diagnose the type of stroke are described in our previous reports (11–14). Stroke was defined as an acute, focal, neurological deficit with vascular etiology that lasts for >24 h. Stroke events included the ischemic stroke (IS) and hemorrhagic stroke subtypes. Hemorrhagic stroke was defined as an intracerebral hemorrhage (ICH) or subarachnoid hemorrhage; IS was defined as a thrombotic brain infarction, cardioembolic stroke, or lacunar infarct. Undefined strokes were those that could not be classified as either of the subtypes (18). The stroke subtypes were identified using neuroimaging examination (computed tomography or magnetic resonance imaging). All included stroke events were those diagnosed as full clinical strokes, demonstrating obvious clinical signs and symptoms. Transient ischemic attacks (TIAs) and silent strokes (diagnosed using imaging only) were excluded, and strokes occurring in individuals with histories of TIAs were considered as incident events. Patients with transient symptoms but with neuroimaging evidence of cerebral infarctions were considered as stroke cases (19). During the early phase of this study (1992–1998), strokes were confirmed mainly based on clinical examinations by senior neurologists for nonhospitalized patients and on medical records for hospitalized patients.

Statistical Analysis

Continuous variables (age, BP, and BMI) were expressed as means (standard deviation), and categorical variables were expressed as 95% confidence intervals (CIs). Age-standardized incidences were calculated using the direct method and standard population age groups: <35, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and ≥75 years (20). Subgroup analyses were conducted to evaluate the risk of first-ever stroke by age (<35,

TABLE 1 | Demographical characteristics of all participants in this study.

Risk factors	Total	Men	Women
Total:	3,906	1,834 (47.0)	2,072 (53.0)
Age, means (SD), years	41.74 (16.58)	42.51(16.89)	41.07 (16.28)
Age group, n (%)			
<35 years	1,582	720 (45.5)	862 (54.5)
35 44 years	906	401 (44.3)	505 (55.7)
45 54 years	466	238 (51.1)	228 (48.9)
55 64 years	470	222 (47.2)	248 (52.8)
65 74 years	320	168 (52.5)	152 (47.5)
≥75 years	162	85 (52.5)	77 (47.5)
Education, n (%)			
0 years	1,588	675 (42.5)	913 (57.5)
1 6 years	978	508 (51.9)	470 (48.1)
7 9 years	1,203	584 (48.5)	619 (51.5)
> 9years	137	67 (48.9)	70 (51.5)
Smoking status, n (%)			
Current smoking	1,002	921 (91.9)	81 (8.1)
Former smoking	112	101 (90.2)	11 (9.8)
Never smoking	2,792	812 (29.1)	1,980 (70.9)
Alcohol consumption, n (%)			
Current drinking	602	577 (95.8)	25(4.2)
Former drinking	16	16 (100)	0
Never drinking	3,288	1,241 (37.7)	2,047(62.3)
SBP, means (SD), mmHg	127.39 (20.27)	127.92 (17.57)	126.92 (22.39)
DBP, means (SD), mmHg	79.95 (11.41)	80.60 (10.59)	79.37 (12.06)
Baseline Hypertension, n (%)			
No	2,695	1,250 (46.4)	1,445 (53.6)
Yes	1211	584 (48.2)	627 (51.8)
BP types, n (%)			
Normal BP	2,708	1,257 (46.4)	1,451 (53.6)
ISH	177	85 (48.0)	92 (52.0)
IDH	328	182 (55.5)	146 (44.5)
SDH	693	310 (44.7)	383 (55.3)
Baseline Diabetes, n (%)			
No	3,902	1,834 (47.0)	2,068 (53.0)
Yes	4	0	4(100)
BMI, means (SD), Kg/m^2	22.58 (2.80)	22.32 (2.37)	22.83 (3.11)
BMI groups, n (%)			
Normal weight	2,897	1,466 (50.6)	1,431 (49.4)
Overweight	847	332 (39.2)	515 (60.8)
Obesity	162	36 (22.2)	126 (77.8)

SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

35–44, 45–54, 55–64, 65–74, or ≥75 years), education level (illiterate, 1–6 years of schooling, 7–9 years, or >9 years), SBP (<130, 130–139, 140–159, 160–179, or ≥180 mmHg), DBP (<80, 80–89, 90–99, 100–109, or ≥110 mmHg), hypertension type (normal BP, ISH, IDH, or SDH), BMI (normal, overweight, or obese), smoking status (never smoked, former smoked, or currently smoked), and alcohol drinking status (never drank, former drank, or currently drinks). The determinants of all stroke subtypes ("total stroke" in succeeding instances) were estimated using Cox regression analysis; the results were presented as adjusted HR and 95% CIs after adjustment for covariates (age, sex, hypertension, diabetes, body mass index [BMI], hypertension types, current smoking and alcohol consumption status). In this model, there were two outcome variables (status and survival time), they were the dependent variables. Status was a dichotomous variable which was categorized stroke group and non-stroke group. Survival time, which was a continuous variable, was defined as the interval time from baseline to onset time for those participants with first-ever stroke, from baseline to June 2018 for those survivals without developing stroke (censored data) and from baseline to death date for those dead participants (censored data). All associated covariates assessed using Kaplan-Meier test were performed the Cox regression analysis. The assumption of model was that the impact of risk factors on occurring stroke events did not vary with survival time. All statistical analyses were performed using SPSS for Windows (version 19.0; SPSS, Chicago, IL, United States). A $P < 0.05$ was considered statistically significant.

RESULTS

Demographic Characteristics of Participants

This study recruited 3,906 individuals (men, 1,834 [47.0%]; women, 2,072 [53.0%]; mean age, 41.74 ± 16.58 years) at baseline, with mean following-up time of 23.16 years. During 27 years of follow-up (total, 85,346.5 person-years), a total of 638 strokes (379 [59.4%] in men and 259 [40.6%] in women) were documented, including 404 ISs (63.3%), 121 hemorrhagic strokes (19.0%), and 113 undefined strokes (17.7%). The stroke incidence per 100,000 person-years in this population was as high as 748 (473 for IS; 142 for ICH). The incidence of total stroke was significantly higher among men than among women (978 vs. 556 for total stroke; 596 vs. 371 for IS; 206 vs. 88 for ICH).

The education level of the participants was very low, with 40.7% of them (men, 42.5%; women, 57.5%) having never received any formal education. The baseline prevalence was 31.0% for hypertension, 0.1% for DM, 25.7% for current smoking, and 15.4% for current alcohol drinking. The average SBP, DBP, and BMI values were 127.39 mmHg, 79.95 mmHg, and 22.58 kg/m^2), respectively (**Table 1**).

Associated Factors for Developing Stroke in the Univariate Analysis

During the follow-up period, the average age at baseline was higher among individuals with stroke (52.4 ± 14.7 years for total stroke; 49.5 ± 13.5 years for IS; 49.6 ± 15.1 years for ICH) than among those without stroke (all $P < 0.05$). Simultaneously, the incidences of total stroke and ICH increased with increasing age at baseline among individuals aged <75 years, and the incidences of ICH decreased with increasing education level ($P < 0.05$). The incidences were higher in ever-smokers (32.1% for total stroke;

25.9% for IS; 4.5% for ICH) and those with hypertension (27.0% for total stroke; 15.9% for IS; 4.7% for ICH; $P < 0.05$) than in those who never smoked or had no hypertension. However, stroke incidence was highest among former alcohol drinkers, except for ICH. Additionally, the incidence of total stroke in patients with DM (50.0%) at baseline was significantly higher than that in patients without DM (16.3%, $P < 0.05$). In terms of hypertension type, the incidence of total stroke was highest in patients with SDH, followed by those with ISH and IDH. Stroke incidence was also greater among overweight or obese participants than among normal-weight participants (**Table 2**).

Determinants of Developing Stroke in the Multivariate Analysis

In the Cox proportional hazards model, a positive correlation was noted between age and stroke incidence. Compared with the <35-year-old group, participants aged ≥75 years had the highest risk of onset (HR, 23.9; 95% CI, 15.5–36.8; $P < 0.001$). Education level was a protective factor for stroke onset, but the stroke risk for those with 7–9 years of formal education was not any higher than the stroke risk for those with >9 years of education (P>0.05). Although smoking was also a risk factor for stroke, the stroke risk among ever-smokers was higher than that among current smokers (HR, 1.8 vs. 1.6; all $P < 0.05$). Stroke risk was also significantly associated with sex (HR, 1.8), previous alcohol drinking (HR, 2.7), baseline hypertension (HR, 3.1), and overweight (HR, 1.3; **Table 3**).

Determinants of Stroke by Stroke Subtype

The risk of IS was higher among men than among women (HR, 1.90; 95% CI, 1.48–2.43; $P < 0.001$). Compared with the <35-year-old group, participants aged 65–74 years had the highest risk of stroke (HR, 9.60; 95% CI, 6.24–14.78; $P < 0.001$). The risk of IS was also significantly associated with current alcohol drinking (HR, 0.69; 95% CI, 0.52–0.93), former alcohol drinking (HR, 2.51; 95% CI, 1.13–5.62), overweight (HR, 1.33; 95% CI, 1.06–1.67), and obesity (HR, 1.91; 95% CI, 1.29–2.82; **Table 4**).

Meanwhile, the risk of ICH was higher in men than in women (HR, 2.88; 95% CI, 1.86–4.47; $P <0.001$). Compared with the <35-year-old group, participants aged 65–74 years had the highest risk of onset (HR, 5.12; 95% CI, 2.60–10.09; $P < 0.001$). Education level was a protective factor for ICH onset, but the risk of ICH in those with 7–9 years of formal education was statistically significant ($P < 0.001$). The risk of ICH was also significantly associated with overweight (HR, 2.18; 95% CI, 1.48–3.20; **Table 5**).

DISCUSSION

To our knowledge, this is the first prospective study to explore the comprehensive risk factors for stroke among low-income and poorly educated individuals in China. In this study, the overall stroke incidence per 100,000 person-years in this population was as high as 748 (473 for IS; 142 for ICH). For total stroke, sex, age, smoking status, alcohol drinking status, baseline hypertension, and overweight were risk factors, while education level was

TABLE 2 | Associated factors of developing stroke in the univariate analysis.

Risk factors	Without stroke (n = 3,268)	Stroke (n = 638)	IS (n = 404)	ICH (n = 121)
Age, means (SD), years	39.7(16.1)	52.4 (14.7)	49.5 (13.5)†	49.6 (15.1)†
Age group, n (%)		*	*	*
<35 years	1,495 (94.5)	87 (5.5)	63 (4.0)	24 (1.5)
35 44 years	785 (86.6)	121 (13.4)	95 (10.5)	22 (2.4)
45 54 years	353 (75.8)	113 (24.2)	80 (17.2)	23 (4.9)
55 64 years	308 (65.5)	162 (34.5)	108 (23.0)	28 (6.0)
65 74 years	198 (61.9)	122 (38.1)	49 (15.3)	21 (6.6)
≥75 years	129 (79.6)	33 (20.4)	9 (5.6)	3 (1.9)
Sex, (%)		*	*	*
Male	1,455 (79.3)	379 (20.7)	231 (12.6)	80 (4.4)
Female	1,813 (87.5)	259 (12.5)	173 (8.3)	41 (2.0)
Education, n (%)		*	*	*
0 years	1,246 (78.5)	342 (21.5)	191 (12.0)	68 (4.3)
1 6 years	786 (80.4)	192 (19.6)	128 (13.1)	39 (4.0)
7 9 years	1,105 (91.9)	98 (8.1)	80 (6.7)	13 (1.1)
> 9years	131 (95.6)	6 (4.4)	5 (3.6)	1 (0.7)
Smoking status, n (%)		*	*	*
Current smoking	802 (80.0)	200 (20.0)	124 (12.4)	42 (4.2)
Former smoking	76 (67.9)	36 (32.1)	29 (25.9)	5 (4.5)
Never smoking	2,390 (85.6)	402 (14.4)	251 (9.0)	74 (2.7)
Alcohol consumption, n (%)		*	*	
Current drinking	482 (80.1)	120 (19.9)	83 (13.8)	19 (3.2)
Former drinking	7 (43.8)	9 (56.3)	7 (43.8)	2 (12.5)
Never drinking	2,779 (84.5)	509 (15.5)	314 (9.5)	100 (3.0)
Baseline hypertension, n (%)		*	*	*
No	2384 (88.5)	311 (11.5)	212 (7.9)	64 (2.4)
Yes	884 (73.0)	327 (27.0)	192 (15.9)	57 (4.7)
SBP, means (SD), mmHg	125.5 (19.0)	137(23.7)†	134.0 (22.0)†	137.1 (24.4)†
DBP, means (SD), mmHg	78.9 (10.8)	85.2(13.0)†	84.0 (12.2)†	85.6 (14.1)†
BP type, n (%)		*	*	*
Normal	2,393 (88.4)	315 (11.6)	215 (7.9)	64 (2.4)
ISH	138 (78.0)	39 (22.0)	21 (11.9)	6 (3.4)
IDH	270 (82.3)	58 (17.7)	43 (13.1)	9 (2.7)
SDH	467 (67.4)	226 (32.6)	125 (18.0)	42 (6.1)
Baseline diabetes, n (%)		*		
No	3,266 (83.7)	636 (16.3)	403 (10.3)	121 (3.1)
Yes	2 (50.0)	2 (50.0)	1 (25.0)	0
BMI, means(SD) , Kg/m^2	22.5 (2.8)	23.2 (3.0)†	23.3 (2.8)†	23.3 (2.8)†
BMI groups, n (%)		*	*	*
Normal weight	2,483 (85.7)	414 (14.3)	261 (9.0)	71 (2.5)
Overweight	664 (78.4)	183 (21.6)	113 (13.3)	45 (5.3)
Obesity	121 (74.7)	41 (25.3)	30 (18.5)	5 (3.1)

SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; ISH, isolated systolic hypertension; IDH, isolated diastolic hypertension; SDH, systolic-diastolic hypertension; BMI, body mass index. † *Presented P < 0.05 comparing to individuals without stroke.* **Presented P < 0.05 in the different groups.*

TABLE 3 | Determinants of developing stroke in the multivariate analysis.

Effected factors	Reference	HR (95%CI)	*P*
Men	Women	1.8 (1.5, 2.1)	<0.001
Age	<35 years		
35 44 years		2.4 (1.8, 3.2)	<0.001
45 54 years		4.7 (3.5, 6.3)	<0.001
55 64 years		9.7 (7.2, 12.9)	<0.001
65 74 years		18.4 (13.5, 25.1)	<0.001
≥75 years		23.9 (15.5, 36.8)	<0.001
Education	>9 years		
0 years		2.9 (1.3, 6.5)	0.011
1∼6 years		3.1 (1.4, 7.0)	0.007
7∼9 years		2.2 (1.0, 5.1)	0.059
Smoking	Never smoking		
Current smoking		1.6 (1.3, 1.9)	<0.001
Former smoking		1.8 (1.2, 2.7)	0.002
Drinking	Never drinking		
Current drinking		0.9 (0.7, 1.1)	0.335
Former drinking		2.7 (1.3, 5.4)	0.007
Baseline hypertension	No		
Yes		3.1 (1.1, 8.3)	0.026
Baseline diabetes	No		
Yes		3.7 (0.9, 15.0)	0.066
BP type	Normal		
ISH		1.0 (0.4, 2.8)	0.996
IDH		0.2 (0.2, 1.4)	0.198
SDH		0.4 (1.5, 0.6)	0.434
BMI groups	Normal weight		
Overweight		1.3 (1.1, 1.5)	0.006
Obesity		1.3 (0.9, 1.8)	0.105

ISH, isolated systolic hypertension; IDH, isolated diastolic hypertension; SDH, systolic-diastolic hypertension.

TABLE 4 | Determinants of developing ischemic stroke in the multivariate analysis.

Effected factors	Reference	HR (95%CI)	*P*
Men	Women	1.90 (1.48,2.43)	<0.001
Age	<35 years		
35 44 years		2.57 (1.85,3.58)	<0.001
45 54 years		4.40 (3.07,6.30)	<0.001
55 64 years		8.38 (5.81,12.07)	<0.001
65 74 years		9.60 (6.24,14.78)	<0.001
≥75 years		8.46 (3.97,18.03)	<0.001
Education	>9 years		
0 years		2.2 (0.9, 5.4)	0.082
1∼6 years		2.6 (1.0, 6.3)	0.052
7∼9 years		2.1 (0.9, 5.2)	0.105
Smoking	Never smoking		
Current smoking		1.07 (0.82,1.39)	0.615
Former smoking		1.17 (0.76,1.81)	0.476
Drinking	Never drinking		
Current drinking		0.69 (0.52,0.93)	0.013
Former drinking		2.51 (1.13,5.62)	0.025
Baseline hypertension	No		
Yes		2.40 (0.74,7.81)	0.146
BP type	Normal		
ISH		0.52 (0.15,1.81)	0.303
IDH		0.57 (0.17,1.92)	0.366
SDH		0.85 (0.26,2.78)	0.788
BMI groups	Normal weight		
Overweight		1.33 (1.06,1.67)	0.013
Obesity		1.91 (1.29,2.82)	0.001

ISH, isolated systolic hypertension; IDH, isolated diastolic hypertension; SDH, systolic-diastolic hypertension.

a protective factor. For IS, sex, age, former alcohol drinking, overweight, and obesity were risk factors, whereas current alcohol drinking was a protective factor. For ICH, sex, age, and overweight were risk factors, while an education level of >9 years was a protective factor.

Previous studies have reported a dramatic increase in the incidence of first-ever stroke. The age-standardized incidence of first-ever stroke per 100,000 person-years increased rapidly from 124.5 in 1992–1998 to 190.0 in 1999–2005 and to 318.2 in 2006–2012; overall, the incidence increased by 6.5% annually for this population (11). The incidences of total stroke were 586.8 per 100,000 person-years in northeastern Greece, 76.5 per 100,000 person-years in Argentina, and 345.1 per 100,000 person-years in China (21–23). However, in our study, the stroke incidence was as high as 748 per 100,000 person-years. The higher prevalence of risk factors for stroke, including hypertension, obesity, smoking, and alcohol drinking, in this population may have contributed to the elevated incidence of stroke (11).

The influence of sex and age on stroke incidence is being increasingly recognized and evaluated. With advancing age, the stroke incidence for both men and women increases exponentially (24), with approximately 75–89% of strokes occurring in individuals aged >65 years (25), consistent with our findings. Compared with individuals aged <35 years, stroke risk was 23.9 times higher among individuals aged ≥75 years, and participants aged 65–74 years had the highest risk of onset of IS and ICH. A study from Sweden also indicated that stroke risk was significantly associated with age (risk ratio [RR] per 1 year of age, 1.12) in individuals with normal BP (26).

Our results showed that stroke risk in men was 1.8 times higher than that in women. Similarly, a Swiss study showed a higher age-specific stroke incidence in men than in women (27). Overall, the global age-adjusted incidence ratio for strokes in men vs. women is 1.33, with the highest ratio occurring among individuals aged of 35–44 years and decreasing after the age of 75 years (28). The excess rate of stroke in women of advanced age may arise from their longer life expectancy than men, which results in increasing age being associated with higher stroke risk (24, 29). However, in our study population, further study is required to investigate the sex-specific differences in age-related stroke incidence. This may be partially explained by studies that have reported that estrogens beneficially affect the vasculature by improving endothelial

TABLE 5 | Determinants of developing hemorrhagic stroke in the multivariate analysis.

Effected factors	Reference	HR(95%CI)	*P*
Men	Women	2.88 (1.86,4.47)	<0.001
Age	<35 years		
35 44 years		1.20 (0.66,2.18)	0.551
45 54 years		2.36 (1.28,4.33)	0.006
55 64 years		3.11 (1.68,5.77)	<0.001
65 74 years		5.12 (2.60,10.09)	<0.001
≥75 years		3.87 (1.08,13.92)	0.038
Education	>9 years		
0 years		5.0 (0.7, 36.7)	0.111
1∼6 years		4.6 (0.6, 33.8)	0.333
7∼9 years		1.6 (0.2, 12.7)	0.629
Smoking	Never smoking		
Current smoking		0.97 (0.63,1.50)	0.898
Former smoking		0.55 (0.21,1.40)	0.207
Baseline hypertension	No		
Yes		969.49 (0.00,6.85)	0.886
BP type	Normal		
ISH		945.73 (0.00,6.70)	0.886
IDH		931.11 (0.00,6.59)	0.887
SDH		2034.18 (0.00,1.44)	0.874
BMI groups	Normal weight		
Overweight		2.18 (1.48,3.20)	<0.001
Obesity		1.38 (0.55,3.48)	0.499

ISH, isolated systolic hypertension; IDH, isolated diastolic hypertension; SDH, systolic-diastolic hypertension.

function, enhancing vasodilation, and increasing blood flow after vascular occlusion; estrogens also have antioxidative and anti-inflammatory effects (30) and inhibit platelet aggregation (31).

Besides sex and age, smoking and alcohol drinking are independent risk factors for stroke (32–36). Although a previous studies failed to show a significant increase in total stroke risk among ever-smokers compared with never-smokers (37–39), a study from Japan found an 18% decrease in total stroke risk within the first 2 years after smoking cessation, with the maximum effect (38% risk reduction) occurring 2–4 years after smoking cessation (32). Our results also showed that smoking was a risk factor for stroke, and stroke risk was higher among former smokers than among current smokers (HR, 1.8 vs. 1.6). The reason may be because this low-education population only quit smoking after they developed a serious disease.

Previous meta-analyses (40, 41) also suggested that heavy alcohol drinking is associated with an increased risk of stroke, but that low-to-moderate intake may be protective against total stroke and IS. In this study, there was a significant increase in the risk of total stroke and IS among those who were former alcohol drinkers, but there was a significant decrease in risk among those who currently drink compared with those who never drank. This may be because low-dose alcohol drinking among current drinkers may have protective effects against stroke. Therefore, further study is needed to quantify the amount of alcohol consumed by this study population.

In our study population, ever-smokers and ever-drinkers often experienced diseases such as hypertension, and we did not have access to statistics regarding the durations of smoking and drinking cessation. Hypertension was more prevalent among ever-smokers than among never-smokers or current smokers (32). Previous studies have shown that alcohol drinking is also associated with elevated BP (42). Hypertension is often reported to be the most common and strongest risk factor associated with strokes. In a Chinese study (43) of five stroke-associated risk factors (hypertension, dyslipidemia, obesity, diabetes, and smoking), hypertension was most strongly associated with stroke risk. The results of the present study also indicated that baseline hypertension was a strong risk factor for stroke (HR, 3.1).

Diabetes is another classic risk factor for stroke. In our analysis, the prevalence of diabetes was significantly higher among stroke patients, but the relationship became nonsignificant in the multivariate analysis. This may have been due to the very low number of patients ($n = 4$) who exhibited known diabetes at baseline. The awareness, treatment, and control rates for diabetes in this population were 42.9, 11.1, and 11.1% in 1992, respectively. The low level of knowledge about diabetes due to the low income and low education status in this population may be the main cause of the lower prevalence of diabetes in this study.

Comparing the lowest and highest education levels, a study has demonstrated that low education level was associated with a 2.5-fold increase in stroke risk (44). Similarly, a Swedish study involving middle-aged women reported an elevated stroke risk among those with less education. In that study, the associated excess risk was largely attributed to lifestyle and biological risk factors for stroke, particularly smoking and alcohol drinking (45). Consistent with these earlier observations, the findings of the present study showed that education was a protective factor for total stroke and ICH.

A previous meta-analysis reported an RR of 1.22 (95% CI, 1.05–1.41) for IS in overweight patients and an RR of 1.64 (95% CI, 1.36–1.99) for IS in obese patients (46). Additionally, multivariate analyses of data from a study involving 76,227 Chinese adults showed that a 2 kg/m^2 increase in baseline BMI increased the total stroke RR by 6.1% (47). Similarly, in the present study, overweight and obesity increased the risk of developing IS. Moreover, overweight was associated with a high risk of stroke and ICH.

This study has some limitations. The study population was selected from a township in northern China that was not representative of the country's overall population. Although this study was a prospective cohort study involving a rural, low-income population, a larger population and a longer study period may have reduced the impact of the limited representativeness of the sample on the study results. Furthermore, we did not

collect information regarding all the medicines used by the participants. However, because of their low socioeconomic status, the frequency of medicine use in this population was low (16) and may not significantly affect the validity of the results.

CONCLUSIONS

This study identified uncontrollable (sex and age) and controllable (education, smoking, alcohol drinking, hypertension, and overweight) risk factors for stroke in a low-income, rural population in China. Therefore, it is critical for clinical doctors to control BP and weight effectively, advocate cessation of smoking/alcohol drinking, and enhance the education level in this population to prevent increase in the burden of stroke.

AUTHOR CONTRIBUTIONS

JW and XN: contributed to the conception and design of the work; YW, ZF, YC, JN, JL, JH, LR, and JT: contributed the data acquisition; JW and XN: contributed the analysis and interpretation of data for the work; YW, ZF, and YC: contributed drafting the work; JW and XN: contributed revising the work for important intellectual content. All authors approved of the final version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Structural Equation Model (SEM) of Stroke Mortality in Spanish Inpatient Hospital Settings: The Role of Individual and Contextual Factors

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Introduction: Traditionally, predictive models of in-hospital mortality in ischemic stroke have focused on individual patient variables, to the neglect of in-hospital contextual variables. In addition, frequently used scores are betters predictors of risk of sequelae than mortality, and, to date, the use of structural equations in elaborating such measures has only been anecdotal.

Aims: The aim of this paper was to analyze the joint predictive weight of the following: (1) individual factors (age, gender, obesity, and epilepsy) on the mediating factors (arrhythmias, dyslipidemia, hypertension), and ultimately death (exitus); (2) contextual in-hospital factors (year and existence of a stroke unit) on the mediating factors (number of diagnoses, procedures and length of stay, and re-admission), as determinants of death; and (3) certain factors in predicting others.

Material and Methods: Retrospective cohort study through observational analysis of all hospital stays of Diagnosis Related Group (DRG) 14, non-lysed ischemic stroke, during the time period 2008–2012. The sample consisted of a total of 186,245 hospital stays, taken from the Minimum Basic Data Set (MBDS) upon discharge from Spanish hospitals. MANOVAs were carried out to establish the linear effect of certain variables on others. These formed the basis for building the Structural Equation Model (SEM), with the corresponding parameters and restrictive indicators.

Results: A consistent model of causal predictive relationships between the postulated variables was obtained. One of the most interesting effects was the predictive value of contextual variables on individual variables, especially the indirect effect of the existence of stroke units on reducing number of procedures, readmission and in-hospital mortality.

Conclusion: Contextual variables, and specifically the availability of stroke units, made a positive impact on individual variables that affect prognosis and mortality in ischemic stroke. Moreover, it is feasible to determine this impact through the use of structural equation methodology. We analyze the methodological and clinical implications of this type of study for hospital policies.

Keywords: stroke, mortality, structural equation model, predictive model, inpatient hospital

INTRODUCTION

Prevalence of Ischemic Stroke

According to the WHO, ischemic stroke (IS) is the third leading cause of death in Western countries, and the first cause of disability in adults, in addition to having a high morbimortality load (1). In the USA alone, there are 800,000 persons every year who experience a stroke incident, either first-time or recurrent. The age-adjusted mortality rate in the most recent American studies has shown that stroke is a direct, underlying cause in 36.2 of every 100,000 exitus per year (2).

In *Europe*, as of today, the age-standardized incidence of stroke falls between 95 and 290 episodes per 100,000 inhabitants, with 1-month mortality between 10 and 35%; stroke represents the second leading cause of morbidity and disability (3). The present situation in Europe is rising incidence among young adults, despite the decreasing trend worldwide. Mortality is not the only parameter of interest; 33% will require readmission to hospital, 7–13% will have another episode, moderate cognitive decline will affect 35–47% and dementia, 7–23% (3). Consequently, morbidity load as well as mortality are pressor elements in this population; they have important repercussions today, and in the case of Europe, can only be expected to worsen in coming years.

In *Spain*, mortality due to cardiovascular causes and stroke in particular began to decline in 1973, thanks to improved attention to cardiovascular risk factors associated with greater stroke mortality, as well as to diagnostic and therapeutic advances in the earliest phases of care. Very heterogeneous values of incidence in Spain have been reported, as seen in the study by Lópoez-Pousa et al. (4). Subsequently, the Ibericus study, led by the Spanish Society of Neurology, allowed access to more up-to-date, quality data, showing an incidence of 118 cases per 100,000 inhabitants per year. In-hospital mortality was also reported as 4% (5, 6). Nonetheless, rising mortality rates are to be expected in the future, due to pronounced aging of the population and the increased prevalence of risk factors in an increasingly elderly population (5). Currently, ischemic stroke is the second leading cause of death in Spain in the general population and the first cause of death in women (6); according to clinical records in our country, it represents 12.9% of total deaths (7).

Risk Factors for Developing a Stroke

The risk factors associated with stroke incidence and mortality are well-known. These factors can be divided into *personal factors* (related to the patient, regardless of modifiability) and *contextual factors*, which are usually associated with availability of specific resources, shorter time to care, and the establishment of specific plans for stroke care (8, 9).

The most notable, prevalent *individual risk factors* for developing a stroke include hypertension (HTN), Diabetes Mellitus (DM), abnormal heart rhythm (especially atrial fibrillation), hyperlipidemia and hypertriglyceridemia, liver disease, smoking, sedentary lifestyle and finally nutritional and genetic factors (2, 10). Sleep apnea and certain psychosocial factors have also been associated. The factors mentioned not only increase incidence, but also subsequent mortality (11). Predictors of poor evolution include the severity of the initial stroke, measured on the National Institute of Health Stroke Scale (NIHSS) or Canadian Neurological Scale (CNS); existence of diabetes mellitus; large or pronounced drops in blood pressure; body temperature; certain coagulation markers; and inflammation and glycemia at hospital admission (12).

In addition to individual factors, there are other important prognosis factors that have seldom been studied in conjunction with the individual factors; we will call these *contextual risk factors.* The existence of a comprehensive plan of action—which maximizes and optimizes patient care from the time of hospital arrival—has been shown to have beneficial results for patients who have suffered an acute stroke, increasing their probability of recovery (13). Over the past 20 years, not only the change in preventive action, but also early, regulated response that follows the most advanced quality standards, and the creation of specific stroke care units, have been shown to bring about a significant decrease in stroke mortality and sequelae.

The Construction of Probabilistic Prediction Models

Extensive work has been done in detecting the risk factors of developing an ischemic event and in estimating the likelihood of death or of sequelae (7). Specifically, work by Smith et al. (14) produced predictive models of in-hospital mortality, whether for ischemic or hemorrhagic stroke, using a limited number of variables; excellent estimated discriminative capacity was attained. Other highly interesting work has shown a successful methodology for elaborating predictive models of stroke (15).

Since the creation of stroke units, there have been numerous studies where these units demonstrate a decrease in mortality and disability, in comparison to the administration of conventional care (Cochrane Database of Systematic Reviews, 2013). More recently, their cost-effectiveness and a shortened average length of stay have also been demonstrated (16).

Aims and Hypotheses

A large part of the literature has focused on individual prognosis factors, while other authors have assessed isolated contextual elements, especially the availability of stroke units. To date, there is insufficient evidence that combines both types of variables and explores their interrelations using a structural, hierarchical equation methodology.

Consequently, our main *objective* was to establish interdependent and predictive relationships among the variables that are most often identified in association with pathogenesis and development of stroke, and the main dependent variables (mortality and readmission to hospital). Specifically, and original to this study, we evaluated the role of certain process and context variables, and how they acted as intermediate, modulating variables in the non-linear relationship between predictive variables and outcome variables.

In order to address the main objective, the initial *hypothesis* states that each individual variable defined in the linear model (primarily age, gender, obesity, and epilepsy) and each contextual variable (year, existence of stroke units) would have a statistically significant effect on the intermediate variables of the previously established linear model, whether individual variables (arrhythmias, dyslipidemia, and hypertension) or contextual (length of stay, number of diagnoses, and procedures). These in turn would have a significant effect on the two final, dependent variables, namely, readmissions, and mortality.

MATERIALS AND METHODS

Participants

Type of Study

A retrospective cohort study using analytical observation of all hospital stays of the Diagnosis Related Group (GRD) 14—non-lysed ischemic stroke—during the time period 2008–2012. All hospital stays of patients age 24 or older were included.

Scope

The study was carried out within the Spanish National Healthcare System (NHS, Spain), a decentralized structure across 17 autonomous regions with their respective regional healthcare systems. Each of the Autonomous Systems has its own structure, with Basic Healthcare Zones grouped in turn into Primary Care Districts and Hospitals. This system is the same throughout the country, despite the drawback of frequent failures in inter-region communication. Healthcare within this network is free of charge; costs are borne by the different regional governments.

Information Source, Sample, and Case Selection

The source of information was the Spanish Minimum Basic Hospital Discharge Dataset, made available by the Ministry of Health, Consumerism and Social Policies. A total of 186,245 hospital stays were analyzed. Diagnostic and procedural coding followed the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD9MC). The selection criteria consisted of identifying the patient stays that were discharged under DRG 14 (AP-DRG classifier, version 21). This diagnostic group includes exclusively those patients admitted for ischemic stroke who undergo medical treatment, but not fibrinolysis or mechanical reperfusion; consequently, this DRG defines a very specific, select group of patients. As in the relevant bibliography, the total group of hospital stays was then limited to patients over the age of 24, given the small incidence and prevalence of these events in younger persons. Additionally, outlier hospital stays were filtered out according to the classical method that defines outliers with the formula T2=Q3+1.5(Q3-Q1), where Q identifies the third and first quartiles and T2 is the maximum value of the stay that results from applying the formula. Using this methodology, patients with stays longer than 21 days were identified and excluded.

Procedure

This project has been approved by the Clinical Ethics Committee of the Province of Almeria, Complejo Hospitalario Torrecardenas, Andalusian Health Service, Ministry of Health, Andalusia (Spain).

Data Analysis

Variables and Analysis Schema

The schema of analysis identified two axes for studying relations and associations between variables. On one hand, variables were classified into two large dimensions in each episode: individual and context dimensions. The *context* variables were identified as year, existence of a stroke unit, length of stay, total count of diagnoses and procedures at discharge, and any readmissions; the remaining variables were considered individual variables (**Table 1**). On the other hand, our second axis of analysis classified variables as independent variables, intermediate/process variables, or outcome/dependent variables—regardless of the dimension to which they belonged.

The main dependent variable in the individual dimension was in-hospital mortality. Secondarily, readmissions were also analyzed as a dependent variable in the context dimension. According to the second axis of analysis, both individual and contextual variables were classified as outcomes (exitus and readmission), intermediate or process variables (arrhythmias, dyslipidemia, HTN, length of stay, NDX, and NPR) or initial variables (age, gender, obesity, epilepsy, year, stroke unit) (**Table 1**). One must keep in mind that the variables that make up the secondary diagnoses cannot always be identified differentially as complications that occurred during hospitalization or as pre-existing patient comorbidities, such as epilepsy.

In order to make the Year variable (6 categories) more homogeneous, the derived variable "Year Gp" was obtained by establishing three bienniums.

Sociodemographic information was obtained from the variables year, age, gender, and Autonomous Region. Administrative elements were assessed through the variables length of stay, readmission within 30 days for the same DRG, type of admission (emergency vs. scheduled), and type of discharge (alive vs. exitus). We used the number of diagnoses at discharge (NDX) as a proxy variable for the patient's comorbidity, and the number of procedures at discharge (NPR) to estimate the procedural complexity of each episode and the main clinical comorbidities associated with ischemic processes (**Table 2**).

TABLE 1 | Classification of the constituent variables of the model along the two axes of coding and analysis.

	Previous or independent var.	Intermediate var.	Final, dependent or outcome var.
VARIABLES CLASSIFIED ACCORDING TO TWO AXES OF ANALYSIS			
Individual variables	Age	Arrhythmias	Mortality
	Gender	Dyslipidemia	
	Obesity	HTN	
	Epilepsy		
Contextual variables	Year	Stay	Readmission
	Stroke unit	N° of Diagnoses	
		N° Procedures	

CODING AND CLASSIFICATION OF INDIVIDUAL VS. CONTEXT VARIABLES	
Individual variables	Renal insufficiency (%)
Age (years)	Anemia (%)
Gender (M/F) (%)	Pulmonary embolism (%)
Obesity (%)	Heart Failure (%)
Epilepsy (%)	Acute Respiratory Insufficiency (%)
Arrythmias (%)	Topographic location of stroke
Dyslipidemia (%)	Exitus (%)
Hypertension (%)	**In-hospital contextual variables**
Diabetes (%)	Year (2008 to 2012)
COPD (%)	Stroke Unit Available (%)
Ischemic Cardiopathy (%)	Length of stay (days)
Valvulopathy (%)	NDX (quantitative)
Myocardiopathy (%)	NPR (quantitative)
Congenital Cardiopathy (%)	Readmission at 30 days (%)

NDX, Number of diagnoses at discharge; NPR, Number of procedures at discharge; COPD, Chronic obstructive pulmonary disease.

For each of the hospitalization episodes, the total number of diagnoses was calculated (including both new comorbidities and pre-existing comorbidities at the time of admission) and coded into 14 fields of variables assigned for that purpose. In this way, diagnosis number 1 is the one that motivates the admission and the rest of the diagnoses are recorded sequentially, some as derivatives of others, until completing the entire spectrum of pathology that existed in each event.

Statistical Analysis

For the statistical analysis, variables were treated as follows, according to the dimension being analyzed: (1) first, the initial variables were the independent variables (IV), and the process and outcome variables were dependent (DV); (2) second, the independent process variables were the IV and the outcome variables *exitus* (death) and readmission were the DV.

Two types of analysis were carried out in order to determine which variables to include in the structural linear model. First, *bivariate analysis* was carried out; Student's *t*-test was used to test the equality of means hypothesis for independent samples or analysis of variance. In cases where they could not be applied, the Mann-Whitney or Kruskall-Wallis non-parametric *U* was applied, as appropriate. The Chi-square test was used for comparison of qualitative variables. Relationships between quantitative variables were determined through Pearson or Spearman correlations. Second, *uni- and multi-variate inferential analysis* was carried out between the variables established in the rational model. Inferential statistical analyses (multivariate analysis, MANOVAs) were carried out using SPSS (v. 23.0) for Windows.

TABLE 2 | Principal and partial effects of independent variables (presage) on dependent variables (process).

Main effect		**F (Pillai)**	**df**	***p*<**	***np*²**	**Power**
AGE		7.748	42.000	0.000	0.000	1.00*
OBESITY		13.291	7.000	0.000	0.001	1.00*
EPILEPSY		7.785	7.000	0.000	0.000	1.00*
YEAR		2.009	28.000	0.001	0.000	0.999*
UNIT		9.428*b*	7.000	0.000	0.000	1.00*
IV	**DV**	**F (Pillai)**		***p*<**	***np*²**	**Power**
PARTIAL EFFECT (ONLY SIGNIFICANT PARTIAL EFFECTS)						
GENDER *						
OBESITY *						
UNIT	ARRHYTHMIAS	3.811		0.051	0.000	0.497*

*General Linear model. *Observed power of effect (only statistically significant). Full table provided in the* ***Complimentary / Supplementary Material****.*

Once the variables were identified, the empirical model of structural equations was finally developed. AMOS (v. 23.0) for Windows was used to construct the structural prediction model—specifically, to verify the structural linear prediction hypothesis (path analysis). To interpret the confirmatory factor analysis (CFA) and the structural equation model (SEM) fit, we focused on the Comparative Fit Index (CFI) and the Root Mean Square Error of Approximation (RMSEA). CFI values equal to or greater than 0.90 and 0.95, respectively, were taken to indicate acceptable and close fit to the data (17). RMSEA values equal to or below 0.05 and 0.08 were taken to indicate close and acceptable levels of fit, respectively (18). Keith (19) proposed the following beta coefficients as research benchmarks for direct effects: less than 0.05 is considered too small to be meaningful, above 0.05 is small but meaningful, above 0.10 is moderate, and above 0.25 is large. For indirect effects, we used Kenny's (20) definition of an indirect effect as the product of two effects; using Keith's benchmarks above, we proposed a small indirect effect = 0.003, moderate = 0.01, and large = 0.06, values that are significant in the sphere of education.

RESULTS

Basic Descriptive Results

The sample was composed of 186,245 hospital stays between the years 2008 and 2012. There were a total of 12,800 exitus during hospitalization. Over the study period, the death rate declined from 7.3% in 2008 to 6.5% in 2012, for an average rate of 6.9% for the whole period. Mean age of the sample was 79.92 (SD 12.54) years, with a mean hospital stay of 7.54 (SD 4.54) days, and 3.27 (SD 2.45) was the mean number of procedures applied. The mean number of diagnoses at discharge was 6.91 (SD 2.95), and 4.8% of

the sample were in a readmission situation under the same DRG. **Table 3** shows the distribution of the main variables by year.

Inferential Relations Among Variables

First, we assessed the effects of the individual-related IVs (age, gender, obesity, and epilepsy) and context-related IVs (year and existence of a stroke unit) on the intermediate individual variables (arrhythmias, dyslipidemia, and HTN) and intermediate contextual variables (length of stay, NDX, and NPR).

Findings showed a significant effect from each of the IVs (both contextual and individual) on the intermediate variables mentioned, except in the case of gender. No statistically significant, main interaction appeared. There were also numerous significant partial effects of each independent variable on the dependent variables; these are marked with an asterisk to the right in **Table 2**.

Afterward, we analyzed the effect of the individual IVs and the contextual IVs on the main dependent, individual variable (exitus). Uni- and multi-variate analyses showed a significant main effect of all the individual and contextual factors mentioned, except gender; in addition, evidence showed that the discrete factors with the greatest effect on mortality were age and epilepsy, followed by the existence of stroke units. Moreover, certain variables produced several significant interaction effects on mortality (**Table 4**), with the greatest observed power detected for the interactions of (*Year*Stroke unit*), (*Age*Epilepsy*Year),* and finally the interaction of *(Year*Gender*Obesity*StrokeUnit*), the latter demonstrating great explanatory power. The most relevant variable, common to two of the interactions detected, was the existence of stroke units. Likewise, the intermediate or process variables, whether related to the individual (arrhythmias, dyslipidemia, and HTN) or to the context (length of stay, NDX, and NPR), had a clear effect on mortality as DV.

By observing the pathologies coded for each hospital stay, we detected a significant main effect from multiple intermediate (or mediating) variables on mortality. This effect was shown for arrhythmias, dyslipidemia, and hypertension; however, the most powerful interaction in determining exitus was the joint effect of the interaction (*Dyslipidemia*Hypertension*) (**Table 5**).

Regarding the discrete contextual variables analyzed, those with the greatest effect were length of stay and NPR, along with readmissions. However, the variables with the greatest explanatory power were the interactions of (*Length of Stay*NDX*NPR),* (*NDX*NPR*Readmissions*), (*Length of Stay*NDX*Readmissions*), and (*Length of Stay*NDX*NPR*Readmissions*).

Linear Relations of Structural Prediction

The results of structural analysis or pathway analysis (SEM) showed an acceptable model of relationships. The relationship parameters of both models are presented below (**Table 6**).

Standardized Direct Effects

In the case of the personal variables, the predictive linear model establishes that the variable GENDER was predicted by AGE (0.259). OBESITY was negatively predicted by AGE (-0.111) and positively by GENDER (0.078). EPILEPSY was positively predicted by GENDER (0.008), and UNIT was positively predicted by AGE (0.013).

The variable ARRHYTHMIAS was significantly predicted by AGE (0.180), GENDER (0.067), OBESITY (−0.055), the number of DIAGNOSES (0.354), and PROCEDURES (−0.029). DYSLIPIDEMIA was predicted by AGE (−0.074), OBESITY (-0.064), and by EPILEPSY (−0.013). HTN was predicted by AGE (0.230), GENDER (0.041), OBESITY (0.137), EPILEPSY (0.021), and ARRHYTHMIAS (−0.103).

TABLE 3 | Baseline description over the period.

	2008	2009	2010	2011	2012
Age (SD) years	73.73 (12.31)	73.89 (12.44)	73.99 (12.54)	73.88 (12.72)	74.09 (12.69)
Hospital stay (SD) days	7.89 (4.67)	7.74 (4.59)	7.58 (4.53)	7.32 (4.45)	7.17 (4.42)
NDX (SD) diagnoses	6.26 (2.73)	6.55 (2.83)	6.82 (2.91)	7.32 (3.00)	7.60 (3.09)
NPR (SD) procedures	3.05 (2.24)	3.16 (2.43)	3.31 (2.51)	3.42 (2.55)	3.42 (2.50)
Female gender (%)	46.4	47	46.9	46.5	46.7
Readmission (%)	4.9	3.8	4.8	4.7	4.8
Emergency admission (%)	97.4	97.2	97.1	97.2	96.6

NDX, Number of diagnoses at discharge; NPR, Number of procedures at discharge.

TABLE 4 | Principal and partial effects of the independent variables (mediator) on the dependent variable (final): exitus.

Principal factor	df	F	*p*<	np^2	Power*
Personal factors					
YEAR	6	5.723	0.000	0.000	0.998*
OBESITY	1	4.239	0.040	0.000	0.539*
EPILEPSY	1	11.077	0.001	0.000	0.914*
Contextual factors					
YEAR	4	2.340	0.053	0.000	0.683*
UNIT	1	8.397	0.004	0.000	0.826*
Interaction factors					
EPILEPSY * YEAR	6	1.974	0.066	0.000	0.731*
UNIT * YEAR	6	2.645	0.014	0.000	0.866*
OBESITY * EPILEPSY	1	5.886	0.015	0.000	0.679*
OBESITY * UNIT	1	6.059	0.014	0.000	0.692*
EPILEPSY * YEAR	4	2.404	0.047	0.000	0.696*
EPILEPSY * UNIT	1	5.374	0.020	0.000	0.640*
AGE * EPILEPSY * YEAR	24	1.757	0.012	0.000	0.989*
AGE * EPILEPSY * UNIT	6	2.713	0.012	0.000	0.876*
OBESITY * EPILEPSY * UNIT	1	5.923	0.015	0.000	0.682*
OBESITY * YEAR * UNIT	18	1.796	0.020	0.000	0.968*

*General linear model. *Observed power of effect (only statistically significant). Full table provided in the* ***Complimentary / Supplementary Material****.*

As for the contextual variables, the variable UNIT was significantly predicted by AGE (0.013), STAY was predicted positively by EPILEPSY (0.035) and negatively by DIAGNOSES (−0.452). The variable DIAGNOSES was predicted by AGE (0.138), EPILEPSY (0.077), YEAR (0.164), UNIT (0.107), ARRHYTHMIAS (−0.114), DYSLIPIDEMIA (0.181), HTN (0.554), and STAY (0.148). The PROCEDURES variable was predicted by AGE (−218), by STAY (0.157), and by DIAGNOSES (0.211).

Finally, the variable READMISSION was predicted negatively by DYSLIPIDEMIA (−0.027), HTN (−0.058) and PROCEDURES (−0.058), and positively by DIAGNOSES (0.102). The variable EXITUS (DEATH) was positively predicted by AGE (0.141), ARRHYTHMIAS (0.064), and READMISSIONS (0.052), and negatively predicted by DISLIPIDEMIA (−0.046), HTN (−0.046), and PROCEDURES (−0.065). All error variances were significant ($p < 0.001$). **Table 7** shows the direct effects of the variables included in the model.

TABLE 5 | Effects of the individual process variables (ARRHYTHMIAS, DYSLIPIDEMIA, and HTN) and of context process variables (YEAR, STROKE UNITS) on the outcome variable (EXITUS).

Principal factor	df	F (Pillais)	$p <$	np^2	power
Individual					
ARRHYTHMIAS	1	1056.446	0.000	0.006	1.00*
DYSLIPIDEMIA	1	695.140	0.000	0.004	1.00*
HTN	1	18.429	0.000	0.000	0.990*
ARRHYTHMIAS * DYSLIPIDEMIA	1	6.748	0.009	0.000	0.738*
ARRHYTHMIAS * HTN	1	6.987	0.008	0.000	0.753*
DYSLIPIDEMIA * HTN	1	2.656	0.000	0.000	1.00*
Contextual					
STAY	3	13.534	0.000	0.000	1.00*
DIAGNOSES	3	4.075	0.007	0.000	0.848*
PROCEDURES	4	24.366	0.000	0.001	1.00*
READMISSION	1	12.411	0.000	0.000	0.941*
STAY * PROCEDURES	9	2.562	0.006	0.000	0.945*
STAY * PROCEDURES	12	3.691	0.000	0.000	0.999*
STAY * READMISSION	3	6.730	0.000	0.000	0.976*
DIAGNOSES * PROCEDURES	12	4.511	0.000	0.000	1.00*
DIAGNOSES * READMISSION	3	4.752	0.003	0.000	0.902*
PROCEDURES * READMISSION	4	3.088	0.015	0.000	0.815*
STAY * DIAGNOSES * PROCEDURES	33	2.180	0.000	0.000	1.00*
STAY * DIAGNOSES * READMISSION	9	2.804	0.003	0.000	0.964*
STAY * PROCEDURES * READMISSION	12	1.804	0.042	0.000	0.897*
DIAGNOSES * PROCEDUR * READMISSION	9	4.248	0.000	0.000	0.998*
STAY * DIAGNOSES * PROCEDURES * READMISSION	23	1.797	0.011	0.000	0.989*

*Lineal General Model.. *Observed power (significant); HTN, Arterial Hypertension. Full table provided in the **Complimentary / Supplementary Material**.*

Standardized Indirect Effects

The model also revealed multiple indirect predictions among the variables. With respect to personal variables, the predictive linear model establishes that AGE was a positive, significant, indirect predictor of OBESITY (0.020). The variable EPILEPSY was not predicted indirectly by any other variable.

The variable ARRHYTHMIA was indirectly predicted, in a positive sense, by AGE (0.080), OBESITY (0.029), EPILEPSY (0.024), UNITS (0.034), DYSLIPIDEMIA (0.088), HTN (0.145), and STAY (0.044), and in a negative sense by ARRHYTHMIAS (−0.088) and DIAGNOSES (−0.092).

DYSLIPIDEMIA was indirectly predicted, in a positive sense, by OBESITY (0.004), UNITS (0.005), ARRHYTHMIAS (0.008), and PROCEDURES (0.004), while negatively predicted by AGE (−0.042), GENDER (−0.004), EPILEPSY (−0.003), YEAR (-0.005), HTN (−0.020), STAY (−0.006), and DIAGNOSES (−0.036).

Hypertension was indirectly and negatively predicted by AGE (−0.125), GENDER (−0.003), OBESITY (−0.016), EPILEPSY (−0.036), YEAR (−0.062), UNITS, ARRHYTHMIAS (−0.044), DYSLIPIDEMIA (−0.127), HTN (−0.210), STAY (−0.070), while predicted positively by DIAGNOSES (0.073) and PROCEDURES (0.003).

In the case of contextual variables, the existence of a stroke unit (UNIT) was not indirectly predicted by any other variable in the model. Length of stay (STAY) was indirectly predicted, in a positive sense, by AGE (0.003), GENDER (0.001), DYSLIPIDEMIA (0.001), and HYPERTENSION (0.001), while negatively predicted by ARRHYTHMIAS (−0.001).

The variable DIAGNOSES was positively predicted by AGE (0.009), GENDER (0.013), OBESITY (0.082) and DYSLIPIDEMIA (0.071), and negatively predicted by EPILEPSY (−0.009), ARRHYTHMIAS (−0.048), HYPERTENSION (−0.136), DIAGNOSES (−0.246), and YEAR (−0.048).

PROCEDURES were positively predicted by AGE (0.003), GENDER (0.003), OBESITY (0.012), EPILEPSY (0.020), DYSLIPIDEMIA (0.053), HTN (0.088), YEAR (0.015) and UNITS (0.032); and negatively by ARRYHTHMIAS (−0.033) and DIAGNOSES (−0.052).

TABLE 6 | Models of structural linear results of the variables.

Model	Degrees of Freedom	Chi-square	$p <$	NFI	RFI	IFI	TLI	CFI	RMSEA	Hoelter
										0.05–0.01
1. 14 F	(119-64): 55	77103.176	0.001	0.374	0.391	0.374	0.391	0.374	0.087	178–199
2. 14 F	(119-73): 46	32527.569	0.001	0.736	0.397	0.736	0.397	0.736	0.062	360–408
3. 14 F	(119-82): 37	4721.698	0.001	0.963	0.935	0.963	0.926	0.963	0.026	2059–2363

TABLE 7 | Standardized direct effects (Default model).

	AGE	GEND	OBES	EPILEP	YEAR	UNIT	ARR	DYSL	HTN	STAY	NDX	NPR	READM
GENDER	0.259												
OBESIT	−0.111	0.078											
EPILEP		0.008		0.077									
ARR	0.180	0.067	−0.055								0.354*	−0.029	
DYSLIP	−0.074		0.064	−0.013									
HTN	0.230	0.041	0.137	0.021			−0.103						
YEAR													
UNIT	0.013												
STAY				0.035							−0.452*		
DIAGN	0.138				0.164	0.107	−0.114	0.181	0.554*	0.148			
PROC	−0.218									0.157	0.211		
READM								−0.027	−0.029		0.102	−0.058	
EXITUS	0.141						0.064	−0.046	−0.040			−0.065.	0.052

*AGE, Age; GEND, Gender; OBES, Obesity; EPILEP, Epilepsy; YEAR, Year; UNIT, Stroke Unit; ARR, arrhythmias; DYSL, Dyslipidemia; HTN, Arterial Hypertension: STAY, Hospital Stay; NDX, Number of Diagnoses; NPR, Number of Procedures; READM, Readmission. * IMPORTANT EFFECT.*

The outcome variable READMISSION was indirectly and positively predicted by the personal variables AGE (0.003), GENDER (0.002), OBESITY (0.001), EPILEPSY (0.007), DYSLIPIDEMIA (0.048), and HTN (0.048), and positively predicted by the contextual variables YEAR (0.012) and UNIT (0.003), while predicted negatively by contextual variables DIAGNOSES (−0.015) and PROCEDURES (−0.001).

The other variable, EXITUS (DEATH), was predicted positively by AGE (0.031), GENDER (0.003), HTN (0.014), DIAGNOSES (0.025), and negatively by OBESITY (−0.002), EPILEPSY (−0.002), DYSLIPIDEMIA (−0.004), UNITS (0.013), and PROCEDURES (−0.005) (see **Table 8**).

Graphic representation of the structural model

The final model is graphically represented in **Figure 1**.

DISCUSSION

Empirical Evidence

This investigation began with the hypothesis that each variable defined in the linear model, whether individual or contextual, would have a statistically significant effect on the intermediate variables of the established model, at the individual level and at the contextual level. These in turn would have a significant effect on the two dependent outcome variables, namely, readmissions and mortality. This hypothesis was in large measure confirmed, having verified in our SEM model that the *individual variables* made a differential, statistically significant impact on the *intermediate* (mediating) variables, and these in turn on exitus. This is not an every-variable-to-every-variable relationship; the particular predictions are made explicit below, as well as some paradoxical relationships that deserve a detailed explanation. The inferential results presented here show effects from combined variables, similar to what has been reported with prior evidence. The clearest effects were produced by the combination of multiple variables.

Individual Variables as Predictors

As seen in other studies, different variables were found to be statistically significant predictors of the presence of arrhythmias as comorbidity in this group of patients. In this context, arrhythmias were significantly, positively predicted by age (21, 22), obesity (23, 24) and the presence of epilepsy among the secondary diagnoses. Some of these linear associations were known previously, but had not been demonstrated to date using a predictive structural model. The literature reflects an association between epilepsy and arrhythmias, whether direct or mediated by antiepileptic treatment (25–27). In the same way, age was associated with the presence of dyslipidemia (28) and HTN (29). The association found between epilepsy and dyslipidemia is consistent with the known effect on lipids from treatment with certain anti-epileptic drugs (30, 31).

One paradoxical result is the negative prediction of dyslipidemia as a function of *age*. A possible explanation would be that stroke-affected patients suffer from vasculopathy and often arteriopathy; they are affected by different types of pathologies that are treated fundamentally with statins. Prior research has demonstrated that the use of statins increases with age. Thus, age might be negatively associated with dyslipidemia through the use of this pharmacological group in the type of patient most prevalent in this study: older people with a background of cardiovascular pathology.

On the other hand, gender (being a woman) positively predicts arrhythmias and HTN, but not dyslipidemia. The association between the female gender and the existence of certain types of arrhythmias is well-documented (32), and probably accounts for our findings. However, the limitations of our information source (CMBD) do not allow us to identify the subtypes of arrhythmias prevalent in our study sample. As for HTN, it is known to be more prevalent and more associated with men at younger ages than women, but in the situation that concerns us, several elements might explain an association with the female gender. On one hand we are working with patients affected by an ischemic

TABLE 8 | Standardized indirect effects (Default model).

	AGE	GEND	OBES	EPILEP	YEAR	UNIT	ARR	DYSL	HTN	STAY	NDX	NPR	READM
GENDER													
OBESIT	0.020												
EPILEP													
ARR	0.080		0.029	0.024		0.034	−0.057	0.088	0.145*	0.044	−0.092		
DYSLIP	−0.042	−0.004	0.004	−0.003	−0.005	0.005	0.008	−0.012	−0.020	−0.066	−0.036	0.004	
HTN	−0.125	−0.003	−0.016	−0.036	−0.062	−0.051	−0.044	−0.127	−0.210*	−0.070	0.073	0.003	
YEAR													
UNIT													
STAY	0.003	0.001					−0.001	0.001	0.001				
NDX	0.009	0.013	0.082	−0.009	−0.048	0.001	−0.048	0.071	−0.136	−0.009	−0.246	0.001	
NPR	0.033	0.003	0.012	0.020	0.015	0.032	−0.033	0.053	0.088	0.029	−0.052		
READM	0.033	0.002	0.001	0.007	0.012	0.003	−0.011	0.021	0.048	0.005	−0.015	−0.001	
EXITUS	0.031	0.003	−0.011	−0.002	0.009	−0.013	0.007	−0.004	0.014	−0.009	0.025	−0.005	

*AGE, Age; GEND, Gender; OBES, Obesity; EPILEP, Epilepsy; YEAR, Year; UNIT, Stroke Unit; ARR, arrhythmias; DYSL, Dyslipidemia; HTN, Arterial Hypertension: STAY, Hospital Stay; NDX, Number of Diagnoses; NPR, Number of Procedures; READM, Readmission. * IMPORTANT EFFECT.*

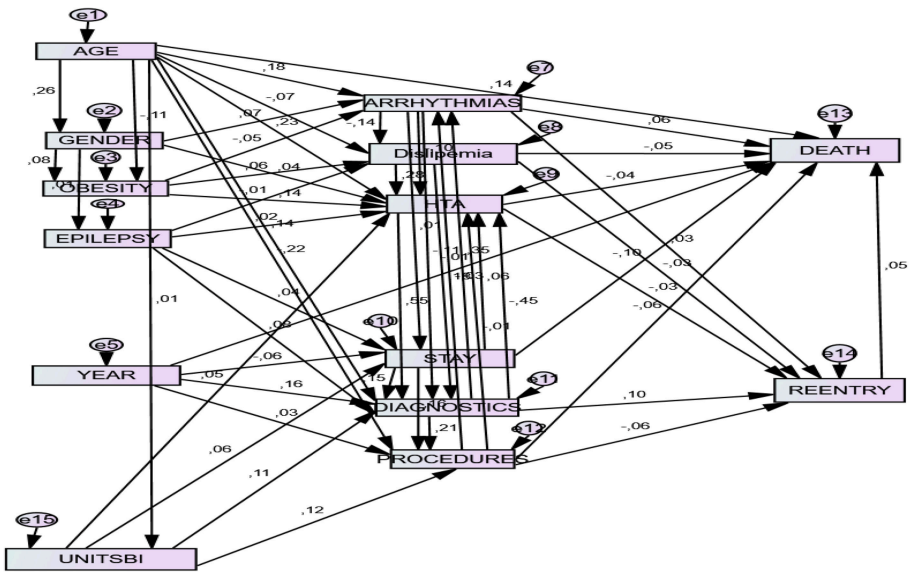

FIGURE 1 | Final structural model. Unitsbi, existence of stroke unit; HTA, Hypertension; Stay, Length of stay; Reentry: readmission within 30 days under the same DRG; Diagnostics: Number of diagnoses upon discharge. Procedures: Number of procedures upon discharge.

stroke and not the general population; on the other hand, the more senile sectors, with higher prevalence of HTN, are also mostly female in our sample and in the general population, due to the longer life expectancy of women.

Another noteworthy result is the positive predictive role of epilepsy with respect to HTN. According to the established literature, HTN is an obvious, crucial risk factor for ischemic stroke, in the same way that stroke itself is a risk factor for developing epileptic crises. We may then suppose, in full agreement with other authors (33), that the relationship between HTN—especially if not properly controlled—and epilepsy can also develop directly, that is, even prior to development of an ischemic event.

These results concur with prior medical evidence showing that *age* positively predicts arrhythmias (21, 23) as well as HTN (29). Although the evidence is not as clear, age influences hemodynamic regulatory mechanisms, which in turn have consequences in blood pressure and brain self-regulation (29). A paradoxical result is the negative prediction of dyslipidemia.

Obesity, for its part, negatively predicts arrhythmias, but positively predicts dyslipidemia and HTN. A consistent model of obesity as a positive predictor of dyslipidemia and HTN is evident and well-documented (34, 35); this falls in line with the relatively new concept of obesity as a chronic, recurring, progressive disease, as suggested by Bray et al. (36). Finally, in our understanding to date, there seems

to be no clear association of obesity and arrhythmias, or at the least, it would occur through some mechanism not yet understood.

There are substantial associations between variables of individual characteristics and the two main dependent variables (readmissions and exitus); in a few cases, they seem paradoxical or difficult to explain, thus indicating a need to investigate some of the predictive effects that were found. Both dyslipidemia and NPR are significant, negative predictors of readmissions, while NDX is a significant, positive predictor. Increased procedural effort or therapeutic intensity can explain the direction of the NPR-Readmissions prediction, such that where greater effort is applied, there is less likelihood of being readmitted to hospital for the same reason in the 30 days following discharge. Similarly, when patients have a greater number of diagnoses (greater comorbidity), prediction of readmissions is positive, demonstrating that the patient's overall complexity undoubtedly influences his or her prognosis.

Elsewhere, the evidence showed dyslipidemia and NPR as negative predictors of mortality, while age and the existence of arrhythmias were positive predictors. It seems logical that more elderly patients, and patients affected by arrhythmias (also more frequent at advanced ages), would have greater mortality. The negative association between dyslipidemia and mortality, to our understanding, can only be understood in that dyslipidemic patients receive greater procedural effort, and probably undergo more frequent medical checks. This assertion is supported by the direct, significant, negative prediction that occurs between the number of procedures applied, and mortality.

To complete this section, we must make note of the central, core prediction between the two dependent variables. Just as each different individual variable on its own has been related through different mechanisms to each of the dependent variables, there is an obvious, significant, and very powerful prediction between readmissions and mortality. This association has been cited in many studies on a variety of pathologies, and we believe it lends even greater biological plausibility to the structural model (37–39).

Contextual Variables as Predictors

There were also statistically significant effects from the *contextual variables*. *Year* was confirmed to have a negative effect on length of stay and on in-hospital mortality. The effect on mortality was mediated by NDX and NPR, variables that in turn depend directly on the existence of stroke units and the ongoing creation of such units during the study period. The period analyzed in this study was a time of marked change, where improved stroke care, both in therapeutic terms and in organization of care, prompted a drop in average length of stay and in short-term mortality—and consequently in in-hospital mortality, which we are analyzing here (16, 40).

In this context, where there is higher patient comorbidity (with NDX as the proxy variable for comorbidity), there are higher levels of 30-day readmissions, and secondarily, there are the above-mentioned increases in mortality. As for NPR, considered a proxy variable for the degree of therapeutic effort applied to the patient, we find that with greater effort, there is a decrease in readmissions and in mortality. Both variables are closely related to the existence of stroke units, such that procedural effort is objectively greater within these units than in conventional hospitalization (41).

Although the moment in time (Year) predicted shorter hospital stays, within stroke units there was greater likelihood of longer stays throughout the whole study period. The most important effect found was that the existence of *stroke units* positively predicted length of STAY, as commented. These units admit the more complex patients in particular (greater comorbidity or NDX), and apply greater therapeutic and procedural effort (higher NPR), which would explain the decrease in both mortality and in readmissions; according to other authors, however, a paradoxical effect can occur due to the patient's own complexity (42, 43). The contextual variable that most clearly affects decreased mortality is procedural effort (NPR), which in turn is higher in stroke units and in patients with greater complexity (NDX); both of these variables (diagnoses and procedures) are associated with the stroke units themselves, due to the type of cases that are admitted in these units (44).

Another noteworthy result is the predictive effect of individual mediating variables on context variables. The most interesting result, from the point of view of how the healthcare system affects disease in subjects, is that the number of DIAGNOSES negatively predicts length of STAY, but positively predicts an increased number of PROCEDURES. This may be interpreted as more complex patients having shorter hospital stays because of the high levels of accumulated mortality in this group. The patient's diagnostic complexity (NDX) itself would lead to greater procedural effort (NPR), but there may also be mechanisms that limit therapeutic effort at the most advanced ages (45). In any case, according to our criteria, the model has the capacity to explain these complex associations that are made evident through structural models and that underlie the clinician's thinking and the physiopathology of disease in a stroke.

Clinical Implications

Regarding the importance of the proposed *illustrated algorithm*, the present analysis yields an empirical model that incorporates a macro and micro view of predictive relationships between the independent, mediating, and outcome factors of the subjects' health in interaction with the contextual, organizational factors. In our view, this model has unquestionable epidemiological value for revealing probabilistic predictive relationships between personal and contextual factors, thereby enabling healthcare organizations to understand and make decisions regarding the detection of diseases that bring increased likelihood of others. It also enables large-scale assessment of the adequacy of resources deployed as a function of the pathologies analyzed, opening the way to cost-benefit analyses. Some previous analyses have contributed evidence in this line of work, using different methodologies (8, 46).

The results of this study are also relevant from the point of view of *clinical management*. Attention to the value of contextual elements (mainly managerial and organizational elements like stroke units) would unquestionably contribute to improved clinical care for the patient and to organizational efficiency itself. An understanding of how the individual and contextual elements of stroke are related to each other gives us a broad, ambitious view of this scenario, now supported by a structural model that provides empirical evidence, in contrast to the formerly fragmented or non-existent evidence in prior contributions to our understanding of this disease.

Methodological Contributions

Contributions from this type of analysis of *large clinical-administrative databases* are obvious. First, this approach goes beyond the classic, correlational methodology that establishes covariation relationships between study variables but has many limitations with respect to establishing causal relationships. In fact, certain prior studies have shown that when empirical models are based on associations between variables, and an SEM model is later developed, some of the previous association relations are not sustained in the new structural model, because of accumulated measurement errors. Second, while carrying out prior inferential analyses ensures that interdependence (or causal) relationships between variables are consistent, this type of analysis is unable to present such relationships in a combined, multidirectional manner, but only as limited to each multivariate analysis. Third, the SEM model makes it possible to establish structural multi-directionality of causation through path analysis. Consequently, this type of analysis would be appropriate to an R&D&I Department (47) within the hospital context, where it would be possible to test the efficiency of hospital interventions and healthcare resources (48, 49).

Limitations and Prospects

A first methodological limitation is that no latent variables have been defined in the model. Latent variables can establish a generic relation between constructs, but not the specific ones that we wanted to find. In our case, we have tried to define the causal relationships between observable variables. From our point of view, this precise relationship is very important.

The data are taken from non-lysed strokes. The clinical situation today is a different one (intravenous fibrinolysis and mechanical thrombectomy), where the role of the stroke unit is even more critical. However, given the high prevalence of this subtype of stroke (ischemic and not subject to reperfusion), we think that establishing a predictive empirical model with personal and hospital variables is of great relevance. It would be interesting to replicate the study with patients who have received treatment for acute stroke, when enough data become available. We believe that the future inclusion of patients subjected to mechanical or chemical reperfusion would probably modify the outputs in the sense of less sequential morbidity, decreased length of stay, and lower mortality in stroke units and even in general hospitalization. We also consider that the contextual dependent variable "readmissions" would be favorably diminished by the inclusion of these new therapeutic techniques. Even in the case of non-lysed stroke, this replication in a real cohort would make it possible to simplify and further divide up the elements of the final model. We could learn more precisely which elements might be implemented in routine clinical care in order to optimize outcomes.

Working with these massive clinical-administrative databases has the advantage of the great statistical power of a large sample size, but such databases are not free from significant drawbacks. On one hand, the data reflect the in-hospital situation exclusively, possibly leading to an external validity issue; in our particular case, acute stroke patients are rarely addressed on an outpatient basis, so we consider this bias to be minimal. We also must consider that the information is limited by the quality of the diagnostic and procedural codings themselves, and that this quality is rather uneven, not only geographically (different healthcare regions) but also over time (the study period), fortunately the latter tends toward improvement.

In addition, we must consider the limitation that variables such as "epilepsy" imply, where we cannot identify whether it is occurring as a result of the stroke or whether the patient has suffered this pathology for some time. This obvious database limitation in not differentiating certain secondary diagnoses as complications or as comorbidity is only partially compensated by the high sample size and the diagnostic position: epilepsy encoded in the second diagnostic position is understood to be an acute complication, while in lower positions it is more likely to be a preexisting comorbidity.

Finally, we must take into account the very critical patients who die shortly after admission: their chronic pathologies are often under recorded, possibly distorting the statistical results and even provoking paradoxical results. The well-known Jencks bias, a phenomenon described in Jencks et al. (50), has been confirmed in multiple studies. Studies by Dahlin et al. (51) are most noteworthy, where under recording was proven to be a constant, even when as many as 25 diagnoses had been reported upon discharge. For all these reasons, such biases in the information source are difficult to control, but given the sample size, power and level of detail, this source provides extremely valuable information for patient care and for improved organizational management.

AUTHOR CONTRIBUTIONS

JdlF development of the conceptual idea. Statistical methodology Global drafting of the manuscript. JG-T general review of the manuscript. Introduction and review-writing of the discussion. MI-E general review of the manuscript and partial wording of the discussion. GS global review of the manuscript. Statistical review. AG-U review of the design evaluation

process used. JF-P review of the global English level of the manuscript.

design of the study, collection, analysis, interpretation of data and in writing 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.2019.00498/full#supplementary-material

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Trajectories of (Bio)markers During the Development of Cognitive Frailty in the Doetinchem Cohort Study

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Background: Long-term changes in (bio)markers for cognitive frailty are not well characterized. Therefore, our aim is to explore (bio)marker trajectories in adults who became cognitively frail compared to age- and sex-matched controls who did not become cognitively frail over a 15 year follow-up. We hypothesize that those who become cognitively frail have more unfavorable trajectories of (bio)markers compared to controls.

Methods: The Doetinchem Cohort Study is a longitudinal population-based study that started in 1987–1991 in men and women aged 20–59 years, with follow-up examinations every 5 years. For the current analyses, we used data of 17 potentially relevant (bio)markers (e.g., body mass index (BMI), urea) from rounds 2 to 5 (1993–2012). A global cognitive functioning score (based on memory, speed, and flexibility) was calculated for each round and transformed into education and examination round-adjusted z-scores. The z-score that corresponded to the 10th percentile in round 5 (z-score = −0.77) was applied as cut-off point for incident cognitive frailty in rounds 2–5. In total, 455 incident cognitively frail cases were identified retrospectively and were compared with 910 age- and sex-matched controls. Trajectories up to 15 years before and 10 years after incident cognitive frailty were analyzed using generalized estimating equations with stratification for sex and adjustment for age and, if appropriate, medication use. Results were further adjusted for level of education, depressive symptoms, BMI, and lifestyle factors.

Results: In men, (bio)marker trajectories did not differ as they ran parallel and the difference in levels was not statistically significant between those who became cognitively frail compared to controls. In women, total cholesterol trajectories first increased and thereafter decreased in cognitively frail women and steadily increased in controls, gamma-glutamyltransferase trajectories were more or less stable in cognitively frail women and increased in controls, and urea trajectories

increased in cognitively frail women and remained more or less stable in controls. Results were similar after additional adjustment for potential confounders.

Conclusions: Out of the 17 (bio)markers included in this explorative study, differential trajectories for three biomarkers were observed in women. We do not yet consider any of the studied (bio)markers as promising biomarkers for cognitive frailty.

Keywords: cognitive frailty, markers, biomarkers, trajectories, Doetinchem Cohort Study

INTRODUCTION

Frailty is a state of increased vulnerability to adverse health outcomes when exposed to stressors caused by the cumulative decline in one or more domains of functioning, including the cognitive domain (1–4). Moderate cognitive decline is part of the normal aging process (5). Some elderly are confronted with accelerated cognitive decline, which could eventually lead to (mild) cognitive impairment or dementia. A (reversible) state of cognitive vulnerability within mild cognitive impairment has been termed "Cognitive frailty" (6). Although the existence of cognitive frailty and its definition are still under debate (7), there seems to be broad agreement that cognitively frail people experience accelerated cognitive decline (i.e., cognitive dysfunction) without having a form of dementia (8). In this study, people were considered to be cognitively frail when their global cognitive functioning was poor, given their level of education.

It is not yet fully understood how cognitive frailty develops and whether it can be detected at an early stage. However, there are indications that processes of inflammation and oxidative stress are involved and that C-reactive protein (CRP) could potentially serve as a biomarker (9). In addition, in previous studies we observed associations between body mass index (BMI), self-reported health, several biomarkers (e.g., β-cryptoxanthin and zeaxanthin), and cognitive frailty (10, 11). Unfavorable changes in these and other (bio)marker levels may precede cognitive frailty. Studying these changes can provide insight into the molecular pathways involved and could point out promising biomarkers for cognitive frailty.

In the Doetinchem Cohort Study (DCS), various markers (e.g., self-reported health, BMI) and biomarkers (e.g., CRP, urea), have been measured over a time span of at least 15 years (12). Out of these (bio)markers, we identified 17 possibly relevant (bio)markers for cognitive frailty. These are mainly cardiometabolic, inflammatory, and oxidative stress markers. These types of markers have been linked to cognitive decline (13) and could therefore possibly serve as biomarkers for cognitive frailty. Since cognitive frailty arises gradually, it is meaningful to study how (bio)markers "behave" in the course of developing cognitive frailty. These insights can be helpful for the development of treatment and prevention. Therefore, our aim is to explore the trajectories of several (bio)markers during the development of cognitive frailty in adults and compare these to the trajectories of age- and sex-matched controls. We hypothesize that those who become cognitively frail have more unfavorable trajectories of (bio)markers compared to controls.

METHODS

Cohort

The DCS is a longitudinal population-based cohort study starting in 1987–1991 (round 1) examining 7,769 men and women aged 20–59 years living in Doetinchem, a town in the Netherlands. Adults who participated in the first round were invited for follow-up examinations in 1993–1997 (round 2, $n = 6{,}117$, mean age: 46 years), 1998–2002 (round 3, $n = 4{,}918$, mean age: 51 years), 2003–2007 (round 4, $n = 4{,}520$, mean age: 56 years), and 2008–2012 (round 5, $n = 4{,}018$, mean age: 60 years). Response rates were 75% or higher in all rounds. Verschuren et al. (14) and Picavet et al. (12) have described the study design in more detail. All participants gave written informed consent in each round and the study was approved by the Medical Ethics Committee of the University Medical Center Utrecht.

Incident Cognitive Frailty

Cognitive functioning was assessed among participants aged ≥45 years. Trained personnel carried out the cognitive tests according to a standardized protocol. In rounds 2–5, global cognitive functioning was measured with a neuropsychological test battery assessing three domains: memory function, information processing speed and cognitive flexibility. These were tested using the 15 Words Verbal Learning Test (VLT) (immediate and delayed recall) (15), the Stroop Color–Word Test (16), the Word Fluency Test (17), and the Letter Digit Substitution Test (18). Nooyens et al. (19) have described the cognitive tests in more detail. From the separate test scores, one global cognitive functioning score was calculated for each round. Next, the global cognitive functioning scores were transformed into z-scores, based on the mean and standard deviation in round 5, and were adjusted for level of education and for the number of tests performed during follow-up to take a possible learning effect into account. The z-score that corresponded to the 10th percentile in round 5 (z-score = −0.77) was applied as cut-off point for incident cognitive frailty in rounds 2, 3, 4, and 5. This is consistent with the definition used in one of our previous studies, where we also defined people as being cognitively frail when their global cognitive functioning was poor, given their level of education (11). Since the prevalence of frailty naturally increases with age, this was not included in the definition of cognitive frailty. Participants with a score below the cut-off point were considered incident cognitively frail and participants with a score above this value were considered not cognitively frail. As cognitive tests were only performed among participants aged ≥45 years, we defined participants <45 years as not being cognitively

frail. Participants aged ≥45 years without data on cognitive functioning were excluded.

Measurements

Markers

Weight and height (to calculate the BMI), waist circumference, and diastolic and systolic blood pressure were measured according to standard protocols (14). Standardized questionnaires were used to obtain data on self-reported health, depressive symptoms (assessed with the Mental Health Inventory-5 and the Vitality dimension of the 36-Item Short-Form Health Survey) (20, 21), level of education, smoking status, alcohol consumption, physical activity (categorized using the Cambridge Physical Activity Index) (22), use of anti-hypertensive medication, cholesterol-lowering medication, and glucose-lowering medication.

Biomarkers

Total and high-density lipoprotein (HDL) cholesterol were measured with standardized enzymatic methods. In 2013–2014, standardized enzymatic methods were used to retrospectively determine triglycerides, alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), high sensitivity CRP, albumin, uric acid, cystatin C, and creatinine of rounds 2–5 using blood plasma that had been stored in freezers. Participants with only one measurement of the (bio)markers were excluded and participants who were pregnant in a particular round were excluded for that round only. Details of all measurements are described in the **Appendix A** (Supplementary Material).

Statistical Analyses

Matching

The time of incident cognitive frailty was the first examination round in which participants scored below the cut-off point of −0.77. From this point in time, we were able to investigate trajectories with a maximum of 15 years before and 10 years after incident cognitive frailty. There were not enough observations to study the trajectories up to 15 years after incident cognitive frailty. Both cognitive frailty and biomarker levels vary strongly by sex and age. Therefore, we used a matching design in which each incident cognitively frail person was matched to two controls based on sex, age (with 5-year age categories), and examination round. We excluded two incident cognitively frail cases, as no suitable controls could be identified.

(Bio)marker Trajectories

Trajectories of (bio)markers for incident cognitively frail cases and controls were analyzed using generalized estimating equations (GEE) with an unstructured correlation structure. The GEE analysis was performed for each (bio)marker (dependent variable) separately and with cognitive frailty ("yes" vs. "no") as the main determinant. This resulted in separate estimates (i.e., adjusted marginal means) at each point in time for cases and controls. With these estimates, trajectories for the cognitively frail and the controls were constructed. This approach is consistent with the method used by Hulsegge et al. (23).

Analyses were stratified for sex and the model included age (linear and quadratic), examination round (categorical variable with round 5 as reference category), and time (categorical variable). Time consisted of six categories ranging from T_{-15} to T_{+10} with T_0 as the moment of incident cognitive frailty. Age was centered at 60 years because this was approximately the mean age at round 5, which resulted in (bio)marker levels of someone who was hypothetically 60 years old. Trajectories of systolic and diastolic blood pressure were adjusted for self-reported anti-hypertensive medication, trajectories of total cholesterol, HDL cholesterol and triglycerides were adjusted for self-reported cholesterol-lowering medication, and trajectories of glucose were adjusted for the self-reported use of glucose-lowering medication.

Triglycerides, ALT, GGT, and CRP had a skewed distribution. Therefore, we log-transformed these biomarkers and reported back-transformed geometric means. Differences between trajectories of cognitively frail people and their controls were tested using an overall interaction term between cognitive frailty and time, and a *p*-value lower than 0.1 was considered statistically significant. This was obtained via the joint tests for GEE, where differences in slopes were calculated based on five interaction terms (frailty*T_{-15}, frailty*T_{-10}, frailty*T_{-5}, frailty*T_{+5}, frailty*T_{+10}) with T_0 (i.e., moment of incident cognitive frailty) as reference category.

To summarize, trajectories up to 15 years before and 10 years after incident cognitive frailty were analyzed and compared to controls using GEE with stratification for sex and adjustment for age and, if appropriate, medication use (model 1). We verified whether the results changed after additional adjustment for level of education, depressive symptoms (model 2), BMI, smoking, alcohol intake, and physical activity (model 3). Trajectories of BMI and waist circumference were not adjusted for BMI.

We performed a sensitivity analysis to study the potential impact of loss to follow-up due to mortality on our results. To this end, we excluded participants who died during the follow-up period (1993–2012) along with their matched case and/or control(s) and compared the results to those obtained in the total population. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, North Caroline, USA).

RESULTS

Population Characteristics

After excluding participants ≥45 years without data on cognitive functioning and applying the additional exclusion criteria, 5,139 participants remained for further analyses. Over the course of the study, 6 participants were defined as incident cognitively frail in round 2, 116 participants in round 3, 134 participants in round 4, and 202 participants in round 5. In total, 455 participants became cognitively frail of which 303 (67%) were men and 152 (33%) were women. At incident cognitive frailty (T_0), men had an average age of 65.5 (SD 7.6) and women of 66.9 (SD 7.8). Cognitively frail people more often had a low level of education and a slightly higher BMI, waist circumference, and systolic blood pressure than controls (**Table 1**). In addition, cognitively frail

TABLE 1 | Population characteristics for incident cognitively frail men and women and their controls at T_0.

	Men		Women	
	Controls ***N* = 606**	**Cognitively frail** ***N* = 303**	**Controls** ***N* = 304**	**Cognitively frail** ***N* = 152**
SOCIO-DEMOGRAPHIC FACTORS				
Age (years), mean (SD)	63.0 (7.8)	65.5 (7.6)	64.6 (8.0)	66.9 (7.8)
Low level of education, %	42	49	62	70
LIFE-STYLE FACTORS				
Current smoker, %	15	24	17	14
Alcohol consumption (1 or more glasses/week), %	77	76	60	39
MEDICATION USE				
Anti-hypertensive, %	24	27	29	34
Cholesterol-lowering, %	17	22	16	20
Glucose-lowering, %	6	10	6	7
HEALTH				
Poor or fair self-reported health, %	16	23	22	34
Mental health (range 0–100), mean (SD)	81.3 (14.3)	78.2 (15.9)	75.6 (15.4)	70.2 (17.3)
Vitality (range 0–100), mean (SD)	71.0 (17.4)	68.9 (18.0)	65.8 (17.4)	59.9 (19.8)
ANTHROPOMETRIC DATA				
BMI (kg/m^2), mean (SD)	26.9 (3.5)	27.4 (3.7)	27.1 (4.7)	28.3 (5.5)
Waist circumference (cm), mean (SD)	100.7 (10.0)	102.7 (10.5)	93.5 (12.0)	97.4 (13.3)
Systolic blood pressure (mmHg), mean (SD)	134.7 (17.2)	138.0 (18.6)	133.8 (18.5)	137.8 (19.4)
Diastolic blood pressure (mmHg), mean (SD)	81.9 (9.8)	81.4 (9.9)	79.9 (9.7)	80.4 (10.1)
BIOMARKERS				
Total cholesterol (mmol/L), median (IQR)	5.5 (4.8–6.1)	5.3 (4.4–6.3)	5.9 (5.1–6.7)	5.9 (5.4–6.5)
HDL cholesterol (mmol/L), median (IQR)	1.21 (1.00–1.44)	1.17 (0.98–1.42)	1.51 (1.23–1.81)	1.39 (1.17–1.67)
Glucose (mmol/L), median (IQR)	5.3 (4.8–6.1)	5.4 (4.9–6.1)	5.2 (4.8–5.8)	5.3 (4.9–5.9)
Triglycerides (mmol/L), median (IQR)	1.45 (1.06–2.07)	1.55 (1.10–2.08)	1.40 (1.05–1.90)	1.54 (1.11–2.10)
ALT (U/L), median (IQR)	18 (14–24)	18 (14–24)	16 (12–20)	14 (11–18)
GGT (U/L), median (IQR)	28 (19–40)	27 (20–41)	19 (15–29)	19 (14–26)
CRP (mg/L), median (IQR)	1.17 (0.62–2.40)	1.61 (0.81–3.07)	1.38 (0.68–2.89)	1.50 (0.70–2.48)
Albumin (g/L), median (IQR)	45 (43–46)	45 (43–46)	45 (43–47)	45 (43–46)
Cystatin C (mg/L), median (IQR)	0.86 (0.78–0.97)	0.91 (0.81–1.02)	0.81 (0.72–0.94)	0.89 (0.79–0.99)
Creatinine (umol/L), median (IQR)	84 (76–93)	83 (76–91)	67 (60–74)	69 (62–77)
Uric acid (mmol/L), median (IQR)	0.34 (0.29–0.38)	0.33 (0.29–0.38)	0.27 (0.23–0.30)	0.27 (0.22–0.32)
Urea (mmol/L), median (IQR)	6.2 (5.4–7.1)	6.2 (5.3–7.4)	5.8 (4.9–6.6)	6.1 (5.1–7.2)

BMI, body mass index; HDL cholesterol, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; GGT, gamma glutamyltransferase; CRP, C-reactive protein.

men and women more often reported to have poor or fair health and their medication use was higher compared to controls.

(Bio)marker Trajectories

In our main model (i.e., model 1), we observed no differences in (bio)marker trajectories between incident cognitively frail men and controls as the trajectories ran parallel and the difference in levels was not statistically significant. In women, we observed differences in the shape of the trajectories of total cholesterol ($p = 0.067$), GGT ($p = 0.008$), and urea ($p = 0.002$) between incident cognitively frail women and controls (**Figure 1** and **Appendix B Table 1** in Supplementary Material). Total cholesterol increased before women became cognitively frail and decreased after incident cognitive frailty (T_0), while in controls, total cholesterol levels steadily increased over time. GGT was more or less stable in incident cognitively frail women, while in controls, GGT levels slowly increased from T_{-10} onwards. Urea increased over time in incident cognitively frail women, while in controls, urea levels remained more or less stable.

After further adjustment for level of education and depressive symptoms (model 2), we found no differences in (bio)marker trajectories for men. In women, we found differences in the same biomarker trajectories as in model 1 (i.e., total cholesterol, GGT, urea) and additionally observed a difference in trajectories for ALT in women ($p = 0.046$) (**Appendix B Table 1** in Supplementary Material). When further adjusting for BMI and life-style factors (model 3), we still observed no differences in (bio)marker trajectories for men. In women, differences in the trajectories for GGT, urea, and ALT between incident cognitively frail women and controls remained, but the difference in total cholesterol trajectory ($p = 0.109$) was just above our threshold (p-value for interaction <0.1).

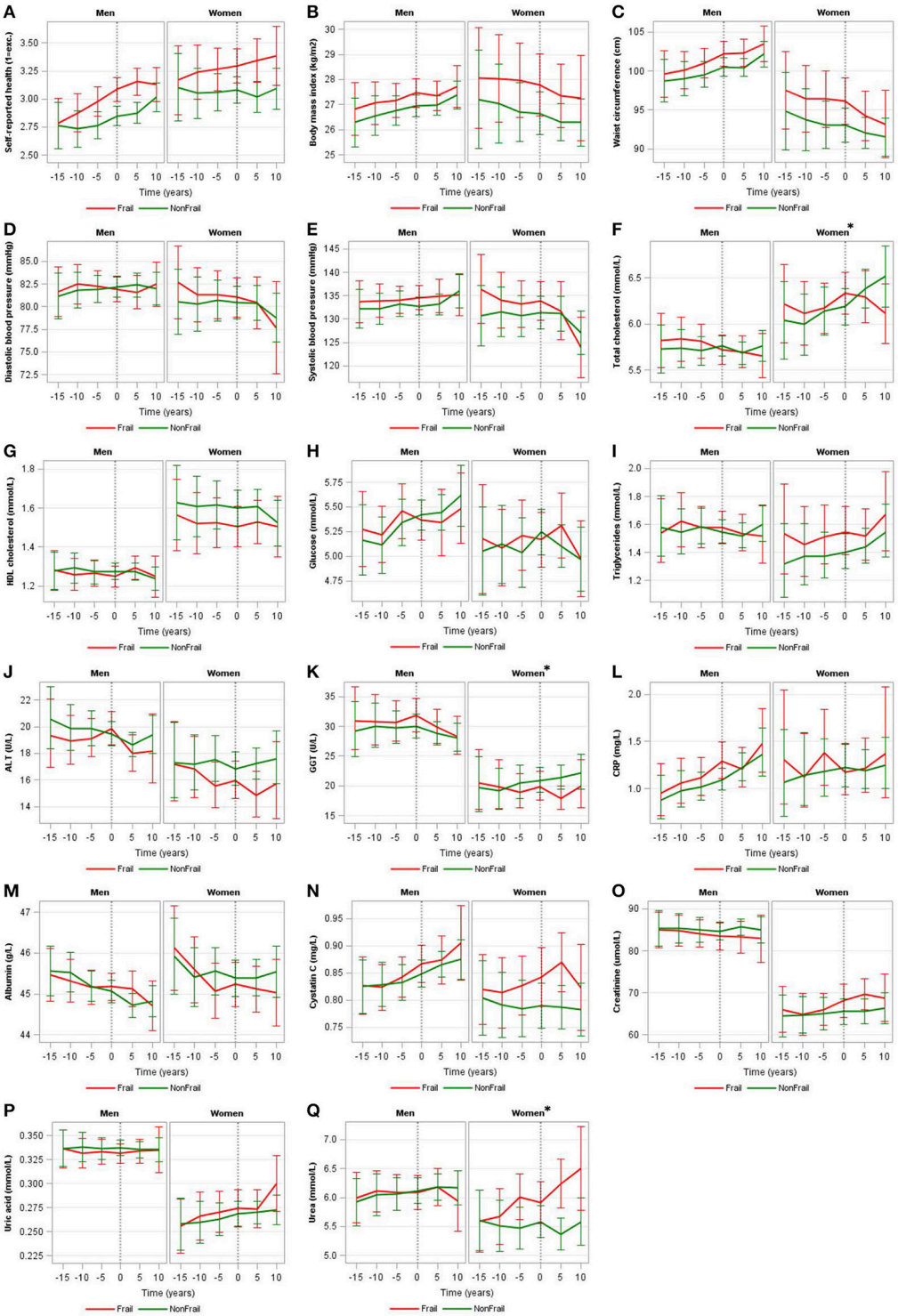

FIGURE 1 | Trajectories of (bio)markers for incident cognitively frail men and women and their controls. Trajectories of self-reported health **(A)**, body mass index **(B)**, waist circumference **(C)**, diastolic blood pressure **(D)**, systolic blood pressure **(E)**, total cholesterol **(F)**, HDL cholesterol **(G)**, glucose **(H)**, triglycerides **(I)**, ALT **(J)**, GGT **(K)**, CRP **(L)**, albumin **(M)**, cystatin C **(N)**, creatinine **(O)**, uric acid **(P)**, and urea **(Q)** of incident cognitively frail people (red lines) and controls (green lines) with 95% confidence intervals stratified by sex and corrected for age and, if appropriate, medication use (model 1), where men and women were hypothetically 60 years old at the time of incident cognitive frailty. A difference (*p*-value for interaction <0.1) in (bio)marker trajectory between those with and without incident cognitive frailty are indicated by an asterisk. HDL cholesterol, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; GGT, gamma glutamyltransferase; CRP, C-reactive protein. Geometric means are shown for triglycerides, ALT, GGT, and CRP.

To explore the potential impact of loss to follow-up due to mortality on our results, we performed a sensitivity analysis using model 1 in which we excluded participants who died ($n = 130$) during the follow-up period (1993–2012). In men, 61 cognitively frail and 40 controls died. In women, 16 cognitively frail and 13 controls died. Excluding these participants, along with their matched case and/or control(s), resulted in the exclusion of 333 participants in total. After exclusion, in men, the trajectories of total cholesterol ($p = 0.061$) and BMI ($p = 0.082$) differed between cognitively frail men and controls. In women, consistent with the observed differences in the total population, the trajectories of total cholesterol ($p = 0.066$), GGT ($p = 0.018$), and urea ($p = 0.001$) differed between cognitively frail women and controls. In addition, the trajectories of ALT ($p = 0.057$), and albumin ($p = 0.057$) also became different between cognitively frail women and controls (**Appendix B Figure 1** in Supplementary Material).

DISCUSSION

Our aim was to examine whether (bio)marker trajectories differ for those who become cognitively frail compared to those who do not over a follow-up of 15 years. In addition, we hypothesized more unfavorable trajectories for those who became cognitively frail compared to controls. In our main model (model 1), we observed no differences in (bio)marker trajectories between incident cognitively frail men and controls as the trajectories ran parallel and the difference in levels was not statistically significant. In women, we observed differences in the shape of the trajectories of total cholesterol, GGT, and urea between incident cognitively frail women and controls.

Against our expectations, most of the 17 (bio)markers included in this study did not show deviating trajectories between those who became cognitively frail and those who did not. This was, for example, surprising for the inflammation marker CRP, since this biomarker has, longitudinally, been linked to physical frailty (24), cognitive decline (25), and risk of dementia (26, 27), and therefore could serve as a biomarker for cognitive frailty. However, also other epidemiological studies report inconsistent findings regarding longitudinal measures of inflammation markers and cognitive decline (28, 29). In addition, Soysal et al. (30) showed that higher CRP and interleukin-6 (IL-6) levels are cross-sectionally associated to physical frailty, but not longitudinally. Although this study focused on physical frailty, it seems consistent with our null findings regarding cognitive frailty.

We did find a difference in the trajectory for total cholesterol in women. Total cholesterol increased before women became cognitively frail and decreased after incident cognitive frailty (T_0), while in controls, total cholesterol levels steadily increased over time. In a previous cross-sectional study in MARK-AGE, we also found lower cholesterol levels among people who were already cognitively frail compared to people without frailty (10). Solomon et al. (31) found that non-demented people with high total cholesterol levels around age 50 had poorer cognition 20 years later. In addition, their total cholesterol levels decreased after age 50. The pattern Solomon et al. (31) describe seems comparable to the trajectory we found in incident cognitively frail women. The decline we observed in total cholesterol levels after becoming cognitively frail could be caused by various factors, one of which is medication use. The analyses were adjusted for self-reported use of cholesterol-lowering medication, but information about medication type, dose and therapy compliance were not collected and could therefore not be included in these analyses. Hence, it is unclear whether the trajectories differ due to the occurrence of cognitive frailty, or whether other effects, like a treatment effect, is underlying this difference.

We also observed different urea and GGT trajectories in incident cognitively frail women compared to controls. Higher urea levels can be caused by disrupted blood flow through the kidneys for example through heart failure (32). In contrast, we found lower GGT levels in incident cognitively frail women, while heart failure would also cause increased, and not decreased, GGT levels (33). Lower GGT levels could be caused, for example, by the use of clofibrate, a lipid-lowering agent controlling high cholesterol and triglyceride levels. When adjusting for the use of cholesterol-lowering medication for GGT, results remained similar. It is suggested that serum GGT within the normal range is an early marker for oxidative stress (34). Oxidative stress has been suggested to be associated with frailty (35) and increased GGT levels in later life (80 years and older) were associated with cognitive decline (36). However, we unexpectedly observed lower instead of higher GGT levels in cognitively frail women compared to controls, indicating that cognitive frail women might have less oxidative stress. Overall, there does not seem to be a reasonable explanation for the course of these trajectories. We cannot exclude the possibility that the trajectories of GGT and urea are chance findings.

Differences in (bio)marker trajectories were observed among women, but not among men. We found that more men had poor cognitive functioning compared to women (i.e., more men were identified as incident cognitively frail than women). On the other hand, differences in cognitive functioning between the incident cognitively frail men and their controls were smaller compared to the differences observed in women. Possibly, the women who we identified as incident cognitively frail were relatively worse off than the incident cognitively frail men, having relatively poorer cognitive function and potentially poorer overall health and therefore we only found differences between trajectories for women.

We studied the potential impact of loss to follow-up due to mortality on our results. This was appropriate since some of the trajectories for women indicated a (rapidly) deteriorating health. For example, decreasing cholesterol levels could be caused by malnutrition and increasing urea levels could be caused by heart failure. As expected, mortality rate was higher among those who became cognitively frail compared to those who did not. However, excluding these participants did not materially change the results. In fact, the differences in trajectories for total cholesterol, GGT, and urea in women remained the same and seemed therefore rather robust.

We considered people as being cognitively frail when their global cognitive functioning was poor, given their level of

education. Since the prevalence of frailty naturally increases with age, this was not included in the definition of cognitive frailty. The most important difference between our operationalization of cognitive frailty and the classic operationalization for mild cognitive impairment (MCI) (37) is that our definition of cognitive frailty did not include subjective memory complaints. Also, we did not include self-reported activities of daily living which is part of the MCI definition. Recently, a definition for cognitive frailty was proposed combining physical frailty with MCI (38). Since we have previously observed that it is possible to be cognitively frail without being physically frail (10), we defined cognitive frailty only based on cognitive functioning. In our manuscript, the term "cognitive frailty" represents cognitive dysfunction, independent of other (physical) limitations and is only based on poor cognitive functioning given the level of education. We explicitly adjusted for level of education, since highly educated people can also experience cognitive dysfunction and this would otherwise be masked by their cognitive reserves.

One of the strengths of this study is that both cognitive functioning, using a comprehensive neuropsychological test battery, and multiple (bio)markers were objectively measured in four rounds over a follow-up of 15 years, making this a unique cohort for studying the relation between (bio)markers and cognitive functioning over time. In addition, all biomarkers of rounds 2–5 were measured in a single run, limiting inter-assay variation.

This study has some limitations. We tried to include all relevant confounders in the analyses (model 3) but residual confounding may still be present. However, adjustment for confounders had a marginal effect in the results. Further, cognitive functioning was not assessed in participants younger than 45 years. We defined these participants as not being cognitively frail under the assumption that people become cognitively frail with advancing age, mostly from 60 years onwards. In addition, since this population was still relatively young, it could have been too young to find (bio)markers for cognitive frailty. Moreover, since cognitive frailty can be described as a complex syndrome, multiple factors can influence the development of this syndrome. This makes it challenging to identify biomarkers for cognitive frailty. Further, we were unable to exclude participants with dementia. However, given the age-distribution of the cohort, the prevalence and incidence of dementia would be quite low and is therefore unlikely to have influenced our results. Finally, due to the age- and sex-matched study design, the power was limited to analyze differences at any time point. However, more power would probably not lead to other differences in trajectories, because most trajectories run almost parallel and that aspect is unlikely to change with more power.

In conclusion, out of the 17 (bio)markers included in this explorative study, different trajectories between incident cognitively frail women and their controls were found for three biomarkers. However, the relation between these biomarkers and the development of cognitive frailty is unclear. Future studies are needed to confirm these findings. Given the results of this study, we do not yet consider any of the studied (bio)markers as promising (bio)markers for cognitive frailty.

ETHICS STATEMENT

The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht.

AUTHOR CONTRIBUTIONS

All authors were involved in interpreting the data, drafting, and approving the manuscript.

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Rate and Determinants of Recurrence at 1 Year and 5 Years After Stroke in a Low-Income Population in Rural China

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Recurrent stroke is becoming an increasingly important public health issue owing to the increased risk of disability and death. However, population-based studies investigating the rate of recurrent stroke in China are rare. We explored the rate and determinants of recurrent stroke within 1 and 5 years after the initial stroke in a rural population in China. Data for stroke events were obtained from the Tianjin Brain Study, conducted between 1992 and 2016. The age-standardized rates of recurrent stroke within the first year and the first 5 years after the initial stroke were calculated for this period. Determinants of recurrent stroke were assessed using Cox regression analyses. The overall age-standardized rate of recurrent stroke within 1 year was 5.7% (men, 6.9%; women, 4.6%); within 5 years, the overall recurrent stroke rate was 22.5% (men, 24.0%; women, 20.2%). The recurrence rate increased with advancing age and decreased with increased educational attainment. Age ≥65 years and a history of alcohol consumption were independent risk factors for recurrent stroke within 1 year after the incident stroke, after adjusting for age, sex, education, hypertension, diabetes, smoking, and alcohol consumption. However, the risk of recurrent stroke within 5 years after the incident stroke was positively associated with male sex, age ≥65 years, a lower level of education, known diabetes, and alcohol consumption, after adjusting for the previously indicated covariates. These findings suggest a crucial need to address risk factor management among stroke patients to reduce the burden of stroke, especially among low-income populations. Furthermore, a multicenter, large sample, nationwide study is urgently needed.

Keywords: stroke, recurrence, predictors, epidemiology, incidence

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INTRODUCTION

Stroke is one of the leading causes of death and disability, worldwide (1) and is responsible for ∼4.4 million deaths (9% of total) annually (2). Over the past two decades, there has been a notable increase (84%) in the absolute numbers of stroke survivors globally although the incidence of stroke has decreased in high-income

countries (3). However, the number of stroke survivors under 75 years old was almost 30% higher in low- and middle-income countries than in high-income countries (3). The risk of recurrent stroke is becoming increasingly important owing to its associated high risk of disability and death (4–9), and the risk varies according to the elapsed time since the incident stroke (10–15). The population-based cumulative risk of recurrent stroke during the 5 year period after the incident stroke has been reported to be 19% in Manhattan (USA), 29% in Rochester (USA), 30% in Oxfordshire (UK), and 32% in Perth (Australia) (16–19).

Each year, there are ∼2.5 million new stroke cases reported in China, and currently there are ∼7.5 million stroke survivors; nationally, the stroke recurrence rate remains high (11.2%) (20). Over the past few decades, the incidence of stroke has increased in China both in urban and rural populations (21–25). Thus, recurrent stroke prevention is of considerable importance to both individuals and overall public health. However, few population-based studies have described the incidence of recurrent stroke in China, especially among rural populations. Therefore, in this study, we aimed to assess the rate of recurrent stroke within 1 and 5 years after the incident stroke in rural China.

METHODS

Study Population

This study was a population-based stroke surveillance study that began in 1985 in Tianjin, China. The study design has been previously described (23–25). Briefly, it included 15,438 residents living in a township in Tianjin, China, where 95% of the adults were low-income farmers. The primary source of income was grain production, and the annual per capita income was <$100 US in 1990 and <$2000 USD in 2015 (26). In 1991, the illiteracy rates among residents 35–74 years old were 30% for men and 40% for women. The population characteristics remained stable over the study period (27). Since neuroimaging technology became available in 1992, this study analyzed recurrent stroke events since that time.

The study protocol was approved by the ethics committee of Tianjin Medical University General Hospital (TMUGH); written informed consent was obtained from each participant.

Stroke Definition and Types

All included stroke events were symptomatic and diagnosed using pre-established criteria, including clinical features and imaging evidence (MRI or CT scan). The initial (incident) stroke was defined as the first occurrence of rapidly developing signs of focal neurologic disturbances of presumed (no other apparent cause) vascular etiology lasting >24 h (28). Transient ischemic attacks (TIAs) and silent strokes (diagnosed by imaging only) were excluded, and stroke cases with TIA histories were regarded as incident events. Patients with transient symptoms and concurrent neuroimaging evidence of brain infarctions were considered to be stroke cases, based on the "tissue" definition (29). Recurrent stroke was defined as a new stroke event occurring at least 28 days after the incident event.

The stroke types included ischemic stroke (IS), intracerebral hemorrhage (ICH), and unknown. IS was defined as a thrombotic brain infarction, cardioembolic stroke, or lacunar infarct.

Event Ascertainment Processes

All incident stroke events included first-ever and recurrent strokes registered according to the previously published procedure (25). Stroke event determinations were performed using a predetermined procedure. First, local village physicians reported stroke events (both initial and recurrent) to the community hospital within 24 h of onset. Second, community hospital physicians then visited the surviving patients' homes to confirm stroke events and obtain clinical feature information within 72 h. Confirmed stroke events, diagnosed using imaging modalities, were reported each month to neurologists at TMUGH. Suspected events (no imaging performed) were reported in a timely manner. Finally, the TMUGH neurologist identified possible stroke events via door-to-door interviews as soon as possible. To ensure that all incident stroke events were registered, three sources were used to obtain information regarding stroke events. First, local physicians reported events according to a predefined procedure. This was the main information resource, as the local physicians were the first medical professionals to contact the patients. Second, in cases involving inpatient stroke events, the medical records were obtained from the hospital or insurance company. Third, information from the all-cause death registry supplemented stroke events missing from the registry.

Information regarding stroke onset was obtained during interviews conducted by the community hospital physicians and the TMUGH neurologist; information included demographics, time of stroke onset, clinical signs, and previous stroke status. Other information, including imaging characteristics, prescribed therapy, and post-discharge outcomes, was obtained by the TMUGH neurologist during interviews with survivors, their family members, or a local health worker.

The recruitment period was from January 1, 1992, to December 31, 2016, and follow-up was completed on December 31, 2017. During the surveillance period, all stroke events and all-cause deaths were registered and followed. The dates of death or emigration from the township were determined using population registries. All changes in demographic information were recorded, including births, deaths, immigrations (including that due to marriages), and emigrations (including that due to entering a high school or university or working in the city). Peasant workers were included in this study because all residents working in the city were seasonal workers who regularly returned to the township during traditional festivals and the farming season.

Inclusion and Exclusion Criteria

Only patients who survived the index event were entered into the present analysis. Death was considered to have been caused by the incident stroke if it occurred within 28 days of symptom onset. All patients with at least 1 year of follow-up after their first-ever stroke events were included in this study. Follow-up evaluations were conducted every month, and recurrent strokes

were classified using information from interviews, conducted directly during follow-up visits or by telephone calls to patients, next of kin, witnesses, or the attending physicians.

All patients with TIAs; suspected stroke deaths without imaging evidence or confirmation by a TMUGH neurologist; and silent strokes, detected only by imaging, were excluded from this study. Patients suffering neuroimaging-confirmed strokes underwent computed tomography or magnetic resonance imaging examinations in the county central hospital.

Statistical Methods

Categorical variables are presented as numbers (%), and continuous variables are presented as means (standard deviations, SD). Patient ages were categorized into 3 subgroups (<45, 45–64, and ≥65 years) when the demographic features of this population were described and the rates of recurrent stroke were assessed; however, only 2 subgroups (<65 and ≥65 years) were used to assess the determinants of recurrent stroke. Education attainment was categorized into 3 subgroups (0, 1–6, and ≥7 years). Smoking status was categorized into 3 subgroups (never smoker, past smoker, and current smoker); similarly, drinking status was also categorized into 3 subgroups (never drinkers, past drinkers, and current drinkers). The recurrent stroke incidence was calculated as the cumulative frequency of recurrent events at 1 and 5 years after the incident stroke. Association of education attainment with the risk of the recurrent stroke was assessed by Kaplan-Meier survival analysis and presented as log rank.

Multivariable Cox regression analyses were used to identify the predictors of recurrent stroke within both time periods after adjusted by covariates (sex, age, education attainment, stroke types, previous history of hypertension and diabetes, smoking and drinking status); the risk of recurrent stroke occurrence is presented as adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The follow-up time was recorded in years and was calculated as the interval between the date of the initial stroke and the date of the recurrent stroke for those patients experiencing recurrent strokes within 1 and 5 years after the initial stroke. For those patients without recurrent strokes within 1 or 5 years after the initial stroke, the follow-up time was defined as 1 or 5 years, respectively. Moreover, for patients who died within 28 days after the initial stroke, the follow-up time was defined as the interval between the initial stroke and the date of death. During the study period, stroke patients who experienced initial strokes before immigrating to the township were included in the study; stroke patients who emigrated from the township after the initial stroke were excluded from the study. However, in this study, no stroke patients immigrated to or emigrated from the township during the study period. SPSS version 15.0 for Windows (SPSS, Chicago, IL, USA) was used for the analyses; statistical significance was defined as $P < 0.05$.

RESULTS

Patient Characteristics

A total of 1,185 individuals experienced initial stroke events, including ICH, IS, and undefined events between 1992 and 2016. All 1,185 patients were included in the determination of the rate and associated predictors of recurrent stroke 1 year after the incident event; patients experiencing incident strokes between January 1, 1992, and December 31, 2012 ($n = 899$), were included in the determination of the 5 year recurrent stroke rate and its associated predictors.

Between 1992 and 2016, 1,185 initial stroke events were included in this study; the mean time to the first recurrent stroke within the first year was 0.82 years; for the 5 year time frame, the mean time to recurrence was 3.08 years. In both study periods, patients experiencing initial strokes were more likely to be men, older, and less educated. Further, IS was the most common stroke event during these periods (**Table 1**).

TABLE 1 | Descriptive characteristics of patients with first-ever stroke by time period in this study.

Groups	1992–2016	1992–2012
SEX, *N* (%):		
Men	707 (59.7)	537 (59.7)
Women	478 (40.3)	362 (40.3)
Total	1,185 (100)	899 (100)
AGE AT STROKE ONSET, MEAN (SD), YEARS		
	65.49 (11.67)	65.54 (11.94)
AGE GROUPS, *N* (%)		
<45 years	54 (4.6)	82 (9.1)
45–64 years	506 (42.7)	422 (46.9)
≥65 years	625 (52.7)	395 (43.9)
EDUCATION ATTAINMENT, MEAN (SD), YEARS		
	3.35 (3.28)	2.89 (3.19)
EDUCATION GROUPS, *N* (%):		
0 years	437 (36.9)	390 (43.4)
1–6 years	570 (48.1)	407 (45.3)
≥7 years	178 (15.0)	102 (11.3)
SUBTYPES OF FIRST-EVER STROKE, *N* (%)		
Ischemic stroke	916 (77.3)	671 (74.6)
ICH	231 (19.5)	192 (21.4)
UND	38 (3.2)	36 (4.0)
DIAGNOSIS BY IMAGING FOR FIRST-EVER STROKE, *N* (%):		
Ischemic stroke	726 (79.3)	498 (74.2)
ICH	218 (94.4)	178 (92.7)
Total	844 (71.2)	676 (75.2)
RECURRENT STROKE EVENTS, *N* (%)		
IS	45 (63.4)	112 (55.4)
ICH	12 (16.9)	31 (15.3)
Unknown	14 (19.7)	59 (29.2)
Total	71 (100)	202 (100)
DIAGNOSIS BY IMAGING FOR RECURRENT STROKE, N (%):		
Ischemic stroke	38 (84.4)	97 (86.6)
ICH	11 (91.7)	22 (71.0)
Unknown	0 (0)	1 (1.7)
Total	49 (69.0)	120 (59.4)

SD indicated standard deviation; 95% CI indicates 95% confidence interval. ICH, Intracerebral hemorrhage; IS, Ischemic stroke; UND, Undefined stroke.

Recurrent Stroke Rate

During the study period, 71 recurrent strokes occurred in the 1 year follow-up group and 202 occurred in the 5 year follow-up group. The overall rate of recurrent stroke within 1 year was 5.7% (men, 6.9%; women, 4.6%); in the 5 year group, the overall rate of recurrent stroke was 22.5% (men, 24.0%; women, 20.2%).

Table 2 shows an increasing rate of recurrent stroke that corresponds with increasing patient age at the time of the initial stroke onset; compared with patients aged <65 years old, the rate of recurrent stroke among patients ≥65 years old was higher (7.4%, $P = 0.037$) in the 1 year follow-up group.

There was no significant association between the rate of recurrent stroke within 1 year and education attainment (log rank = 1.103; $P = 0.576$; **Figure 1A**). However, there was a negative association between the rate of recurrent stroke within 5 years and education attainment (log rank = 8.462; $P = 0.015$; **Figure 1B**).

TABLE 2 | Age-adjusted rates of recurrent stroke by subtypes [% (95% CI)].

Groups	Recurrence rate within 1 year	Recurrence rate within 5 years
SEX:		
Men	6.9 (5.1, 8.8)	24.0 (20.4, 27.6)
Women	4.6 (2.7, 6.5)	20.2 (16.0, 24.3)
Total	5.7 (4.4, 6.9)	22.5 (19.7, 25.2)
SUBTYPES OF FIRST-EVER STROKE:		
IS	6.2 (4.7, 7.8)	24.4 (21.2, 27.7)
ICH	6.1 (3.0, 9.2)	19.8 (14.1, 25.5)
Other	0	0
AGE GROUPS:		
<45 years	0	10.6 (1.5, 19.8)
45–64 years	4.9 (3.0, 6.8)	23.8 (19.4, 28.2)
≥65 years	7.4 (5.3, 9.4)	22.6 (18.9, 26.4)
EDUCATION: ATTAINMENT:		
0 year	5.3 (3.2, 7.4)	18.2 (14.4, 22.1)
1–6 years	6.8 (4.8, 8.9)	28.5 (24.1, 32.9)
≥7 years	5.1 (1.8, 8.3)	14.7 (7.7, 21.7)
PREVIOUS DISEASE: HISTORIES:		
Hypertension		
Yes	6.2 (4.8, 7.7)	22.9 (20.0, 25.8)
No	4.2 (0.9, 7.5)	19.2 (11.3, 27.1)
Diabetes		
Yes	9.4 (4.5, 14.3)	39.0 (28.2, 49.8)
No	5.5 (4.2, 6.9)	20.8 (18.0, 23.6)
LIFESTYLE:		
Smoking status		
Never smoked	5.7 (3.9, 7.6)	22.3 (18.5, 26.2)
Ever smoked	6.5 (1.4, 11.7)	30.0 (19.0, 41.0)
Current smoking	6.3 (4.1, 8.4)	21.2 (17.1, 25.4)
Drinking status		
Never drank	5.7 (4.1, 7.2)	22.1 (18.9, 25.4)
Ever drank	11.5 (4.7, 18.3)	43.9 (30.6, 57.1)
Current drinker	5.3 (2.7, 7.9)	17.9 (12.8, 23.0)

Determinants of Stroke Recurrence

Compared with patients aged <65 years old, the risk of stroke recurrence within 1 year after the initial stroke more than doubled among patients ≥65 years ($P = 0.004$) after adjusting for age, sex, education level, hypertension, diabetes, smoking status, and drinking status; there was a lower risk of recurrence for those experiencing an IS than for those with an initial ICH. The risk of recurrent stroke within 5 years after the incident stroke was 1.65-fold higher among men than among women ($P = 0.017$). Compared with patients aged <65 years, the risk of recurrence in patients ≥65 years old increased 1.54-fold ($P = 0.009$). Similarly, the risk of recurrence in patients with <7 years of education was almost double that of patients with at least 7 years of education ($P = 0.017$). The risk was also 1.71-fold higher among those with a previous diabetes diagnosis than among those without diabetes ($P = 0.008$), and the risk of recurrence was more than two-fold higher among patients who ever drank compared to those who never drank ($P = 0.008$; **Table 3**).

Determinants of Stroke Recurrence Stratified by Age

Table 3 shows the determinants of recurrent stroke after stratifying the population by age. A history of diabetes was the most common risk factor for recurrent stroke within 1 and 5 years after the initial stroke among patients aged <65 years; the recurrence risk increased 2-fold compared to patients without diabetes. Moreover, the risk of recurrence within 5 years was 1.9-fold higher among those with 1–6 years of education compared to those with more than 6 years of education ($P = 0.028$).

Among patients aged ≥65 years, the risk of recurrence within the first post-stroke year was 57% lower in patients experiencing initial IS than in those experiencing initial ICH ($P = 0.033$); this patient group also had a 79% lower risk of recurrent stroke among those who ever smoked than among those who had never smoked ($P = 0.046$). However, there was a 3.6-fold higher risk of recurrence for those who ever drank than among those who never drank ($P = 0.025$). The risk of recurrence within 5 years increased >2-fold among patients who ever drank compared to that among those who never drank ($P = 0.021$).

DISCUSSION

This is the first population-based report evaluating the recurrent stroke rate in rural China. In this study, we assessed the rate of recurrent stroke within 1 (5.7%) and 5 (22.5%) years after the first-ever stroke. The recurrence rate over both time periods increased significantly with advancing age. After adjusting for age, sex, education level, hypertension, diabetes, smoking, and alcohol consumption, advanced age was an independent predictor of recurrent stroke within both time frames among the overall population. Moreover, male patients, patients with lower educational attainment, and those with a known diabetes history had higher risks of recurrent stroke within the 5 year period. Further, age-stratified analysis showed that known diabetes history was an independent risk factor of stroke recurrence at both 1 and 5 years after the initial stroke among stroke patients

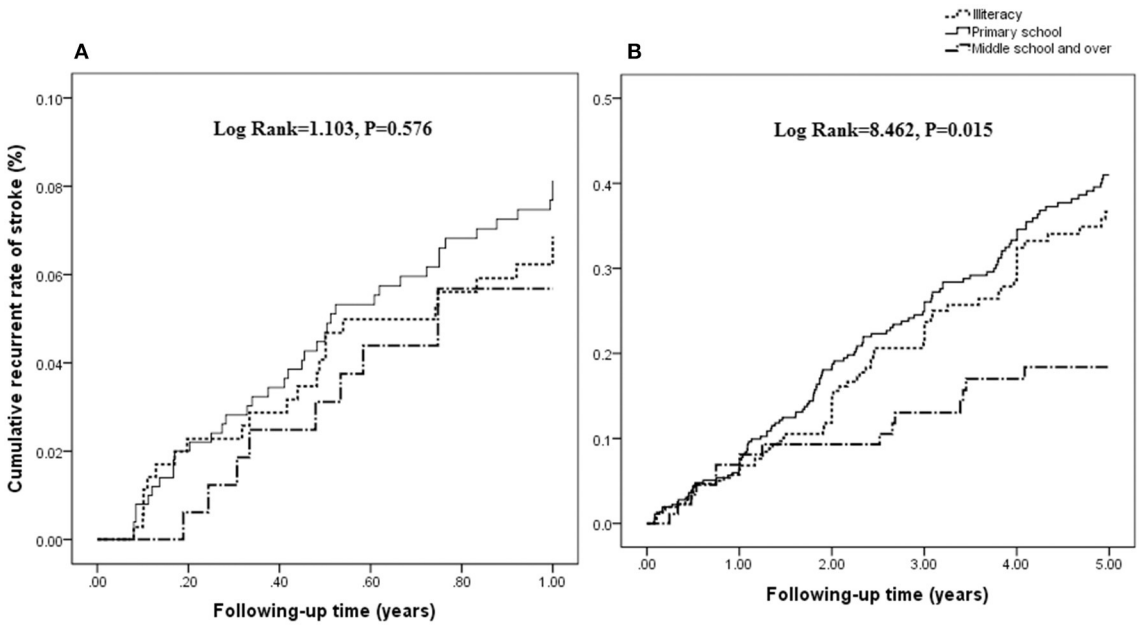

FIGURE 1 | Association between the rate of recurrent stroke and education attainment. There was no significant association between the rate of recurrent stroke within 1 year and education attainment (log rank = 1.103; $P = 0.576$; **A**). However, a negative association is shown between the rate of recurrent stroke within 5 years and education attainment (log rank = 8.462; $P = 0.015$; **B**).

aged <65 years old. Moreover, patients with a lower educational attainment (1–6 years) had a high risk of stroke recurrence. However, for patients aged 65 years and over, ever drinking was an independent risk factor of recurrent stroke at both 1 and 5 years after initial stroke onset. In addition, experiencing initial IS and ever smoking were independent protective factors for risk of stroke recurrence among elderly individuals.

The stroke recurrence rate remains controversial. The risk of stroke recurrence is reported to range from 7.0 to 20.6% over the first year (4, 12, 13), from 16.2 to 35.3% over the first 5 years (4, 10, 14), and from 14 to 51.3% over the first 10 years after the initial stroke (4, 10, 15). A population-based cohort study from the Middle East indicated that the cumulative incidence of stroke recurrence was 14.5% by the end of 5 years, with the highest rate occurring during the 1st year after the initial stroke (5.6%) (29). In the present study, the 1 and 5 year recurrence rates were 5.7 and 22.5%, which are within the range reported previously. This finding suggests that more than 20% of patients will suffer a recurrent stroke within the first 5 years. The relatively low recurrence rates observed in this study are most likely due to the relatively young (average age <65 years) study population.

The disparity among the reported recurrence rates may be partially explained by the differing definitions of stroke recurrence. There is wide variation in the definition of recurrent stroke, ranging from any focal neurological deficit lasting >24 h and occurring after an initial stroke (14, 16, 18, 30) to an event occurring >28 days after an initial stroke (31, 32). In the present study, recurrent stroke was defined as a stroke occurring >28 days after the incident stroke.

In the present study, age was identified as a predictor of recurrent stroke. A previous study from northern Sweden indicated that the risk of stroke recurrence rose by 3% for every additional year of age (8). A similar trend was reported in a study from the Middle East where a 2% increase in risk was observed for every additional year of age (29). Another study suggested that the risk of recurrence significantly increased among patients >75 years old compared to patients <65 years old; the risk of recurrence increased by 13% in patients 76–85 years old and by 16% in those >85 years old (33). In the present study, relative to patients who were <65 years old, we observed a 129% and a 54% increase in the 1 and 5 year risks, respectively, of recurrent stroke among patients ≥65 years old.

Reports of sex-based differences in stroke outcomes are also inconsistent. Several previous studies have reported worse outcomes among women than among men, with women demonstrating greater functional impairment, mortality, recurrence, and dependency rates 3 and 12 months post-stroke (1, 34, 35). However, other studies have not reported these sex-based differences (36). In the present study, there was a higher risk of recurrence among men than among women within the 5 year period after the incident stroke, but this difference was not evident within the first year. In this population, the young age of stroke onset and the poor management of post-stroke risk factors among men may have contributed to the observed sex-based differences in recurrence.

There is strong evidence for an inverse relationship between socioeconomic status (SES) and stroke incidence and mortality (37–39). However, evidence for a potential association between SES and stroke recurrence is limited (39). Previous studies

TABLE 3 | Determinants of recurrent stroke at 1 and 5 years after the first-ever stroke among the study population (HR with 95% CI).

Predictors	Reference	Overall		<65 years		≥65 years	
		Within 1 year	Within 5 years	Within 1 year	Within 5 years	Within 1 year	Within 5 years
Sex:	Women						
Men		1.67 (0.85, 3.26)	1.65 (1.09, 2.50)*	1.75 (0.47, 6.44)	1.79 (0.82, 3.89)	1.59 (0.72, 3.47)	1.55 (0.94, 2.55)
Age groups:	<65 years						
≥65 years		2.29 (1.31, 4.00)*	1.54 (1.11, 2.12)*	—	—	—	—
Education attainment:	≥ 7 years						
0 year		0.88 (0.37, 2.11)	1.55 (0.83, 2.87)	0.36 (0.04, 3.03)	0.91 (0.37, 2.23)	2.29 (0.30, 17.37)	—
1–6 years		1.21 (0.57, 2.58)	1.96 (1.13, 3.42)*	1.10 (0.46, 2.62)	1.90 (1.07, 3.38)*	2.96 (0.40, 22.16)	—
First-ever stroke types:	ICH						
IS		0.53 (0.29, 0.96)*	0.70 (0.48, 1.01)	0.63 (0.24, 1.64)	0.63 (0.39, 1.03)	0.43 (0.20, 0.94)*	0.73 (0.41, 1.29)
Hypertension:	No						
Yes		1.39 (0.59, 3.26)	0.98 (0.60, 1.60)	1.16 (0.27, 5.01)	0.89 (0.38, 2.09)	1.65 (0.57, 4.74)	1.17 (0.64,2.12)
Diabetes:	No						
Yes		1.73 (0.93, 3.22)	1.71 (1.15, 2.54)*	3.19 (1.30, 7.79)*	2.95 (1.75, 4.96)*	1.11 (0.43, 2.88)	0.88 (0.45, 1.73)
Smoking status:	Never						
Past smoker		0.36 (0.11, 1.15)	0.52 (0.27, 1.00)	0.76 (0.11, 5.35)	0.63 (0.23, 1.78)	0.21 (0.05, 0.98)*	0.43 (0.16, 1.14)
Current smoker		0.84 (0.43, 1.65)	0.70 (0.46, 1.06)	0.59 (0.13, 2.70)	0.73 (0.32, 1.63)	0.95 (0.45, 2.01)	0.70 (0.42, 1.15)
Drinking status:	Never						
Past drinkers		2.46 (0.99, 6.11)	2.23 (1.24, 4.01)*	1.82 (0.35, 9.42)	1.74 (0.77, 3.92)	3.60 (1.18, 11.01)*	3.09 (1.19, 8.05)*
Current drinkers		0.90 (0.44, 1.84)	0.86 (0.56, 1.32)	1.41 (0.36, 5.53)	0.92 (0.48, 1.79)	0.70 (0.28, 1.75)	0.73 (0.39, 1.37)

$P < 0.05$ compared to reference.

suggested that this relationship was sex-based (40, 41), but no significant association between SES and stroke recurrence was found in another population-based-study (10). In the present study, a higher risk of recurrent stroke within 5 years after the incident stroke was observed in patients with lower levels of education (1–6 years) than in those with higher levels of education (≥7 years) in the overall population and in those aged <65 years old. However, the risk of recurrent stroke within 5 years after the incident stroke was not higher in those without education attainment (illiteracy) in the overall population and among those aged <65 years old; the lower number of patients with higher levels of education (≥7 years) in the overall population (11.3%) and the lower number of patients with lower levels of education among those aged <65 years old (15%) may partly explain this disparity. Furthermore, the higher percentage of female patients in the illiterate group may contribute to the association of lower education levels with poor stroke outcomes. Poor risk factor management and limited access to medicine among those with lower educational attainment and income may partially explain this relationship (42, 43).

The association between smoking and stroke risk remains controversial. In the Framingham Heart Study, smoking cessation was associated with a significantly lower risk of cardiovascular disease within 5 years among heavy smokers relative to current smokers; however, relative to never smokers, former smokers' cardiovascular disease risk remained significantly elevated beyond 5 years after smoking cessation (44). Another study from the Intracerebral Hemorrhage Outcomes Project found that the functional outcomes among patients with intracerebral hemorrhage were similar between recent smokers and former smokers (45). In the present study, a lower risk of recurrent stroke was found in patients who had ever smoked in the overall population and among elderly stroke patients within 1 year after their initial stroke. The neuroprotective effect of nicotine might explain this finding partly (46–48). The exact cause however needs further research.

Heavy alcohol consumption is well-known risk factor for stroke (49, 50), but the relationship between the risk of recurrent stroke and alcohol consumption remains unknown, especially in China. Alcohol consumption independently predicted impairment 2 years after stroke in one study (51), but no association with functional outcomes after stroke was found in other studies (52–54). In this study, ever drinking was an independent risk factor for recurrence in the overall population and among elderly stroke patients at both 1 and 5 years after the initial stroke. In this population, patients drank in the past ceased drinking alcohol after developing severe diseases; this may explain the positive association between ever drinking and stroke recurrence.

Several studies have suggested that diabetes mellitus is an important predictor of recurrent stroke (55–57). Consistent with these studies, in the present study, we observed a significant association between diabetes mellitus and stroke recurrence for the whole study population and those patients aged <65 years.

This study has several limitations. First, the study population was from a township in northern China, which is not representative of the overall population of China. However, the prospective study design and long study period may have decreased recall and selection bias. Moreover, the 362,596 person-years of total follow-up fulfill the 100,000 person-years

of follow-up criterion for population studies (58). Second, we did not collect detailed information regarding dietary habits and medication use; therefore, other possible determinants of stroke recurrence could not be assessed in this study. Third, data on smoking and alcohol consumption were not available in this study; this may affect the specific evaluation of the relationship between smoking or alcohol consumption and stroke recurrence. Fourth, our study lacks data on medication usage. However, in this low-income population, the rate of using medicine was lower; thus, the impact of medication usage on stroke recurrence may be ignored. Finally, information regarding medical care among these stroke patients was not available. This was a low-income, poorly educated population, and few had medical insurance before 2008. Thus, they would have been taken care of by family members, including spouses, children, siblings, and others. Only unmarried men who suffered strokes were sent to the official nursing home.

CONCLUSIONS

This report assessed the rate of recurrent stroke in rural China using a population-based study design. The rates of recurrent stroke within 1 and 5 years after the first-ever stroke were 5.7 and 22.5% and increased significantly with advancing age. The determinants of stroke recurrence were associated with age. After adjusting for covariates, a known diabetes history was an independent risk factor for stroke recurrence at both 1 and 5 years after the initial stroke among patients aged <65 years old; moreover, lower educational attainment (1–6 years) increased the risk of stroke recurrence. However, for patients aged 65 years and over, ever drinking was an independent risk factor for recurrent stroke at both 1 and 5 years after the initial stroke onset; experiencing an initial IS and ever smoking were protective factors for the risk of stroke recurrence. These findings suggest a crucial need to address risk factor management among stroke patients to reduce the burden of stroke, especially among low-income populations. Furthermore, a multicenter, large sample, nationwide study is urgently needed.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the artical/supplementary material.

ETHICS STATEMENT

The study protocol was approved by the ethics committee of Tianjin Medical University General Hospital (TMUGH); written informed consent was obtained from each participant.

AUTHOR CONTRIBUTIONS

JW and XN contributed to the study design, performed data collection, data interpretation, and critical review. JW performed data analysis. JH and WM contributed to drafting of the article. JH, WM, JN, YW, JL, LB, MS, and JT performed data collection, case diagnoses, and confirmation of case diagnoses. All authors read, revised, and approved the final version of the paper.

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