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Strategies for improving hypertension management

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Strategies for improving hypertension management

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Editorial: Strategies for improving hypertension management

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Editorial on the Research Topic
Strategies for improving hypertension management

Despite preventive strategies and major advances in pharmacological treatment, the prevalence of hypertension has been increasing (1). To curb this rise, there is a need to gather new evidence and critically re-evaluate preexisting evidence so strategies can be formulated to prevent hypertension and improve its management.

The pathogenesis of hypertension cannot be entirely elucidated by genetics and conventional risk factors (2). There is a need to identify and mitigate additional risk factors, evaluate the efficacy of anti-hypertensive drugs in different populations (3), and explore non-pharmacological treatment that could improve treatment adherence and long-term BP control (4). In this collection" Strategies for improved management of Hypertension," Li C. et al. identified the role of impaired gut health in hypertension. They found elevated intestinal barrier serum markers diamine oxidase, lipopolysaccharide, and D-lactate in hypertensive patients compared to normotensives. The patients with longstanding hypertension history (≥20 years), poor control of diastolic blood pressure, and cardiac and renal complications had elevated diamine oxidase and lipopolysaccharide, while patients on multidrug therapy for hypertension had higher D-lactate levels. This study suggests the association of the intestinal barrier with hypertension.

In another study on the association of the ABO blood group with preeclampsia, Li T. et al. found that the AB blood group patients have an increased risk of preeclampsia (PE), and the A blood group is associated with early-onset PE. Clinicians could proactively manage pregnant women with these blood groups who have raised blood pressure and are potentially at high risk of developing PE.

Besides accumulating new evidence, the preexisting evidence applicability in different sets of populations could also be helpful. Ojji et al. found the selective beta-1 blocker nebivolol has significant antihypertensive efficacy and satisfactory tolerability in

reducing both systolic blood pressure (SBP) and diastolic blood pressure (DBP) in Blacks with stage I hypertension residing in sub-Saharan Africa, indicating the potential use of nebivolol as monotherapy in grade 1 hypertension or as the fourth drug in multitherapy after maximum doses of a combination of long-acting calcium channel blockers, thiazide diuretics, and renin-angiotensin-aldosterone blockers have been used.

Sun et al. investigated the effect of an incremental rise in the risk of cardiovascular diseases (CVD) with increasing SBP in older adults above 65 years of age, having SBP between 90 and 129 mm Hg. The authors found a non-linear association between normal range SBP levels and all-cause and cardiovascular death. Also, when SBP $<$115 mmHg, the risk of mortality gradually increased with decreasing SBP, and when SBP $\geq$115 mmHg the risk of mortality gradually increased with SBP level. The findings suggest that SBP level 110–120 mmHg could be optimal, and the SBP level in the normal range might have a dose-response relationship with all-cause and cardiovascular mortality.

Yang et al. examined the relationship between SBP and in-hospital deaths in Type -A Aortic dissection (AAD) patients and found a non-linear correlation between admission SBP and in-hospital mortality of AAD patients when SBP was $\leq$120 mmHg. A SBP $\leq$120 mmHg negatively correlated with in-hospital mortality and a 10 mmHg rise in admission SBP was found to be associated with 12% lower odds of in-hospital mortality.

Fu et al. identified two sub-phenotypes in masked hypertension (MHT); the low-risk metabolic syndrome (MetS) and the high MetS (characterized by larger waist circumference, lower HDL-C, higher fasting blood glucose, and triglycerides, and prevalence of diabetes) sub-phenotype. The authors found a significant correlation between sub-phenotypes and clinical results and the sub-phenotypes have different metabolic characteristics and prognoses. For patients with MHT and high-risk MetS, antihypertensive therapy alone may be insufficient. In addition to antihypertensive treatment, the management of the metabolic disorder in MHT populations may be also considered in the future.

Visco et al. retrospectively analyzed the database of 177 essential hypertensives and found an independent positive correlation of serum uric acid (sUA) with left ventricular mass index (LVMi) which is a common complication of hypertension and increases the risk of cardiovascular morbidity. The results showed that the sUA above 5.6 mg/dl predicts larger LV sizes. The results suggest hyperuricemia is an early marker of increased left ventricular mass that can be used to identify a hypertensive population with target organ damage.

Meng and Xu stated that the ideal blood pressure for the treatment and management of Atrial Fibrillation (AF) is not clear. The eight major hypertension guidelines that were updated between 2016 and 2019 vary in the recommended target BP for preventing new-onset AF. The authors expressed that the ideal approach to assess the impact of hypertension on AF in large population-based cohort studies remains unclear because of the increased beat-to-beat BP variability in the presence of AF which may affect BP estimation and thus the assessment of the correlation between BP and AF. Also, the insufficient sensitivity in detecting sporadic arrhythmias (such as paroxysmal AF) by intermittent monitoring adds to the complexity of accuracy in answering the question. The authors suggested the use of a continuous rhythm monitoring strategy to overcome the limitations of intermittent monitoring in assessing the rate of incident AF and help evaluate the real effect of hypertension on AF.

Meier et al. evaluated whether the financial incentives are more effective than evidence-based educational feedback reports in the increasing proportion of patients with diabetes mellitus meeting specific quality indicators (QIs). The authors found that the intervention group achieved an improvement of 2% in the proportion of patients achieving the recommended blood pressure target levels, whereas the proportion of patients receiving annual HbA1c measurements remained stable. After the withdrawal of financial incentives for the General Practitioners after 12 months, some quality of life indicators (QIs) still improved, but there was a decrease in QI achievement rates after 18 months suggesting that the positive effects of time-limited financial incentives eventually diminish.

In summary, the articles on this Research Topic discussed some pertinent issues in the field of hypertension. The association of the intestinal barrier with hypertension, the association of hyperuricemia with left ventricular mass, and the AB blood group with preeclampsia was revealed. These findings will help clinicians identify the at-risk population and treat them proactively for the prevention and improved management of hypertension and related cardiovascular disease. The articles also discussed treating masked hypertension based on subphenotype in patients having associated metabolic syndrome and treating hypertension with nebivolol in sub-Saharan Africa. These findings could prove useful in hypertension treatment in specific populations.

The non-linear association of normal range systolic BP with all-cause mortality and cardiovascular death in older patients above 65 years of age and the non-linear association of SBP with in-hospital mortality of type A Aortic Dissection will help in determining an optimal BP target in these populations.

The suggested use of intermittent monitoring for assessing the rate of incident AF in hypertensives will help in assessing the association between blood pressure and incident AF. This will help in reaching the consensus on target BP for preventing new-onset AF. Lastly, a positive effects of time-limited financial incentive to general practitioners (GPs) was found on the proportion of patients achieving the recommended blood pressure target levels. After the withdrawal of financial incentives for the GPs after 12 months, some quality of life indicators (QIs) still improved, but there was decrease in QI achievement rates after 18 months, suggesting that 1 year might be too short to observe the full effect of such interventions and the positive effects of time-limited financial incentives eventually wane.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Serum Uric Acid and Left Ventricular Mass in Essential Hypertension

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Serum uric acid (sUA) has been associated with cardiovascular risk. Although the recent mechanistic hypothesis poses the basis for the association between sUA and left ventricular mass index (LVMi), the issue remains poorly investigated in a clinical setup. Through a retrospective analysis of the database of the departmental Hypertension Clinic of University Hospital of Salerno Medical School, we identified 177 essential hypertensives (age 60.3 ± 13.3 years; 85 men), free from uric acid-modulating medications and severe chronic kidney disease, and whose sUA values, anthropometric, clinical, and echocardiographic data were available. In the studied cohort, the average duration of hypertension was 8.4 ± 7.1 years. LVMi associated with classical determinants, such as age, blood pressure, and kidney function, although after multivariate correction, only age remained significant. Also, sUA correlated positively with LVMi, as well as body size, metabolism, and kidney function. In a multivariate analysis, sUA confirmed the independent association with LVMi. Also, levels of sUA >5.6 mg/dl are associated with larger cardiac size. We confirmed our data in a replicate analysis performed in a larger population (1,379 hypertensives) from an independent clinic. Our results demonstrate that sUA increases with LVMi, and a cutoff of 5.6 mg/dl predict larger LV sizes. Our data suggest that hyperuricemia might help to stratify the risk of larger cardiac size in hypertensives.

Keywords: hypertension, uric acid, left ventricular mass, risk factors, hypertrophy

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INTRODUCTION

Serum uric acid (sUA) is the final product of purine catabolism; its levels depend on the equilibrium of production and elimination, which occurs through the kidney. By routine, the normal distribution of sUA among the general population is considered below 6 mg/dl in women and 7 mg/dl in men (1). Hyperuricemia results from either an overproduction and/or a reduced UA renal excretion, thus explaining a complex interaction of physiological conditions and exogenous factors that can affect sUA (2).

In recent years, sUA has become an important parameter to consider when assessing cardiovascular risk. Indeed, sUA is associated with insulin resistance, hypertension, diabetes mellitus, dyslipidemia, obesity, metabolic syndrome, renal dysfunction, and hypothyroidism

(3–5), which may explain enhanced cardiovascular (CV) risk among hyperuricemic individuals (6, 7). Noteworthy, ESC /ESH guidelines (8) have drawn new attention in the definition of CV risk based on sUA, capitalizing on a series of large studies reviewed by Borghi et al. (9); indeed, the 2018 European guidelines on the management of hypertension include sUA in the routine workup (8).

Recently, Kuwabara et al. showed that in the Japanese population, having higher sUA could be a risk for hypertension, dyslipidemia, and chronic kidney disease (CKD) (10).

Moreover, we reported that the optimal cut point for sUA to discriminate cardiovascular disease (CVD) mortality was 5.6 mg/dl (11) in population with high CV risk; in keeping with these results, the information on levels of sUA above or below 5.6 mg/dl incrementally predicted CVD mortality over Heart Score (11). The ability of sUA to predict CV risk probably associates with its ability to identify target organ damage (TOD), which participates in the definition of CV risk. For translational properties, it is possible to speculate that sUA and TOD indeed associate, as demonstrated, for instance, for renal dysfunction and atherosclerosis (3–5). Less evidence is available for the association of sUA and cardiac damage, in particular with increased left ventricle mass indexes (LVMi) (7, 12, 13). This is an independent, powerful predictor of CV morbidity and mortality in patients with hypertension and is associated with an increased incidence of arrhythmia, myocardial infarction, and stroke (14). Effective treatment can lead to regression of LVMi, in particular in young hypertensives, with a recent history of the disease, since superimposed age-related biochemical and histologic changes compromise LVMi response to therapy (15).

Our study aims to investigate the relationship between sUA and cardiac structural and functional variables in a cohort of hypertensive patients.

EXPERIMENTAL SECTION

Recording and Organizing Data

The population enrolled in the departmental Hypertension Clinic of University Hospital of Salerno Medical School is included in a central electronic database (Wincare, Gesan, Napoli, Italy), which contains separate electronic sheets for medical history, physical examination, clinical data, laboratory tests, electrocardiogram, and cardiac and vascular ultrasounds.

Study Population

The database was interrogated to extract data of patients according to the following inclusion criteria: patients visited consecutively over a period of 3 months, with at least an average follow-up of 3 years, both males and females, age 18–80, with blood pressure $<140/90$ mmHg in office, on active antihypertensive treatment. We excluded those patients that were actively treated with diuretics (also including the 6 months before enrollment and during the follow-up), with sUA lowering agents, pregnant women, patients diagnosed with gout, malignancies, rheumatic disease, in chronic treatment with anti-inflammatory or anti-pain agents, and no use of daily doses of alcohol>3 drinks per day. Patients with chronic kidney disease at stage 4 and higher were also excluded. The diagnosis of hypertension was based according to current guidelines (8). Data were then checked for quality to exclude patients with incomplete databases. For a list of the independent variables considered in this cohort, please see **Table 1**.

To replicate and validate the results of our study, we obtained the database of 1,379 hypertensive patients from the Hypertension Clinic of the Federico II University, which is located in the nearby city of Naples, in Campania, Italy. The Hypertension Clinic of the Federico II University uses a similar electronic chart for the management of outpatients (Wincare, Gesan), which has been in use for almost 40 years (16). Patients were selected from a database of over 25,000 hypertensives, according to the very same inclusion criteria described above.

Informed consent was obtained from each patient, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institutions' human research committee (NCT03305276). The validation group data were obtained from the anonymized database of a previously approved, completed trial (ClincalTrials.gov: NCT00408512).

Baseline Clinical Characteristics

The visit includes an update of anamnestic data and medical history with particular attention to lifestyle habits and pharmacological treatments, physical examination (including anthropometric measurements, blood pressure values, and heart rate), and standard electrocardiography.

Blood pressure (BP) measurement was obtained with an automated oscillometer (Afib screen, Microlife, Italy), validated according to international standardized protocols, and adequately maintained to verify calibration. Cuff placement was preceded by the selection of the appropriate cuff size for the patient's arm circumference; the lower end of the cuff was 2 to 3 cm above the antecubital fossa. The BP reading was obtained in the supine position (after a resting period of at least 10 min), in sitting and standing positions; the cuff was at the heart level, whatever the position of the patient. At least two BP measurements were recorded in every position (timed 1–2 min apart), and additional measurements were obtained if the first two assessments were largely different. In this study, we considered the average BP in the sitting position according to the current guidelines (8). In subjects resting in the supine position for 10 min, the ankle to brachial index (ABI) was determined using an automated oscillometric BP device at the right limb.

Laboratory Analysis

Venous blood samples were collected in the morning after an overnight fast as a general rule. Blood chemistry was evaluated according to standardized methods by trained personnel. sUA levels were determined using the uricase-peroxidase system. Triglycerides and total and HDL cholesterol were assayed enzymatically, while LDL cholesterol was calculated with the formula of Friedewald. Serum glucose was measured using the glucose oxidase method. The estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) equation.

TABLE 1 | Clinical, serum biochemistry, and cardiac ultrasound parameters.

	Overall ($n = 177$)	sUA>5.6 mg/dl ($n = 51$)	sUA ≤5.6 mg/dl ($n = 126$)	*p*
Clinical				
Age, years	60.3 ±13.3	60.0 ±13.3	60.5 ±13.3	0.71
Men, *n* (%)	85 (48.0)	33 (64.7)	52 (41.3)	**0.005**
BMI, kg/m^2	28.9 ±5.6	29.1 ±5.3	28.8 ±5.8	0.15
HR, beats/min	71.5 ±12.3	72.1 ±10.1	71.7 ±13.2	0.51
SBP, mmHg	144.7 ±19.2	146.7 ±19.9	143.9 ±18.9	0.74
DBP, mmHg	86.3 ±12.1	87.1 ±13.5	85.9 ±11.5	0.64
Pulse pressure, mmHg	58.4 ±14.1	59.6 ±14.8	57.0 ±13.8	0.96
ABI	1.3 ±0.2	1.2 ±0.2	1.3 ±0.1	**0.01**
Duration of hypertension, years	8.4 ±7.1	9.4 ±7.8	8.0 ±6.8	0.21
Current-smokers, *n* (%)	46 (27.5)	16 (32.0)	30 (25.6)	0.40
Serum biochemistry				
TC, mg/dl	193.7 ±40.1	192.8 ±41.2	194.0 ±39.8	0.85
HDL, mg/dl	54.3 ±14.9	48.4 ±12.4	56.7 ±15.2	**0.001**
LDL, mg/dl	114.5 ±36.6	113.9 ±39.7	114.7 ±35.4	0.89
Triglycerides, mg/dl	124.6 ±59.6	152.6 ±61.2	113.3 ±55.3	**0.001**
sGlucose, mg/dl	103.9 ±22.00	110.9 ±27.6	101.1 ±20.3	**0.01**
sCreatinine, mg/dl	0.9 ±0.2	1.0 ±0.2	0.9 ±0.2	**0.01**
sUrea, mg/dl	40.3 ±11.5	43.0 ±13.4	39.2 ±10.5	**0.045**
eGFR, ml/min/1.73m^2	91.9 ±33.4	88.3 ±36.06	93.4 ±32.3	0.36
sUA, mg/dl	4.99 ±1.30	6.52 ±0.77	4.38 ±0.88	**0.001**
Cardiac ultrasound				
LVMi, g/m$^{2.7}$	51.4 ±13.8	54.7 ±15.2	49.1 ±13.0	**0.04**
LVEF, %	65.9 ±10.1	65.8 ±11.1	66.9 ±9.8	0.49
RWT, %	0.4 ±0.1	0.4 ±0.1	0.4 ±0.1	0.57
LAD, mm	39.1 ±5.8	39.0 ±4.8	38.9 ±6.2	0.56
E/A	0.9 ±0.3	0.9 ±0.3	0.9 ±0.3	0.96
DT, ms	204.2 ±56.0	207.5 ±55.0	202.4 ±56.5	0.60
E/E'	7.4 ±2.1	6.9 ±2.2	7.8 ±2.0	0.15
IVSd, mm	11.4 ±2.1	12.3 ±2.3	11.0 ±2.0	**0.001**

BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABI, ankle-brachial index; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; LVMi, left ventricular mass index; LVEF, left ventricular ejection fraction; RWT, relative wall thickness; LAD, left atrial diameter; E, early-wave transmitral diastolic velocity; A, late-wave transmitral diastolic velocity; E', early-diastolic velocity at tissue Doppler imaging; DT, deceleration time; IVSd, diastolic intraventricular septum diameter; sGlucose, serum glucose; sCreatinine, serum creatinine; sUrea, serum urea; sUA, serum uric acid. Data are presented as means ± SD unless otherwise indicated. p-values were calculated by unpaired t-test for continuous variables, or χ^2 test for frequencies. Bold values indicate statistical significance ($p < 0.05$).

Cardiac Ultrasounds

All patients of this study received cardiac ultrasounds (Vivid E80, GE Healthcare) with M-mode, 2D, pulsed, and color-flow Doppler within 4 months from the first visit. To eliminate the confounding effect of gender on cardiac size, in this study, LVMi was adjusted for height $^{2.7}$ (8). Simpson's ejection fraction evaluated LV systolic function. A pulsed Doppler estimated the diastolic function from an apical four-chamber view at the level of mitral valve tips; early- (E) and late-wave (A) diastolic velocities and their ratio (E/A) were measured. Tissue Doppler imaging (TDI) was also performed, to calculate the E/E' ratio, where E$'$ is the early diastolic velocity at TDI measured at the septal and lateral corner of the mitral annulus.

Statistic Analysis

The data are expressed as frequencies and percentages for qualitative variables and as mean ± standard deviation (SD) for quantitative ones. Using ANOVA, we analyzed continuous variables; categorical data were compared using the χ^2 test. Linear univariate regression analyses, with confidence intervals, were tested on sUA and LVMi; multivariable regression analyses were performed on the significant continuous and categorical variables. Statistical analysis was performed using SPSS software for Windows, version 26.0 (SPSS Inc, Chicago, IL, United States).

RESULTS

Population Features

We enrolled 300 hypertensives consecutively admitted to our clinic from February to May 2017; we followed up for 12 months to collect all clinical, cardiac US, and serum biochemistry data. After 1 year of follow-up, 31 patients were lost, and 92 were discarded for the incompleteness of the data. The analysis was therefore completed on 177 patients. The

TABLE 2 | Univariable linear regression analysis with LVMi.

	Beta	*p*	Lower 95%	Upper 95%
Clinical				
Age	0.337	**0.001**	0.199	0.492
Gender	0.083	0.27	−1.833	6.369
HR	−0.078	0.31	−0.253	0.080
SBP	0.157	**0.04**	0.008	0.220
DBP	−0.048	0.53	−0.214	0.126
Pulse pressure	0.255	**0.001**	0.103	0.387
ABI	0.099	0.22	−5.609	23.949
Serum biochemistry				
TC	−0.089	0.24	−0.081	0.021
HDL	−0.151	**0.046**	−0.277	−0.003
LDL	−0.031	0.68	−0.068	0.044
Triglycerides	−0.014	0.86	−0.038	0.031
sGlucose	0.201	**0.007**	0.033	0.208
sCreatinine	0.159	**0.04**	0.703	18.662
sUrea	0.179	**0.02**	0.038	0.39
eGFR	−0.109	0.15	−0.106	0.016
sUA	2.099	**0.009**	0.539	3.659

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sGlucose, serum glucose; sCreatinine, serum creatinine; sUrea, serum urea; eGFR, estimated glomerular filtration rate; sUA, serum uric acid. Bold values indicate statistical significance ($p < 0.05$).

TABLE 3 | Multivariate linear regression analysis with LVMi.

	Beta	*p*	Lower confidence limit	Upper confidence limit
Age	0.306	**<0.0001**	0.173	0.463
SBP	0.127	0.07	−0.008	0.19
HDL	−0.118	0.11	−0.244	0.026
sGlucose	0.138	0.052	−0.001	0.166
sCreatinine	0.04	0.64	−7.655	12.469
sUrea	0.12	0.14	−0.046	0.333

SBP, systolic blood pressure; HDL, high-density lipoprotein; sGlucose, serum glucose; sCreatinine, serum creatinine; sUrea, serum urea. Bold values indicate statistical significance ($p < 0.05$).

clinical, biochemical, and cardiac ultrasound (US) parameters of the study patients are summarized in **Table 1**. Men had greater LVMi and intraventricular septum dimensions than women (data not shown).

Anthropometric and Hemodynamic Parameters Influencing LVMi

LVMi was significantly and directly correlated with age, serum glucose, blood pulse pressure, and kidney function (**Table 2**). Interestingly, LVMi was significantly and inversely related to HDL (**Table 2**). After a correction in a multivariate analysis, only age significantly correlated with LVMi (**Table 3**).

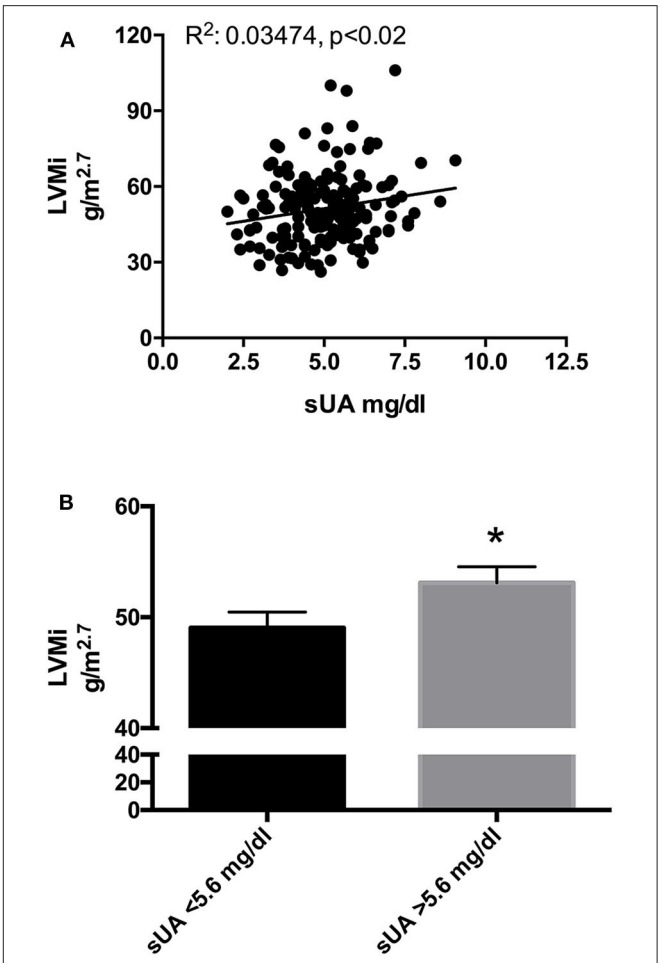

FIGURE 1 | (A) Scatter plots of left ventricular mass index (LVMi) vs. serum uric acid (sUA) in the original population (177 patients). The graph shows that LVMi was significantly and directly related with sUA ($p = 0.01$). **(B)** LVMi in patients with sUA ≤ 5.6 mg/dl (left graph) and in patients with sUA >5.6 mg/dl (right graph). The graph shows higher value of LVMi in hypertensives with sUA > 5.6 mg/dl ($p = 0.045$). *Indicates $p < 0.05$.

Association Between sUA and LVMi

To verify the association of sUA and cardiac TOD, we assessed the correlation between sUA on LV parameters. A statistically significant linear correlation was found between sUA and LVMi (**Figure 1A**); also, the univariate analysis indicated a positive relationship between the two parameters [Beta: 2.099; $p < 0.009$; (95% CI: 0.539–3.659)]. Furthermore, sUA levels displayed a significant correlation with gender, metabolism (BMI, weight, sGlucose, triglycerides, and HDL), and kidney function (creatinine, serum urea, eGFR) (**Table 4**).

Since previous literature had demonstrated that sUA might impact the outcome "death" on top of other determinants (11), also in this population, given the small number of patients, we tested the effect of sUA on LVMi in a multivariable analysis that included the above-indicated determinant, i.e., age and BMI. Both age and sUA independently correlate with LVMi (**Table 5**).

TABLE 4 | Univariate linear regression analysis with sUA.

	Beta	*p*	Lower 95%	Upper 95%
Clinical				
Age	0.012	0.87	−0.013	0.016
Gender	0.330	**0.001**	0.488	1.214
Weight	0.235	**0.001**	0.007	0.029
BMI	0.162	**0.03**	0.003	0.071
HR	0.007	0.93	−0.015	0.016
SBP	0.068	0.36	−0.005	0.015
DBP	0.083	0.30	−0.007	0.025
ABI	−0.096	0.23	−2.214	0.539
Pulse pressure	0.022	0.77	−0.012	0.016
Duration of hypertension	0.061	0.45	−0.016	0.038
Serum biochemistry				
TC	0.0047	0.36	−0.007	0.003
HDL	0.13	**<0.001**	−0.04	-0.016
LDL	0.0015	0.60	−0.007	0.004
Triglycerides	0.08	**<0.001**	0.003	0.009
sGlucose	0.03	**0.02**	0.002	0.018
sCreatinine	0.12	**<0.001**	1.182	2.779
sUrea	0.026	**0.03**	0.002	0.035
eGFR	0.026	**0.03**	−0.006	0.005
Cardiac ultrasound				
LVMi	0.186	**0.01**	0.005	0.032
LV ejecton fraction	0.0043	0.39	−0.028	0.011
RWT	<0.001	0.96	−2.032	2.505
LAD	0.015	0.12	−0.008	0.058
E/A	0.0005	0.78	−0.772	0.578
DT	0.006	0.36	−0.002	0.006
IVSd	0.02	0.09	0.035	0.212

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ABI, ankle-brachial index; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sGlucose, serum glucose; sCreatinine, serum creatinine; sUrea, serum urea; eGFR, estimated glomerular filtration rate; LVMi, left ventricular mass index; RWT, relative wall thickness; LAD, left atrial diameter; E, early-wave transmitral diastolic velocity; A, late-wave transmitral diastolic velocity; DT, deceleration time; IVSd, diastolic intraventricular septum diameter. Bold values indicate statistical significance (p < 0.05).

Recently, we have proposed lower limits of sUA (5.6 mg/dl) to identify the increased risk of CV death (11). To verify whether this cutoff could also be helpful to identify a population with larger LVMi, we dichotomize our population by sUA > 5.6 mg/dl and observed a larger size of LV in hypertensives with sUA above the fixed threshold (**Figure 1B**).

Replica Analysis in a Larger Population

To overcome some of the small sample size limitations of our study, we sought the collaboration of the Hypertension Outpatient Clinic of the Federico II University, which provided data regarding the first access to their database of 1,379 hypertensives selected out from a pool with over 25,000 patients, using the same inclusion criteria. The available clinical characteristics are illustrated in **Table 6**, grouped by sUA and gender.

TABLE 5 | Multivariate linear regression analysis of Age and sUA on LVMi.

Model 1	Beta	*p*	*Lower 95%*	*Upper 95%*
Age	0.32	**0.001**	0.2	0.465
BMI	0.374	**0.001**	0.598	1.228
sUA	0.133	**0.04**	0.04	2.786

BMI, Body Mass Index; sUA, Serum Uric Acid. Bold values indicate statistical significance (p < 0.05).

We then performed a correlation analysis between sUA and LVMi in this larger population, confirming the association between the two parameters, with a similar amplitude than that observed in the original smaller population (**Figure 2A**). In the univariable and multivariable analyses using the above-identified parameters, sUA remained significantly associated with LVMi (**Table 7**). Finally, when we dichotomize this population by the sUA cutoff of 5.6 mg/dl, we identify a population with a larger LVMi (**Figure 2B**). One might question the total independency of sUA with cardiac parameters based on the distribution of gender between sUA >5.6 and <5.6 groups. It is noteworthy that we used LVMi calculated by correction by height elevated at 2.7, a correction that reduces the differences of cardiac size indexes between genders. Anyway, we dichotomized the replica population according to gender. **Figure 3** shows that sUA >5.6 identifies in both genders a population with larger LVMi.

DISCUSSION

Our results show for the first time in a real-life situation that sUA is in direct correlation with the LVMi, independently from other confounders. Furthermore, the use of the newly proposed cutoff of 5.6 mg/dl can help to predict the hypertensive population with a larger cardiac size. Our results agree with the growing role that this biochemical parameter plays in the definition of the CV risk of events in the hypertensive population.

Our data have been confirmed in two independent populations admitted at the University of Salerno and the Federico II University Hypertension Clinics. Apart from the confirmation of all the major observations, it is interesting to note that the association between sUA and LVMi comes with very low levels of R^2, thus indicating that the two phenomena (sUA and LVMi), although associated, have distant mechanisms underlying. Nevertheless, the use of sUA in the management of hypertension might be helpful to identify patients with TOD.

The precise mechanism underlying the relationship between sUA and LVMi is still undetermined. It is possible to advocate pathophysiological mechanisms linking the two phenotypes. It has been reported that sUA increases tumor necrosis factor-alpha, stimulates mitogen-activated protein kinases, and activates the renin–angiotensin system, all of which are known to promote cardiac hypertrophy (17, 18). Alternatively, Cicero et al. (19) reported that sUA associates with increased pulse wave velocity (PWV) and augmentation index, the gold standard to estimate arterial stiffness in patients with hypertension, and to cause the increase in LV afterload, the major determinant of LV

TABLE 6 | Clinical, serum biochemistry, and cardiac ultrasound parameters in the replica population.

	Overall (n = 1,379)	sUA>5.6 mg/dl (n = 532)	sUA ≤5.6 mg/dl (n = 847)	p	Females (n = 587)	Males (n = 782)	p
Clinical							
Age, years	52.9 ±13.7	52.0 ±14.6	53.5 ±13.1	**<0.05**	55.9 ±12.4	50.6 ±14.1	**<0.001**
Men, *n* (%)	786 (57)	436 (82)	350 (42)	**<0.01**	587 (43)	782 (57)	**n.a.**
BMI, kg/m^2	27.5 ±4.4	28.6 ±4.1	26.8 ±4.4	**<0.01**	27.3 ±4.9	27.5 ±3.9	0.29
SBP, mmHg	143.7 ±18.9	144.5 ±18.5	143.2 ±19.1	0.21	144.8 ±19.8	142.2 ±18.1	0.07
DBP, mmHg	88.9 ±11.5	89.9 ±11.6	88.3 ±11.5	**<0.02**	87.8 ±11.5	89.6 ±11.4	**<0.006**
HR, beats/min	75.1 ±27.9	74.2 ±12.6	75.6 ±34.2	0.39	74.9 ±12.0	75.1 ±35.2	0.86
Serum biochemistry							
Triglycerides, mg/dl	122.9 ±69.4	138.9 ±74.1	112.7 ±64.1	**<0.01**	111.9 ±58.0	130.9 ±75.5	**<0.001**
TC, mg/dl	200.1 ±38.1	200.8 ±36.7	199.7 ±38.9	0.60	206.0 ±38.2	195.0 ±37.2	**<0.001**
HDL, mg/dl	52.6 ±13.7	48.6 ±12.5	55.2 ±13.9	**<0.01**	59.3 ±13.5	47.7 ±11.6	**<0.001**
LDL, mg/dl	122.6 ±35.5	124.6 ±33.3	121.3 ±3, 696	0.12	125.7 ±34.8	120.2 ±35.8	**<0.034**
sGlucose, mg/dl	96.7 ±20.5	98.4 ±18.5	95.6 ±21.6	**<0.01**	96.1 ±24.3	97.0 ±17.0	0.46
sCreatinine, mg/dl	0.9 ±0.3	1.1 ±0.3	0.9 ±0.2	**<0.01**	0.8 ±0.3	1.0 ±0.2	**<0.001**
sUrea, mg/dl	37.4 ±12.6	39.2 ±13.5	36.3 ±11.9	**<0.01**	37.7 ±14.1	37.2 ±11.3	0.47
sUA, mg/dl	5.2 ±1.4	6.6 ±0.9	4.3 ±0.8	**<0.01**	4.4 ±1.1	5.8 ±1.3	**<0.001**
Cardiac ultrasound							
LVMi, g/m$^{2.7}$	43.6 ±9.0	44.2 ±8.5	43.1 ±9.2	**<0.05**	43.6 ±9.4	43.5 ±8.6	0.90
LVEF, %	67.5 ±4.4	67.304.5	67.6 ±4.4	0.30	67.8 ±4.4	67.1 ±4.4	**<0.01**
RWT, %	0.38 ±0.04	0.38 ±0.04	0.38 ±0.04	0.98	0.38 ±0.04	0.37 ±0.03	**<0.013**
E/A	1.1 ±0.3	1.1 ±0.3	1.0 ±0.3	0.10	1.0 ±0.3	1.1 ±0.3	**<0.001**

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sGlucose, serum glucose; sCreatinine, serum creatinine; sUrea, serum urea; sUA, serum uric acid. LVMi, left ventricular mass index; LVEF, left ventricular ejection fraction; RWT, relative wall thickness; E, early-wave transmitral diastolic velocity; A, late-wave transmitral diastolic velocity; Data are presented as means ± SE unless otherwise indicated. p-values were calculated by unpaired t-test for continuous variables, or χ^2 test for frequencies. Bold values indicate statistical significance ($p < 0.05$).

hypertrophy. Finally, sUA levels might reflect the degree of xanthine oxidase activity and resultant oxidative stress, which plays an essential role in the development of increased cardiac size (20). Furthermore, allopurinol, via inhibition of xanthine oxidases, could induce regression of LV mass in humans in a broad spectrum of diseases, including CKD, ischemic heart disease, and type 2 diabetes mellitus (21–23). Most likely, though, the identification of a common pathophysiological mechanism is still far to be identified, and at the moment, sUA represents a powerful biomarker that associates with cardiac TOD.

The need for biomarkers for the stratification of CV risk among hypertensives is a sensitive issue. Indeed, in the general definition of hypertension, we include multiple intermediate phenotypes: males and females, easy and difficult to treat, young and old, lean and obese and so on (24, 25). In the attempt to identify novel biomarkers that facilitate the identification of patients with a greater risk to develop CV events, sUA levels recently attained renewed emphasis (8). In particular, increased LVMi is reported in hypertensive patients (7, 26, 27). The combination of hyperuricemia combined with increased LVMi is an independent and powerful predictor for CV events, including myocardial infarction, angina pectoris, congestive heart failure, cerebral infarction, and transient cerebral ischemia (26).

The association between sUA and LVMi was previously shown in a different condition. In 540 patients with CKD, sUA directly correlated with LVMi (28); similarly, a significant and independent relationship between sUA and LVMi was observed also in renal transplant recipients after adjustment for potential confounding factors (12). At the opposite, in hypertension, conflicting data exist. While some authors report no independent association of sUA levels with LV size (29, 30), other studies showed a gender-related association between sUA and LVMi (31, 32). The reasons for these different observations can relate to methodological differences and heterogeneity of patient characteristics. Also, the use of higher cutoff to define hyperuricemia could have caused a bias in selecting a very high-risk population, where other conditions (i.e., CKD) might play a confounding effect. In our study, we use the recently proposed cutoff of sUA ≥5.6 mg/dl to define hyperuricemia (11). This cutoff allows the association of sUA and LVMi to emerge regardless of age and gender. Our results, therefore, further confirm that this cutoff can help to identify hypertensives with TOD, which in turn increases the risk of CV events.

Nakanishi et al. demonstrated that in a sample of the general population without overt cardiac disease, elevated sUA was independently associated with subclinical LV dysfunction, assessed as abnormal LV global longitudinal strain (GLS). Interestingly, the authors do not report the association between sUA and classical US parameters of LV function such as ejection fraction (33). Our results confirm therefore that sUA is not significantly related to LVEF (**Table 4**); furthermore, the two groups do not differ in diastolic function parameters (**Table 1**)

TABLE 7 | Univariate and multivariable linear regression analysis in the replica population.

	Beta	*p*	Lower limit	Upper limit
Univariate analysis				
Clinical				
Age	0.296	**<0.001**	0.160	0.226
Gender	−0.003	0.9	−1.019	0.895
HR	−0.080	**0.004**	−0.043	−0.008
SBP	0.161	**<0.001**	0.051	0.102
DBP	0.010	0.72	−0.034	0.050
Serum biochemistry				
TC	−0.005	0.85	−0.014	0.011
HDL	−0.085	**0.003**	−0.092	−0.019
LDL	−0.011	0.70	−0.018	0.012
Triglycerides	0.089	**0.001**	0.004	0.018
sGlucose	0.179	**<0.001**	0.055	0.102
sCreatinine	0.112	**<0.001**	1.895	5.413
sUrea	0.168	**<0.001**	0.080	0.158
sUA	0.068	**0.011**	0.097	0.765
Multivariable analysis				
Age	0.266	**<0.001**	0.140	0.209
SBP	0.140	**<0.001**	0.042	0.091
sGlucose	0.124	**<0.001**	0.032	0.078
sUA	0.070	**0.008**	0.116	0.772
Triglycerides	0.056	0.056	0.000	0.015
sCreatinine	0.040	0.22	−0.794	3.444
sUrea	0.052	0.11	−0.009	0.087
HR	−0.045	0.12	−0.030	0.004

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sGlucose, serum glucose; sCreatinine, serum creatinine; sUrea, serum urea; sUA, serum uric acid. Bold values indicate statistical significance ($p < 0.05$).

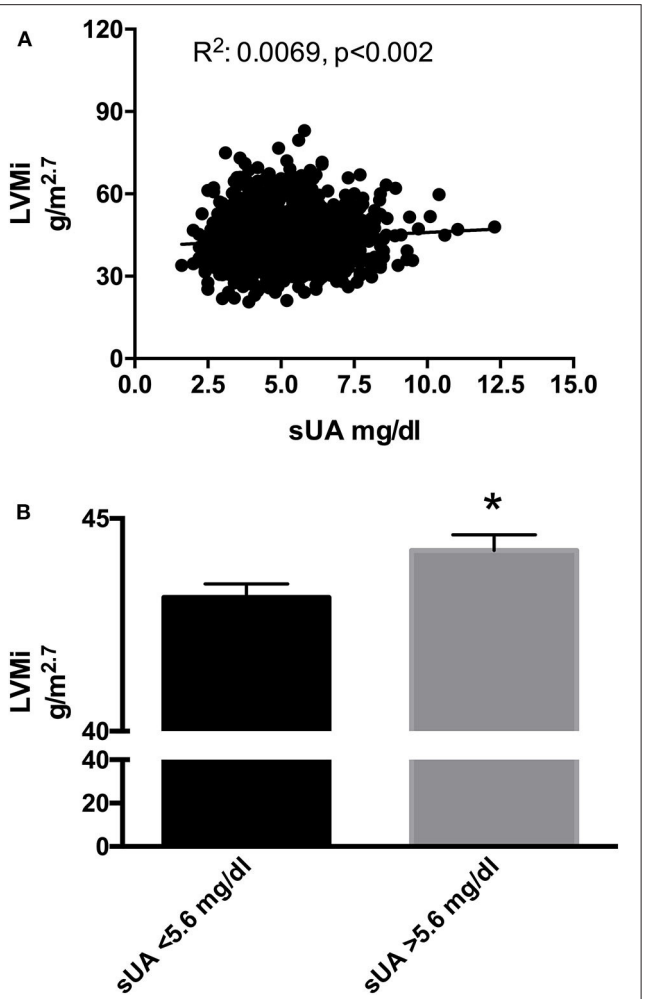

FIGURE 2 | (A) Scatter plots of left ventricular mass index (LVMi) vs. serum uric acid (sUA) in the replica population (1,379 patients). The graph shows that LVMi was significantly and directly related with sUA ($p = 0.01$). **(B)** LVMi in patients with sUA ≤5.6 mg/dl (left graph) and in patients with sUA >5.6 mg/dl (right graph). The graph shows higher value of LVMi in hypertensives with sUA > 5.6 mg/dl ($p = 0.02$). *Indicates $p < 0.05$.

and sUA is not significantly related to them (**Table 4**). Since we have not collected GLS data, we cannot confirm the existence of a relationship between sUA and GLS dysfunction.

Some studies have shown that sUA is related to markers of increased vascular damage, such as a low ABI (34) and higher sUA levels are associated with peripheral artery disease in the US general population (35). In our study, we found such association; accordingly, several studies reported that higher sUA was associated with a low ABI in women (36, 37), potentially related to estrogen effects (38–40).

A corollary in our study is the significant correlation of sUA with metabolic parameters such as BMI, weight, HDL, sGlucose, and TG (**Table 4**). It is notorious that sUA can be sensitive to diet, as well as other metabolic patterns. There is now a large body of evidence supporting a role for dietary changes in management of BP and metabolic disorders (41) and we have recently established that the length of food supply chain plays a key role in determining the risk of metabolic syndrome in a population adhering to the Mediterranean diet (42). Moreover, several observational studies and randomized control trials have demonstrated associations between dietary patterns and sUA levels (43, 44); specifically, a report from the Dietary Approaches to Stop Hypertension (DASH)–Sodium randomized trial demonstrated that consuming the DASH diet significantly reduced sUA compared to a typical American diet (45). The existence of a relationship between sUA levels and metabolism is extensively reported in the literature, in particular, a close relationship with BMI and waist circumference. In the PLAD study, patients with higher BMI had significantly higher uric acid levels (46). The Framingham Study demonstrated that subjects with higher levels of sUA had significantly higher BMI (47). This relationship is also confirmed by the evidence that the stable reduction of body weight is associated with the reduction of sUA, as demonstrated in intervention studies on the reduction of body weight obtained by bariatric surgery or with the use of anorectic drugs (48, 49).

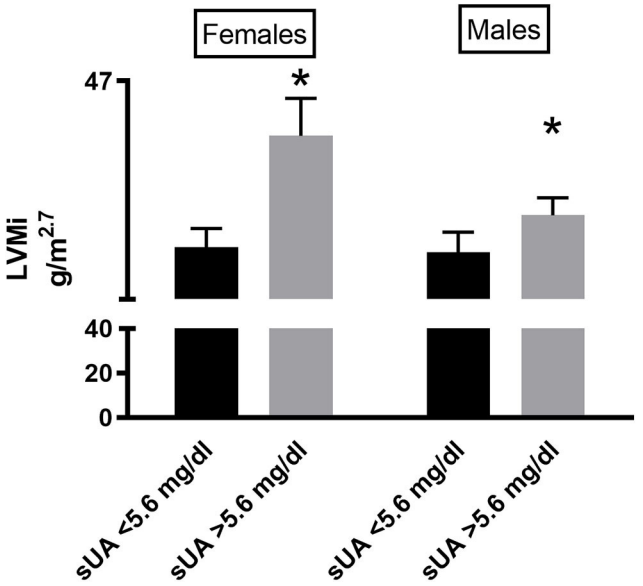

FIGURE 3 | LVMi in female (left graph) and male (right graph) patients according to sUA ≤5.6 or sUA >5.6 mg/dl (right graph). The graph shows a higher value of LVMi in hypertensives with Sua >5.6 mg/dl ($p < 0.05$), independent from gender. *Indicates $p < 0.05$.

Independently from BMI, metabolic parameters correlate with sUA. Hikita et al. investigated the relationship between sUA, body fat distribution, and metabolic syndrome, and showed a significant direct correlation with triglycerides, visceral fat, and the Homa index (50). According to these results, our data demonstrate the presence of a significant and linear correlation between sUA levels and some metabolic parameters (BMI, weight, triglycerides, and blood glucose) (**Table 4**). Moreover, in our results, sUA is significantly and inversely related to HDL (**Table 4**).

Study Limitations

LVMi assessment by echocardiography could be considered a limitation due to lower sensitivity compared to more precise technological assessments. On the other hand, the cardiac US is more accessible for the larger part of hypertensive patients, making our results more relevant for daily practice. We followed up the patients for 12 months to collect all clinical, cardiac US, and serum biochemistry data, and this could be considered a limitation since the data were not collected at the same time; we calculated that from the first visit to the collection of the data elapsed an average time of 52 ±89 days for serum data and of 11 ±65 days to execute the cardiac US. We believe that this time is close enough to consider the collection of data to be contemporary.

CONCLUSIONS

In summary, our results in a small population and their replication in a larger cohort demonstrate that sUA directly correlates with LVMi and that a cutoff of 5.6 mg/dl can identify patients with larger left ventricular mass. Our data suggest that hyperuricemia is an early marker of increased left ventricular mass that can be used to identify a hypertensive population with cardiac TOD.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Campania sud. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VV, MC, and GI: conceptualization, formal analysis, investigation, resources, writing – original draft, and writing – review & editing. VV, AP, NV, FM, FCi, RG, RF, PM, CM, MM, RI, FR, FCe, MC, and GI: data curation. All authors contributed to the article and approved the submitted version.

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OPINION
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What Is the Ideal Blood Pressure Treatment Target for Primary Prevention and Management of Atrial Fibrillation?

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INTRODUCTION

Atrial fibrillation (AF), which is the most common cardiac arrhythmia, accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances. Each year, more than 5 million people develop AF on this planet, with a significant impact on health care (1). AF is independently associated with significant morbidity and mortality, including a four- to five-fold increased risk for stroke, a three-fold risk for heart failure, a two-fold increased risk for dementia, and a significant risk for premature death (1, 2).

For all patients with AF, the current guidelines report that we think about not only stroke prevention, rate/rhythm control, but also risk factor modification (3, 4). Evidence accumulated in recent years indicates that risk factor management is associated with significant clinical and cost-effectiveness benefits on AF. Many potential modifiable risk factors that contributed to the underlying atrial substrate and, therefore, to AF development have been described, such as hypertension, obstructive sleep apnea, obesity, and diabetes (1, 3, 4). Due to its high prevalence in the general population, hypertension is the most common modifiable risk factor associated with AF (5), and poorly controlled blood pressure (BP) has been associated with elevated AF risk (6, 7). A study showed that hypertension (defined as systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure >90 mmHg or receiving antihypertensive treatment) increased the risk of AF by 56% (8). In a recent large, observational study in close to 1 million Koreans, Kim et al. showed that the incidence of incident AF gradually increased in response to increased BP (9). Even "pre-hypertension" (SBP 130–139 mmHg) was associated with incident AF (9). Besides, hypertension increases the risk of cardiovascular events in patients with AF. In the ROCKET AF trial, a prospective, multicenter, double-blind, randomized controlled trial in patients with non-valvular AF and moderate to high risk of stroke, 90.5% of 14,256 anticoagulated patients had hypertension (10). Vemulapalli et al. found that the risk of stroke or systemic embolism in these patients increased significantly for every 10-mmHg increase in screening SBP (10). In the ARISTOTLE trial of more than 18,000 patients (mean age 70 years) with non-valvular AF, patients with uncontrolled BP at any point during the 2-year trial were associated with a 53% increased risk of ischemic stroke, a 38% increased risk of myocardial infarction, and an 85% increased risk of hemorrhagic stroke (11). These data underscore the importance of intensive antihypertensive therapy to achieve intensive BP control to reduce the risk of new-onset AF and improve the outcome of AF. However, the ideal BP treatment goals for improving the substrate and outcome of AF remain to be defined.

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MECHANISMS OF HYPERTENSION-RELATED AF

When someone has high BP, the heart needs to pump against that stress hour after hour, day after day. The stress results in left ventricular (LV) hypertrophy, decreased diastolic function with impaired LV filling, with subsequent rising left atrial pressures with left atrial hypertrophy and enlargement, increased atrial fibrosis, and slowing of intra-atrial and interatrial elec-velocities (12, 13). Such a distortion of atrial anatomy and physiology ultimately predisposes to AF. In a study of patients with essential hypertension free of other cardiovascular conditions ($n = 2,482$), the incidence of AF was 0.46% per year, and age or increased LV mass was the only independent predictors of incident AF during a 5-year follow-up (14). Left atrial pressure also increases with ischemic or valvular heart disease and myopathies that are often associated with systemic hypertension, potentially leading to AF (15). Atrial remodeling induced by hypertension is known as atrial cardiomyopathy, which is described in detail in a recent expert consensus (16).

The abnormal atrial substrate is reversible. A study demonstrated that the renin–angiotensin–aldosterone system blockers could improve atrial electrical and structural remodeling (17). BP reduction following renal sympathetic denervation (RSD) in patients with resistant hypertension was associated with the global atrial conduction improvement (18).

LONG-TERM BENEFIT OF GOAL-DIRECTED BP REDUCTION IN AF

BP control can reduce the occurrence and progression of AF. In patients referring to AF ablation, a previous study demonstrated that poorly treated hypertension almost wholly eliminated the effect of AF ablation (19). Conversely, the ARREST-AF trial showed that aggressive risk factor management, including achieving a target BP of <130/80 mmHg at least 80% of the time, could improve the long-term success of AF ablation (20). Similarly, in a recent randomized trial of 302 patients with hypertension and symptomatic AF randomized to AF ablation with or without RSD, RSD was associated with a significant reduction in BP and AF recurrence at 12 months (21). Besides, in a *post hoc* analysis of the LIFE study of more than 8,831 patients (mean age 67 years) with LV hypertrophy, compared with placebo (SBP ≥142 mmHg) during a mean of 4.6 years follow-up, antihypertensive treatment targeting SBP <140 mmHg and SBP <130 mmHg was associated with a 24 and 40% lower risk of new-onset AF, respectively (22). The benefit for the achievement of an SBP of ≤130 mmHg in the prevention of AF was also evidenced in the prespecified secondary outcome of the Cardio-Sis trial, which demonstrated that new-onset AF occurred in 3.8% of patients in the usual control group (SBP <140 mmHg) and 1.8% of patients in the tight control group (SBP <130 mmHg) (23).

BP control can also improve outcomes in AF patients. Patients with both AF and hypertension had an increased risk of stroke when compared with patients with either condition alone (24). Active treatment lowering mean BP by 7.3/3.4 mmHg was associated with a 34% reduction in stroke (25). In a retrospective study from China, conducted in anticoagulated hypertensive patients with AF, those who achieved a target BP <130/80 mmHg showed a lower incidence of ischemic stroke and a similar risk of major bleeding and intracranial bleeding than patients with higher BP values (26).

WHAT IS THE IDEAL BP IN THE PREVENTION OF AF?

The role of hypertension as a modifiable risk factor for AF is established but still incompletely known. In particular, what is the ideal BP treatment target from the perspective of improving the substrate of AF? For this objective, Parcha et al. conducted a *post hoc* analysis aiming to study the influence of a more intensive reduction in SBP to <120 mmHg on incident AF. A total of 8,549 participants in the SPRINT Trial were eligible for primary analysis (27). The results showed that there was a similar rate of new-onset AF in intensive (target SBP <120 mmHg) and standard (target SBP <140 mmHg) treatment arms (27). That is, a more intensive reduction in SBP to <120 mmHg would not reduce new-onset AF compared with the goal SBP <140 mmHg. This result was consistent with the results of Thomas et al., who conducted a case-controlled study of patients undergoing treatment for hypertension (28). Compared with a reference SBP level of 120–129 mmHg, both SBP ≥150 mmHg and SBP <120 mmHg were at higher risk of incident AF in multivariable logistic regression models (28). The J-curve relationship between BP and new-onset AF was also observed in the control of hypertension in patients undergoing catheter ablation. In a randomized study, Parkash et al. randomly assigned 184 patients with AF and a BP >130/80 mmHg to aggressive BP (target <120/80 mmHg) or standard BP treatment (target <140/90 mmHg) prior to their scheduled AF catheter ablation (29). This study found that targeting SBP to <120 mmHg did not reduce atrial arrhythmia recurrence after catheter ablation of AF during a median follow-up period of 14 months (29).

These findings suggest that a target SBP of 120–129 mmHg may be the ideal SBP in the prevention of AF. However, this aspect was not confirmed in a *post hoc* analysis of the Women's Health Study, which showed a negative linear association between BP and the risk of incident AF during a median follow-up period of 14 years (6). Their time-updated analyses suggested that the substantial risk of incident AF reductions might be obtained even if SBP was ≤120 mmHg (6). Optimal BP targets to improve the substrate of AF need to be verified in future randomized trials.

WHAT IS THE IDEAL BP FOR IMPROVING THE OUTCOME OF AF?

Whether stricter BP control provides additional protection in patients with both AF and hypertension is unclear. Kim et al. analyzed data in 298,374 Korean adults with hypertension and non-valvular AF to determine the optimal BP threshold in patients with AF (30). They reported that in comparison

TABLE 1 | Blood pressure treatment targets in patients with atrial fibrillation across major hypertension guidelines.

Guideline	Population	BP treatment targets
2019 UK NICE	Do not list patients with AF as a specific population	–
2019 JSH	Patients with AF	<130 mmHg
2018 Canada	Do not list patients with AF as a specific population	–
2018 ESC/ESH	Patients with AF	<140 mmHg (well-tolerated <130 mmHg)
2018 South Korea	Patients with AF	Not <120/70 mmHg
2018 China	Patients with AF	<140 mmHg (well-tolerated <130 mmHg)
2017 ACC/AHA	General (including patients with AF)	<130/80 mmHg
2016 Australia	Do not list patients with AF as a specific population	–

UK, United Kingdom; NICE, National Institute for Health and Care Excellence; JSH, Japanese Society of Hypertension; ESC, European Society of Cardiology; ESH, European Society of Hypertension; AF, atrial fibrillation; BP, blood pressure; ACC, American College of Cardiology; AHA, American Heart Association.

with a reference BP level of 120–129/80 mmHg, patients with BP >130/80 mmHg or <120/80 mmHg presented significantly higher risks of major cardiovascular events, including intracranial hemorrhage, ischemic stroke, myocardial infarction, and heart failure requiring hospitalization (30). In the SPRINT trial, ∼35% ($n = 281$) of participants with preexisting AF achieved the BP level of <120/80 mmHg at 3 months (27). Similarly, SBP <120 mmHg was not associated with a lower risk of adverse cardiovascular events compared with those with preexisting AF and BP of ≥120/80 mmHg (27). That implies that a BP of 120–129/80 mmHg might be the optimum BP for patients with AF undergoing hypertension treatment.

BP TREATMENT TARGETS IN PATIENTS WITH AF ACROSS MAJOR HYPERTENSION GUIDELINES

Table 1 compares eight sets of hypertension guidelines last updated between 2016 and 2019 (15, 31–38). With gaps in the evidence base, expert panels disagree on whether guidelines of hypertension should list patients with AF as a specific population and provide a recommendation for BP goal to be achieved in this specific circumstance. The 2019 Japanese Society of Hypertension guidelines recommend that an SBP target of 130 mmHg is effective in preventing the new onset of AF, cardiovascular events (e.g., stroke), and anticoagulation-related bleeding in patients with both AF and hypertension (32). The 2018 European Society of Cardiology and European Society of Hypertension guidelines and 2018 Chinese Guidelines of Hypertension suggest that BP treatment targets in individuals with AF should be at least <140 mmHg, and that <130 should be considered if tolerable (34, 38). The 2018 Korean Society of Hypertension guidelines state that in patients with AF and hypertension, lowering BP can decrease the incidence of fatal bleeding during antithrombotic treatment. However, BP should be maintained above 120/70 mmHg (37). The 2017 American Heart Association/American College of Cardiology (AHA/ACC) guidelines of hypertension recommend BP targets <130/80 mmHg in all hypertensive patients with different recommendation levels according to the risk of cardiovascular disease (15). The Canadian, United Kingdom, and Australia guidelines of hypertension neither list patients with AF as a specific population nor suggest a BP target goal in this situation (31, 33, 35).

THE DIRECTION OF FUTURE RESEARCH

Note, though, that new-onset AF was detected by hospital admissions, medical records, and the scheduled study ECGs in the trials mentioned in this paper. The results of intermittent ECG may not always reflect the "true" incidence of new-onset AF. AF can come and go, particularly early in the course of the disease. It is not uncommon for paroxysmal AF to go undetected in intermittent monitoring, which results in a low detection rate of new incident AF cases. Even an ECG taken over a longer period (>24 h) using a Holter monitor does not always lead to a reliable diagnosis of existing AF. In a study of 82 outpatients ≥65 years old with hypertension, diabetes mellitus, and no history of AF or any other cardiovascular, Philippsen et al. found that only 11.8% of patients with asymptomatic AF, which was detected by implantable loop record (ILR), had AF episodes on a 72-h Holter monitoring (39). Another difficult issue is regarding BP measurement in AF. In the presence of AF, variations in ventricular filling time, stroke volume, and contractility may lead to increased beat-to-beat BP variability, which may affect BP estimation using both the auscultatory and oscillometric methods (40). All these would critically impact the result of correlation analyses. An optimal approach to assess the impact of hypertension on AF in large population-based cohort studies remains unclear. Given insufficient sensitivity in detecting sporadic arrhythmias (such as paroxysmal AF) by intermittent monitoring, a continuous rhythm monitoring strategy (such as ILR), although invasive, overcomes many of the limitations of intermittent monitoring in assessing the rate of incident AF and helps evaluate the real effect of hypertension on AF. New mHealth technologies may also provide a promising infrastructure for a more objective and longitudinal assessment of new-onset AF. For this reason, the AF detection function

of wearable devices, which receive extensive attention from device manufacturers and cardiologists, has become a focus of research (41). Although current guidelines do not recommend automated BP monitor in the presence of AF (31, 34, 35, 42), the research results about its ability of AF detection during routine BP measurement are promising and worth further studies (43, 44).

CONCLUSION

Hypertension is a powerful trigger for AF and increases the risk of cardiovascular events in patients with AF. To date, the available evidence supports targeting BP at guideline-recommended levels for primary prevention and management of AF, with J- or U-curve relationship existing between BP and substrate/outcome of AF.

AUTHOR CONTRIBUTIONS

XM and XX wrote the manuscript, conceptualized the idea, and reviewed and approved the final manuscript for publication. Both authors contributed to the article and approved the submitted version.

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The Effect of Nebivolol on Office Blood Pressure of Blacks Residing in Sub-Saharan Africa (A Pilot Study)

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Introduction: There is substantial clinical evidence that monotherapy with beta-blockers are less effective in reducing blood pressure among hypertensive Black patients compared to Whites. The highly selective beta-1 agents like nebivolol and bisoprolol have, however, been reported to be effective in reducing blood pressure in African Americans. However, results in African Americans cannot be extrapolated to native Africans because of genetic admixture and gene-environment interaction. There is, therefore, the need for us to generate data that are applicable to Africans residing in sub-Saharan Africa. We therefore decided to evaluate the efficacy and tolerability of highly selective beta-1 agent nebivolol in hypertensive Black patients residing in sub-Saharan Africa.

Materials and Methods: The nebivolol study was a multicenter, prospective, observational program among hypertensive patients with 4- and 8-week follow up which was conducted in 5 cities in Nigeria of Abuja, Calabar, Enugu, Oghara, and Port Harcourt. Dosages of nebivolol used in keeping with local prescribing information were 5 and 10 mg once daily each. The effectiveness of treatment was assessed by change from baseline in mean office systolic and diastolic blood pressures, and the proportion of patients achieving the therapeutic goal of <140/90 mmHg. Safety and tolerability of this medication were also assessed.

Results: We report the results of the 140 patients studied. The mean age and body mass index were 46.9 ± 7.3 years and 22.3 ± 5.8 kg/m^2, respectively, and 57.1% were female. Nebivolol reduced SBP and DBP by 7.6 and 6.6 mmHg, respectively, in 4 weeks, and by 11.1 and 8.0 mm Hg, respectively, in 8 weeks. Blood pressure control was achieved in 54.8% of the patients in 4 weeks and increased to 60.4% in 8 weeks. There was no change in metabolic profile between randomization and at 8 weeks, and erectile dysfunction occurred in 1.3% of the study population.

Conclusions: Nebivolol 5 and 10 mg appear efficacious in Nigerian Africans with no negative metabolic effect and minimal side effect profile.

Clinical Trial Registration: www.ClinicalTrials.gov, Study Identification: NCT 03598673.

Keywords: nebivolol, efficacy, tolerability, hypertensive, black patients

INTRODUCTION

Although hypertension affects every racial group, complications such as heart failure, chronic kidney disease and cerebrovascular accidents are more prevalent in the Black population (1). For example, in the Abuja Heart Study, about seventy-five percent (75%) of hypertensive patients presenting *de novo* to a tertiary healthcare institution had one or more complications on presentation (2). In addition, there is substantial clinical evidence indicating that monotherapy with beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are less effective in reducing blood pressure among hypertensive Black patients compared to Whites (3–5). The beta-blocker class is however a highly heterogeneous group in terms of its pharmacologic and hemodynamic properties (6, 7), with the low efficacy of beta-blockers as monotherapy being reported only with the more traditional agents like Atenolol and Metoprolol, while the highly selective beta-1 agents have been more recently reported to be effective in reducing blood pressure in both Blacks and Whites (8–10).

Although nebivolol, a highly selective beta-1 agent, has been shown to be effective in reducing blood pressure in Blacks (11), this was in African Americans with no study in African Blacks residing in sub-Saharan Africa. It might be argued that findings in African Americans can be extrapolated to African Blacks since they have the same ancestral origin. The differences in selection in previous generations, ethnic admixture, and differences in lifestyle suggest that such extrapolation may be inappropriate (12–14). We therefore, decided to study the effectiveness and safety of nebivolol in Black patients with stage 1 hypertension (systolic BP of 140–159 and/or diastolic BP of 90–99 mmHg) presenting to primary care clinics in tertiary health care facilities in Nigeria.

MATERIALS AND METHODS

Study Design

The Nebivolol Hypertension study was a multicenter, prospective, observational program among hypertensive patients with 2-month follow-up carried out in the Cardiology units of five (5) public tertiary hospitals in Nigeria. It was conducted as a non-interventional study, and therefore study-specific patient visits, tests and monitoring were not imposed, and only data originating from routine clinical practice were collected. Therapy was prescribed according to clinician preference and on the prescribing pattern in Nigeria.

Study Participants

Male or female patients aged 30–60 years of age with sitting office systolic BP of 140 mmHg or above and <160 mmHg, and diastolic BP of 90 mm Hg and above but less 100 mmHg and on no antihypertensive treatment for a minimum of six (6) months were recruited into the study. Patients with congestive heart failure, renal failure, coronary heart disease including chronic stable angina, myocardial infarction or acute coronary syndrome, stroke or transient ischemic attack, suspected secondary hypertension, concomitant illness, physical or mental impairment that could interfere with the effective conduct of the study and those who are pregnant or of child-bearing age who are not taking reliable contraception were excluded from the study.

Outcome Measures

Primary Endpoint

The primary outcome measure was a change in office BP value from baseline to 2 months which was calculated as the difference between the mean office BP at randomization and at the end of follow up.

Secondary Endpoint

Other outcome measures include: the proportion of patients who achieved BP <140 mmHg systolic and <90 mmHg diastolic in 2 months, the proportion of patients who have adverse events, change in plasma fasting blood glucose and fasting lipid profile from baseline to 2 months and proportion of male patients who complain of erectile dysfunction at both the fourth and eighth weeks.

Study Procedure

Patients were commenced on 5 mg of nebivolol at a starting dose of 5 mg once daily if the BP is not controlled (140/90 mmHg or above) after 4 weeks, the dose is doubled to 10 mg once daily.

Blood Pressure Measurement

Office BP was measured after five (5) min of rest in the sitting position using semi-automated blood pressure devices (semi-automated blood pressure monitors (Omron MIT5 Connect). Three BP measurements were taken, and the last two values were used for the calculation of the mean. Patients had their fasting blood glucose and lipid profile assessed at baseline and the 8th week.

Study Duration

Each patient was followed up for 2 months at the fourth and eighth weeks. Patients were still followed up till the 8th week even when study medication was discontinued. In the

case of discontinuation of study medications, the reason(s) for discontinuation was recorded and reported. The study was completed when the last enrolled patient completed two (2) months of observation.

Ethical Issues

The study was conducted according to the guidelines laid down by the International Conference on Harmonization for Good Clinical Practice (15). All investigators obtained ethical approval from their local institutional review boards which are affiliates of their national review boards. Eligible patients were approached regarding potential participation in the study, and the study purpose, procedures, risks, and potential benefits explained to them by the site investigators. Patients were given the opportunity to ask questions, and those who voluntarily agreed to participate in the study were asked to sign informed consent.

Statistical Analysis

Due to the observational nature of the study, descriptive statistical methods were used and supplemented by calculation of confidence intervals wherever this aids interpretation. The calculation of *p*-values was used either as an aid to evaluating a specific difference of interest or as a "flagging" device applied to a large number of safety and tolerability—efficacy variables to highlight differences worth further attention. This was particularly useful for laboratory data which were subjected to quantitative analysis. Patients enrolled in the program with at least one follow-up visit, or a documented adverse event were considered analyzed.

Systolic and diastolic BP were modeled using linear mixed models fitted with restricted maximum-likelihood method which include adjustment for baseline BP, age (<45 or ≥45 years), gender, smoking status, body mass index (BMI) and we considered subject and time as random effects. Site level was not considered in the random effect because it was not adding significant value to the model, and in addition, some sites had very small sample which could bias our results if included in the model.

All other patients were included in the evaluation even if they had partially missing data. We investigated existence of interaction within model predictors, and in case of significant interaction between statistically significant predictors in the final model, we explored specific difference between means of blood pressure amongst the groups using pairwise test with Tukey adjustment.

Moreover, we presented the adjusted mean reductions in SBP and DBP in interesting subgroups.

Firstly, we constructed all models without accounting for missing data and secondly performed a sensitivity analysis, in which we performed several logistic regressions with binary variable (missing and not missing) and added other variables in the models as covariates in order to eliminate the "Missing Completely at Random" hypothesis. With the assumption that all missing data that were missing at random (MAR), we performed multiple-imputation analysis using chained equations. We generated 20 amputated data sets with a maximum of 20 iterations. Variables included in the imputation model were systolic BP, diastolic BP, age, gender, weight, height, BMI, smoking status, site including individuals. All analyses were

TABLE 1 | Baseline characteristics of the patients.

Characteristics	Value
Age ($n = 140$)—Mean-year (yr)	46.9 ± 7.3
Gender, no. (%)—($n = 140$)	
Male	60 (42.8)
Female	80 (57.1)
Body Mass Index (BMI)	
Mean—kg/m²	22.3 ± 13.6
Distribution—*n* (%)	
Normal	56 (41.8)
Overweight	38 (28.4)
Obesity	40 (29.9)
Smoking habit, no (%)	
Non-smoker	138 (98.6)
Smoker	2 (1.4)
Duration of hypertension	
<5 years, %	114 (81.4)
5–10 years, %	18 (12.9)
>10 years, %	8 (5.7)
Blood pressure—mmHg	
Systolic	148.2 ± 6.8
Diastolic	94.8 ± 5.3
Mean heart rate-bpm ($n = 68$)	79.3 ± 6
Fasting blood glucose—mmol/L ($n = 75$)	5.2 ± 1.9
Total cholesterol—mmol/L ($n = 81$)	5.0 ± 1.1
HDL cholesterol—mmol/L ($n = 80$)	1.4 ± 0.6
LDL cholesterol—mmol/L ($n = 82$)	3.1 ± 1.0
Triglyceride—mmol/L ($n = 52$)	1.3 ± 0.4

HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; bpm, beats per minute.

TABLE 2 | Differences in blood pressure and heart rate at baseline, 4th and 8th week.

Variable	Baseline	4th week	Mean difference (95% CI)	*P*-value
SBP, mmHg ($N = 140$)	148.20	140.80	7.55 (5.00, 10.11)	<0.0001
DBP, mmHg ($N = 140$)	94.78	87.94	6.56 (4.95, 8.17)	<0.0001
HR, bmp ($N = 68$)	79.30	75.10	4.02 (3.32, 4.71)	<0.0001
Variable	**4th week**	**8th week**	**Mean difference (95% CI)**	***P*-value**
SBP, mmHg	140.8	137.0	3.70 (1.36, 6.05)	0.002
DBP, mmHg	87.94	86.63	1.54 (−0.26, 3.35)	0.09
HR, bpm	75.10	74.40	0.77 (−0.191, 1.732)	0.1

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate.

performed with R Software 4.0.0 (The R Foundation for Statistical Computing platform).

Management of the Study

The Trial Steering Committee consisted of the Principal Investigator, the site Investigators, the Statistician, and the representative of Micronova Pharmaceutical team. This committee was chaired by the Principal Investigator. The various site investigators were responsible for entering patients' data into paper case report forms which were subsequently entered into Microsoft data spreadsheet.

RESULT

Study Setting

One hundred and eighty-three (183) patients were screened, but one hundred and forty (140) met the inclusion criteria and these consist of sixty-four (64) patients from University of Abuja Teaching Hospital, thirty (30) patients from Delta State University Teaching Hospital, twelve (12) patients from University of Nigeria Teaching Hospital, seventeen (17) patients from University of Port Harcourt Teaching Hospital and another seventeen (17) patients from University of Calabar Teaching Hospital. The first patient was recruited 2nd February 2018 at the University of Abuja Teaching Hospital, and the last patient was followed up 3rd September 2019 at the University of Calabar Teaching Hospital.

Baseline Characteristics of Patients

Table 1 shows the baseline characteristics of the patients. Patients on average were middle-aged (46.9 years ± 7.3), mean body mass index of 22.3 kg/m^2 ± 13.6 with 38 (28.4%) overweight and 40 (29.9%) obese, with a female predominance (57.1%). Duration of hypertension was <5 years in majority of them (81.4%), and the mean systolic and diastolic blood pressures were at 148.2 mmHg ± 6.8 and 94.8 mmHg ± 5.3, respectively.

Effect of Nebivolol on Blood Pressure Parameters and Pulse Rate

Table 2 and **Figure 1** show the effect of Nebivolol on blood pressure parameters and heart rate at baseline, the fourth week, and the 8 weeks. At four (4) weeks, systolic and diastolic blood pressures were significantly

TABLE 3 | Comparison of mean change in blood pressure, heart rate, fasting blood glucose and fasting lipid of patients at baseline and 8th week.

Variable	Baseline	8th week	Mean difference (95% CI)	*P*-value
SBP, mmHg	148.0	137.00	11.01 (8.80,13.44)	<0.0001
DBP, mmHg	94.8	86.60	8.03 (6.45, 9.62)	<0.0001
HR, bpm	79.30	74.40	4.8 (4.17, 5.44)	<0.0001
FBG, mmol/L	5.20	5.20	−0.125 (−0.71, 0.46)	0.70
Total cholesterol, mmol/l	5.00	4.70	0.19 (−0.15, 0.54)	0.15
LDL cholesterol, mmol/l	3.10	2.90	0.21 (−0.12 0.54)	0.21
HDL cholesterol, mmol/l	1.40	1.30	0.07 (−0.13, 0.27)	0.50
TG, mmol/l	1.30	1.20	0.04 (−0.12, 0.19)	0.60

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; FBG, Fasting Blood Glucose; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; TG, Triglyceride.

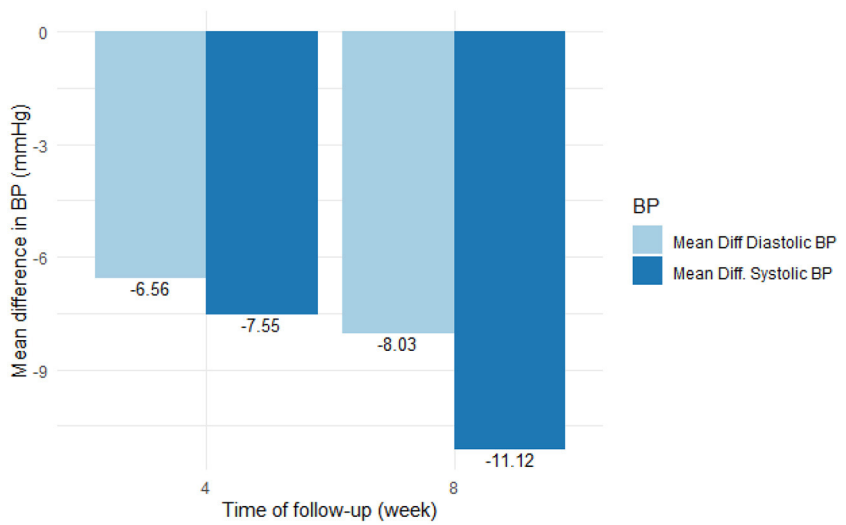

FIGURE 1 | Reduction in blood pressure from baseline to 4 and 8 weeks.

reduced by 7.6 mmHg (95% CI [5.0–10.1]) and 6.6 mmHg (95% CI [4.95–8.17]), respectively, and by 11.1 mmHg (95% CI [8.8–13.4]) and 8.03 mmHg (95% CI [6.45–9.62]), respectively, in the 8 weeks. BP control (BP <140/90 mmHg) was achieved in 54.8% of the patients in four (4) weeks and increased to 60.4% in eight (8) weeks.

Pulse rate was reduced by 4.02 beats per minute (95% CI: 3.32–4.71, $p < 0.0001$) at 4 weeks and by 4.8 beats per minute (95% CI: 4.17–5.44, $p < 0.0001$) at 8 weeks. There was however no significant difference in pulse rate between the fourth and 8 weeks.

Effect of Nebivolol on Laboratory Parameters

Table 3 shows the effect of Nebivolol on laboratory parameters. There was no change in fasting blood glucose, total cholesterol,

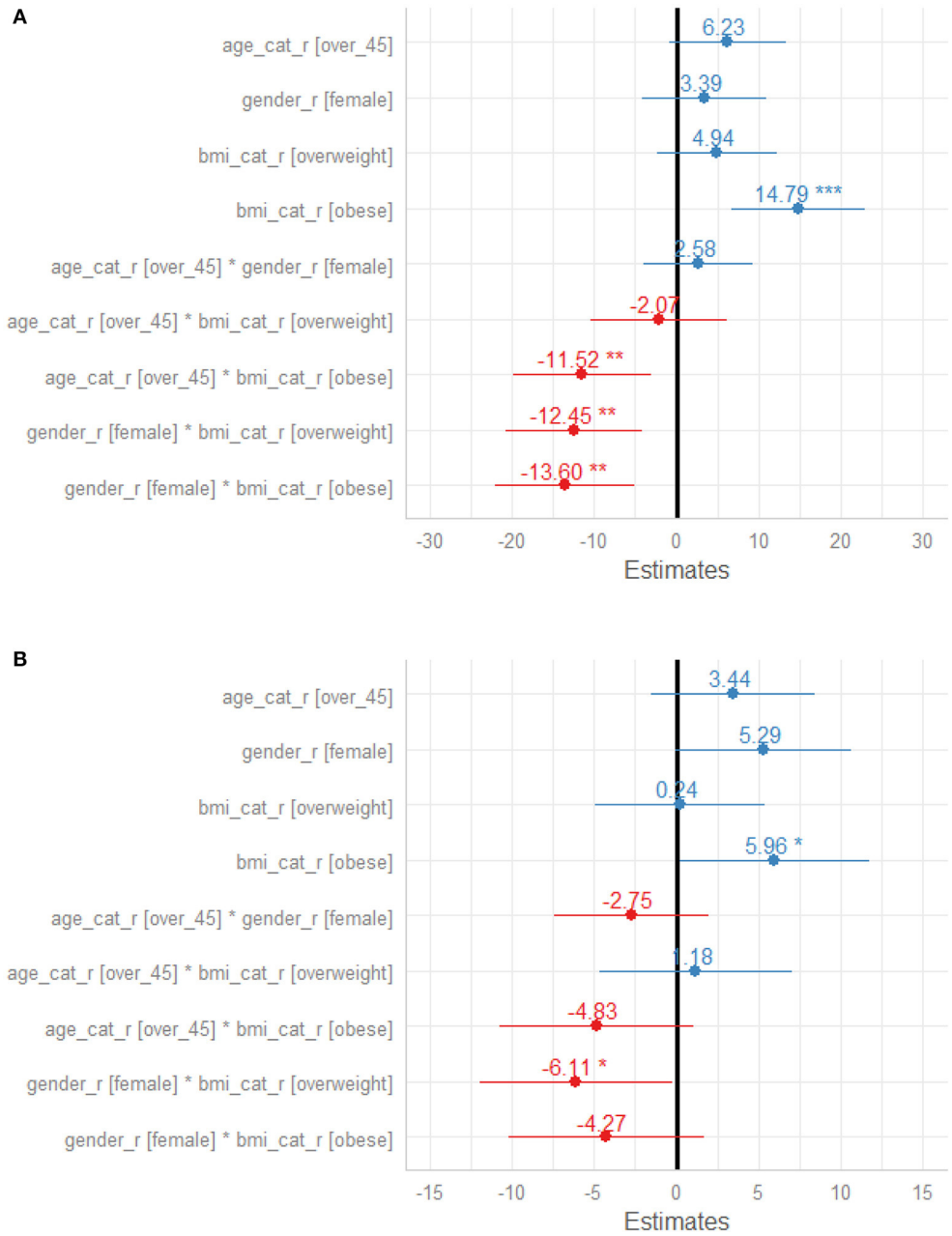

FIGURE 2 | (A) Forest plot of factors influencing Systolic Blood Pressure response to Nebivolol treatment. **(B)** Forest plot of factors influencing Diastolic Blood Pressure response to Nebivolol treatment.

high-density lipoprotein cholesterol, in low density lipoprotein cholesterol or triglyceride between baseline and eight (8) weeks.

Factors Influencing Blood Pressure Response to Nebivolol in Patients

In a linear mixed model as shown in **Figures 2A,B**, obesity was significantly associated with changes in Systolic BP, but there was significant interaction between obesity and gender (95% CI; −20.67, −6.53, $p = 0.001$), overweight and gender (95% CI; −19.36, −5.54, $p = 0.04$). Therefore, the effect of BMI on systolic BP depend significantly on gender, but gender alone was not significantly associated with systolic BP ($p = 0.087$). A *post-hoc* test, exploring specific difference between male with normal weight, male with overweight, male with obesity and respective female subgroups revealed that the changes in SBP in male with overweight compared to female with overweight, in male with obesity compared to female with obesity and in male with obesity compared to female with overweight were significantly different. The adjusted mean reduction of SBP from baseline to 8 weeks follow-up was not statistically different in male regardless of the BMI status and these results were similar female regardless of their BMI status (**Table 4**). Similarly, obesity was significantly associated with changes in diastolic BP ($p = 0.044$) but there was no interaction with gender (95% CI; −9.27 0.73, $p = 0.163$) or age above 45 years (95% CI; −9.80 0.14, $p = 0.113$). The adjusted mean reduction of SBP from baseline to 8 weeks follow-up for male was 8.2 mmHg (95% CI; 7.00 9.40) and 8.1 mmHg (95% CI; 6.90 9.30) for female (**Table 5**).

A sensitivity analysis that included all patients who were treated in all study sites after multiple imputations confirmed these patterns in treatment effects on systolic BP and diastolic BP.

Side Effect Profile

Table 6 shows the side effect profile of Nebivolol. Side effects occurred in 6 (4.4%) of the patients with 3 (2.2%) discontinuing their medication. The commonest side effect was dizziness in 5 (3.3%), followed by headaches in 3 (2.2%). Erectile dysfunction occurred in 2 (1.2%) of the study population. Four (2.7%) of the patients had more than one side effect occurring in them.

TABLE 4 | Adjusted mean reductions in Systolic Blood Pressure (SBP) in subgroups gender and BMI.

Subgroups	Baseline	4th week	Adjusted mean reduction (95% CI)
Male with normal weight	146	138	8 (6.68, 9.32)
Male with overweight	150	142	8 (6.70, 9.30)
Male with obesity	155	147	8 (6.66, 9.34)
Female with normal weight	151	142	9 (7.65, 10.35)
Female with overweight	142	134	8 (6.69, 9.31)
Female with obesity	146	138	8 (6.74, 9.26)
	4th week	**8th week**	**Adjusted mean reduction (95% CI**
Male with normal weight	138	135	3 (1.68, 4.32)
Male with overweight	142	139	3 (1.72, 4.28)
Male with obesity	147	144	3 (1.66, 4.34)
Female with normal weight	142	139	2 (0.64, 3.36)
Female with overweight	134	131	3 (1.69, 4.31)
Female with obesity	138	135	3 (1.73, 4.27)
	Baseline	**8th week**	**Adjusted mean reduction (95% CI)**
Male with normal weight	146	135	11 (9.68, 12.32)
Male with overweight	150	139	11 (9.72, 12.28)
Male with obesity	155	144	11 (9.66, 12.34)
Female with normal weight	151	139	12 (10.65, 13.35)
Female with overweight	142	131	11 (9.69, 12.31)
Female with obesity	146	135	11 (9.74, 12.26)

TABLE 5 | Adjusted mean reductions in Diastolic Blood Pressure (DBP) of subgroup gender.

Subgroups	Baseline	4th week	Adjusted mean reduction (95% CI)
Male	94.5	87.7	6.8 (5.6, 8.0)
Female	94.9	88.1	6.8 (5.6, 8.0)
	4th week	**8th week**	**Adjusted mean reduction (95% CI)**
Male	87.7	86.3	1.4 (0.20, 2.6)
Female	88.1	86.8	1.3 (0.10, 2.5)
	Baseline	**8th week**	**Adjusted mean reduction (95% CI)**
Male	94.5	86.3	8.2 (7.00, 9.40)
Female	94.9	86.8	8.1 (6.90, 9.30)

DISCUSSION

This study has demonstrated that nebivolol which is a cardio-selective beta-1 blocker with vasodilating effects given once-daily as 5 or 10 mg effectively reduced both systolic and diastolic blood pressure in Blacks with stage I hypertension who are residing in sub-Saharan Africa. In addition, 5 or 10 mg nebivolol resulted in response rates of >55%. These findings are of clinical importance, especially because of the excessive burden of hypertension and its complications and the low rates of blood pressure control in sub-Saharan Africa (2, 16). The results imply that beta-1-selective beta-blockers like nebivolol apart from being used as monotherapy in grade 1 hypertension could be the fourth class of medication to be considered after maximum doses of a combination of long-acting calcium channel blockers, thiazide diuretics and renin-angiotensin-aldosterone blockers have been used in this population group. Current hypertension guidelines prefer aldosterone antagonist or alpha-1 blocker as the fourth class of medication (17, 18).

The findings in this study are also very important as Physicians both in sub-Saharan Africa, Europe and the Americas are

TABLE 6 | Adverse events.

Adverse events	Percentage (%)
Dizziness	5 (3.3)
Headaches	3 (2.2)
Dry cough	3 (1.8)
Difficulty in breathing	3 (1.8)
Erectile dysfunction	2 (1.2)

3 (2.2%) stopped their medications because of side effects.

less likely to prescribe beta-blockers as monotherapy to Blacks compared to white patients in the general community (19, 20). This prescription pattern is influenced by data suggesting that beta-blockers as a class are less effective than other agents in African Americans and that they may be associated with poor tolerability and adverse metabolic effects (21, 22). The present study provides evidence to suggest that this generalization may not apply to beta-1 selective agents like nebivolol that has demonstrated significant antihypertensive efficacy and satisfactory tolerability in this patient population.

At 8 weeks, nebivolol reduced systolic blood pressure by 11.1 mmHg and diastolic blood pressure by 8.03 mmHg from baseline similar to values recorded in earlier studies in African Americans (8–11). Also similar to previous study in African Americans, nebivolol reduced pulse rate significantly at the fourth and eighth weeks compared to baseline (11). It has been suggested that the important pharmacologic attribute that may contribute to nebivolol's effectiveness in black patients as demonstrated in this and earlier studies is the vasodilating properties, contrary to the mode of action of cardio-selective non-vasodilating beta-blockers, like atenolol which primarily reduce BP by reducing cardiac output (6, 23). This type of mechanism of action by non-vasodilating beta-blockers does not favor hypertensive Black patients, who often have a decreased cardiac output with increased peripheral vascular resistance (24–26). These hemodynamic actions by nebivolol are also shared by other vasodilatory beta-blockers (27, 28). The efficacy of nebivolol at both the fourth and eighth week in reducing blood pressure can also be attributed to the young population studied. Clinical studies have shown that young African American patients respond better to beta-blocker therapy than the elderly patients as a result of their tendency toward normal renin levels with renin levels eventually declining with age (29, 30). In this study, plasma renin levels were not measured.

Apart from being at higher risk for cardiovascular and renal disease, it has been shown that black patients also generally report poorer antihypertensive medication adherence compared with the general hypertensive population (31, 32), and such poor compliance with therapy is often associated with poor tolerability (33). The good tolerability profile of nebivolol in this study could have accounted for the high compliance rate in this study, with only 2.4% of the patients discontinuing their medications because of side effects.

Unlike traditional beta-blockers, nebivolol had no negative metabolic impact on glucose and lipid profile as demonstrated in this study. LDL cholesterol was however found to be significantly lower at 8 weeks in our study. The mechanism of this reduction is not clear and has to be explored further.

One important strength of this trial is that the results were adjusted to account for the heterogeneity of the study population and potential confounding variables such as age, sex, diabetes, and obesity, which are known to determine BP response to treatment within racial groups (33).

The main limitations of this study include the apparently small sample size and the low proportion of diabetic patients who were enrolled in the study, making the extrapolation of results to this population rather difficult. In addition, plasma renin activity and adrenaline levels were not measured making it difficult to fully define the mechanism of action of nebivolol in this population.

In conclusion, nebivolol monotherapy is safe and effective in lowering BP in hypertensive black patients residing in sub-Saharan Africa. Nebivolol also has favorable metabolic effect in this population. Studies in a larger population is however needed to confirm these findings.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Abuja Teaching Hospital, Human Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DO was involved in the design and the management of the study and drafted the initial manuscript. BA was involved in the analyzing the data and critical review of the manuscript. LS, EU, EE, CAl, HE, CAg, UN, and VA were involved in data collection and critical review of the manuscript. All authors contributed to the article and approved the submitted version.

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Risk Factors for Intestinal Barrier Impairment in Patients With Essential Hypertension

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Background: Previous studies have indicated an association between hypertension and intestinal barrier dysfunction in mice models. The present study aims to investigate the association between hypertension and intestinal barrier impairment in humans and identify the novel potential risk factors for hypertension.

Methods: Medical data from consecutive inpatients were retrospectively pooled from patient records. We compared intestinal barrier serum markers [diamine oxidase (DAO), lipopolysaccharide (LPS), and $_D$-lactate] between those patients with and without hypertension. Moreover, the associations between intestinal barrier markers and cardiovascular risk, hypertension history, blood pressure control, hypertensive complications, and antihypertensive medication history were also analyzed.

Results: Overall, 106 hypertensive and 251 normotensive subjects were included. Patients with hypertension had a higher level of DAO (28.30 vs. 18.73%, $P = 0.044$) and LPS (22.64 vs. 11.16%, $P = 0.005$). In hypertensive patients, multivariate logistic regression analyses showed that long hypertension history (≥20 years), poor control of diastolic blood pressure, cardiac and renal complications, and use of multiple antihypertensive medications were risk factors for elevated DAO, while the use of multiple antihypertensive medications was a risk factor for elevated $_D$-lactate ($P < 0.05$).

Conclusions: Hypertension is associated with impairment of intestinal barrier, especially in patients with long duration, poor blood pressure control, cardiac and renal complications, and use of multiple antihypertensive medications. The current study indicates that intestinal barrier dysfunction might be a potential predictor of hypertension.

Keywords: hypertension, risk factor, intestinal barrier, gut microbiota, prediction

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BACKGROUND

Hypertension is a significant public health issue worldwide, which is the strongest modifiable factor related to cardiovascular disease and strokes, causing high morbidity and mortality (1, 2). The global prevalence of hypertension was about 1.13 billion in 2015, and it is estimated to rise to 1.56 billion by 2025 (3).

The association between the gut and cardiovascular disease has begun to draw our attention in recent years (4, 5). The concepts of the "gut–heart" and "gut–kidney" axes link the gut to blood pressure (BP) (6, 7). As the largest mucosal surface in the body, the intestinal barrier maintains host homeostasis by providing a barrier against luminal bacteria, dietary antigens, and toxins (5). Intestinal barrier impairment may trigger or exacerbate many diseases including infections, metabolic diseases, and cancer (8–10). Additionally, multiple diseases can also cause intestinal barrier alterations. The spontaneously hypertensive rat (SHR) model shows obvious alterations in intestinal pathology, including decreased goblet cells and villi length and increased gut permeability and inflammation, suggesting that hypertension led to intestinal barrier impairment (11, 12).

Endoscopy is common used to diagnose intestinal barrier impairment, only severe injuries such as erosion, ulcers, and bleeding can be detected. Early-stage damage, such as small intestinal epithelium injury, endotoxin translocation, and increased intestinal permeability, is difficult to detect. Serum diamine oxidase (DAO) (13, 14), lipopolysaccharide (LPS) (15, 16), and D-lactate (14, 17, 18) are convenient and well-accepted biomarkers for intestinal barrier function.

Currently, the correlation between hypertension and intestinal barrier impairment is far from known. The present study aims to investigate the role of typical serum markers of intestinal barrier function in hypertensive patients and to find novel potential risk factors for predicting and treating hypertension.

METHODS

Study Population

In this retrospective study, we reviewed the medical data of all inpatients in the Department of Gastroenterology of the First Affiliated Hospital of Guangdong Pharmaceutical University treated from January to December 2017. The exclusion criteria were as follows: (i) carcinoma; (ii) severe heart, lung, liver, or kidney disease, except hypertensive cardiac or renal complications; (iii) non-steroidal anti-inflammatory drug use in the previous month; (iv) intestinal diseases such as ulcerative colitis, Crohn's disease, or intestinal obstruction; (v) history of gastrointestinal surgery; (vi) bacterial infection, except *Helicobacter pylori*; and (vii) secondary hypertension caused by renal parenchymal, adrenal, renovascular, or thyroid disease. Patients hospitalized more than once during the study period were recorded only once. A total of 1372 patients were detected with the three serum biomarkers in the department of gastroenterology in 2017, and a final 357 subjects were included in the present study.

This study was performed in accordance with the Declaration of Helsinki and with the approval of the Ethical Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University. Given that this was a retrospective study, informed consent from the research subjects was waived.

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence intervals; DAO, diamine oxidase; DBP, diastolic blood pressure; LPS, lipopolysaccharide; OR, Odds ratio; SBP, systolic blood pressure; SHR, spontaneously hypertensive rat.

Data Collection

We collected data from patient records on demographics (age and gender), height, and weight [to calculate the body mass index (BMI)]. We also collected data on hypertension-related factors including hypertension status, cardiovascular risk, duration, BP control, complications, and antihypertensive medication use. Diagnosis of hypertension was based on the classic criteria: systolic BP (SBP) $\geq$140 mmHg and/or diastolic BP (DBP) $\geq$90 mmHg (19). Subjects who did not meet these criteria were categorized as normotensives. Cardiovascular risk assessment was based on demographic characteristics, laboratory parameters, hypertension-mediated organ damage, and comorbidities. Good BP control was defined as SBP $\leq$130 mmHg and DBP $\leq$80 mmHg. Hypertensive complications comprised cardiac complications (left ventricular hypertrophy, severe arrhythmias, and heart failure), vascular complications (atherosclerosis, arteriosclerotic stenosis, and aortic aneurysm) (20), renal complications (proteinuria, increased serum creatinine, and increased blood urea nitrogen), and cerebral complications (hemorrhagic and ischemic strokes).

We also collected data on the history of smoking, alcohol consumption, history of liver diseases (fatty liver disease or any kind of hepatitis), history of diabetes, cholesterol level, *H. pylori* status, and three intestinal barrier markers. Smokers were defined as patients who had smoked at any stage in their life. Alcohol consumption was defined as drinking >140 g of alcohol per week. Hypercholesterolemia was defined as serum cholesterol >5.2 mmol/L (21). *H. pylori* infection was diagnosed based on gastric mucosa pathobiology, a ^{13}C-urea breath test, and a rapid urease test. Elevated DAO, LPS, and D-lactate were defined as $\geq$15, $\geq$20, and $\geq$10 U/L, respectively.

Statistical Analysis

IBM SPSS software version 22 (IBM Corp., Armonk, NY, USA) was used to perform statistical analyses. Categorical variables are presented as frequencies and proportions. Non-normally distributed continuous variables are presented as medians and interquartile ranges. The statistical significance levels of differences between the hypertensive and normotensive subjects were tested using Chi-square or Fisher's exact tests for categorical variables and Mann–Whitney *U*-tests for medians. To identify risk factors for elevated intestinal barrier markers, we performed logistic regression analyses with a backward stepwise approach. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. $P < 0.05$ (two-sided) was considered statistically significant.

RESULTS

Demographics and Clinical Characteristics

In total, 357 patients (251 without hypertension and 106 with hypertension) were included, but specific subsets were used in different analyses (detailed below) due to patients having

TABLE 1 | Patient demographics and clinical characteristics.

	Hypertension ($n = 106$)	No hypertension ($n = 251$)	*P*-value
Age (years)	63.0 (57.0–72.0)	56.0 (46.0–63.0)	<0.001
Male gender	61 (57.55)	131 (52.19)	0.354
Body mass index (kg/m^2)	23.73 (21.78–25.98)	22.23(20.00–24.91)	0.001
Disease duration (years)	($n = 82$)		
<20	69 (84.15)		
≥20	13 (15.85)		
Diabetes status	24 (22.64)	17 (6.77)	<0.001
Liver disease	48 (45.28)	75 (29.88)	0.005
Alcohol consumption	12 (11.32)	26 (10.36)	0.788
History of smoking	23 (21.70)	46 (18.33)	0.461
Hypercholesterolemia	29 (31.87)	72 (33.64)	0.763
	($n = 91$)	($n = 214$)	
Helicobacter pylori infection	24 (22.64)	64 (25.50)	0.567

Data are presented as medians (interquartile ranges) or n (%).

TABLE 2 | Intestinal barrier markers in patients with or without hypertension.

	Hypertension ($n = 106$)	No hypertension ($n = 251$)	*P*-value
Elevated DAO	30 (28.30)	47 (18.73)	0.044
Elevated LPS	24 (22.64)	28 (11.16)	0.005
Elevated $_D$-lactate	76 (71.70)	171 (68.13)	0.504

Data are presented as n (%). DAO, diamine oxidase; LPS, lipopolysaccharide.

missing data for some variables. The demographics and clinical characteristics of the included patients were shown in **Table 1**.

Elevated DAO and LPS but Not $_D$-lactate in Hypertensive Patients

To detect the association between intestinal barrier impairment and hypertension, two groups of hypertension and no hypertension were analyzed with DAO, LPS, and $_D$-lactate. **Table 2** shows that patients with hypertension had a significantly higher prevalence of elevated DAO (28.30 vs. 18.73%, $P = 0.044$) and elevated LPS (22.64 vs. 11.16%, $P = 0.005$) but not $_D$-lactate (71.71 vs. 68.13%, $P = 0.504$). After adjustment for gender, age, BMI, smoking, alcohol consumption, liver disease, diabetes, and *H. pylori* infection, the logistic regression analysis showed that hypertension was a risk factor for elevated DAO (OR = 1.71, 95% CI: 1.01–2.91, $P = 0.046$) and elevated LPS (OR = 2.64, 95% CI: 1.42–4.92, $P = 0.002$). In addition, representative images of capsule endoscopy showed that edema, hyperemia, and mucosal lesions were frequently detected in the small intestine of patients with hypertension, whereas they were rarely observed in those participants without hypertension (**Figure 1**).

In the group of hypertensive patients, there were no significant differences in the prevalence rates of elevated intestinal barrier markers among patients with different cardiovascular risk levels (**Supplementary Table 1**).

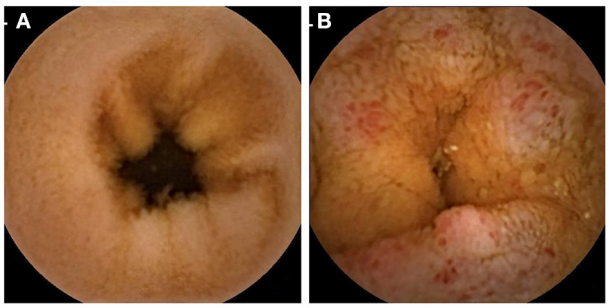

FIGURE 1 | Representative capsule endoscopic images. **(A)** Normal small intestine of normotensive participants; **(B)** Mucosal edema (enlarge villi) and moderate to severe mucosal hyperemia (area of reddish villi) were observed in the small intestine of patients with hypertension.

TABLE 3 | Intestinal barrier markers in patients with different durations of hypertension.

	Duration ≥20 years ($n = 13$)	Duration <20 years ($n = 69$)	*P*-value
Elevated DAO	7 (53.85)	16 (23.19)	0.040
Elevated LPS	3 (23.08)	17 (24.64)	1.000
Elevated $_D$-lactate	9 (69.23)	48 (69.57)	1.000

Data are presented as n (%). DAO, diamine oxidase; LPS, lipopolysaccharide.

DAO Is a Primary Marker Associated With Hypertension-Related Factors

Based on the evidence of barrier markers in hypertensive patients, logistic regression analyses were performed to test the association between barrier impairment and hypertension-related factors. We compared this with patients with a hypertension history of fewer than 20 years, the prevalence of elevated DAO but not LPS, and $_D$-lactate in patients with long-term hypertension (≥20 years) (53.85 vs. 23.19%, $P = 0.040$, **Table 3**).

After adjustment, logistic regression analysis showed that hypertension history ≥20 years (OR = 5.92, $P = 0.028$), poor DBP control (OR = 8.93, $P = 0.011$), cardiac complication (OR = 12.00, $P = 0.024$), renal complication (OR = 8.01, $P = 0.034$), and use of multiple antihypertensive medication (OR = 3.61, $P = 0.010$) were risk factors for elevated DAO (**Table 4**). In addition, the logistic regression analyses showed that use of multiple antihypertensive medication was associated with elevated $_D$-lactate after adjustment (OR = 3.24, $P = 0.011$) (**Table 4**).

Association Between Blood Pressure Control and Hypertensive-Related Complication With Intestinal Barrier Impairment in Hypertensive Patients

The association between blood pressure control and the intestinal barrier biomarker was further determined. Compared with patients with good DBP control, those with poor control showed

a trend toward a higher prevalence of elevated DAO, although there is no significant difference (43.48 vs. 24.10%, $P = 0.068$, **Table 5**). In addition, no significant relationship was found between DBP or SBP control and the other intestinal barrier markers (**Table 5**).

DISCUSSION

Our findings show that hypertensive patients had higher prevalence rates of elevated DAO and LPS than normotensive subjects, which indicates that hypertension is associated with serious intestinal barrier impairment, including small intestinal epithelium injury and endotoxin translocation. These important findings might improve early diagnosis and potential therapeutic target for hypertension-related intestinal damage in hypertensive patients. To the best of our knowledge, this is the first study to assess the association between hypertension and intestinal barrier integrity in humans.

These clinical findings (**Table 2**, **Figure 1**) are consistent with those in animal models, which showed that hypertension was associated with obvious intestinal pathology. Santisteban and colleagues tested gut epithelial integrity and gut wall pathology in SHRs (12) and found that high BP was associated with morphological changes (e.g., decreased goblet cells and shorter villi), a leaky intestinal barrier (involving increased permeability and decreased tight junction proteins), and increased small intestine inflammation. Notably, the intestinal barrier impairment in this animal model was reversed by antihypertensive medications (12). Jaworska and colleagues reported similar results using the same animal model (11). In addition, the antihypertensive drug candesartan attenuates hypertension-induced gut leakage (22).

Several mechanisms might explain why hypertensive patients have intestinal barrier impairments. First, hypertension can cause decreased intestinal blood flow (11, 12). One study showed that elevated BP in hypertensive rats could cause changes in arterioles, including thicker walls and smaller lumens, which can decrease intestinal blood flow (11). Additionally, clinical research showed that hypertension-induced vascular pathologies (such as arterial stiffness, atherosclerosis, and vascular stenosis) could reduce intestinal perfusion (19, 23). Chronic ischemia due to decreased perfusion can cause intestinal mucosa damage and barrier impairment (24). Second, gut microbiota dysbiosis is frequently found in hypertensive patients, although the causal relationship needs to be further investigated (25). Compared with normotensive subjects, hypertensive patients have dramatically decreased microbial richness and diversity, reduced short-chain fatty acid production, and overgrowth of opportunistic pathogens such as *Klebsiella* spp. and *Streptococcus* spp. (25, 26). These changes weaken the intestinal barrier by reducing short-chain fatty acid levels (which enhance intestinal barrier integrity and inhibit gut inflammation) and can even directly damage the intestinal epithelium (27, 28). Finally, hypertension-induced vascular endothelial cell injury is associated with subepithelial mononuclear cell infiltration (11). Inflammatory mediators and reactive oxygen species subsequently released by inflammatory cells can trigger intestinal barrier injury (24).

Vice versa, intestinal barrier dysfunction plays an important role in the etiology of hypertension. Gut microbiota is considered as a composition and regulator of the intestinal barrier, which plays a critical role in the metabolism and maturation of the immune system (29). A leaky intestinal barrier may promote LPS and metabolites of gut microbiota to the host, thereby inducing host inflammation and, finally, cardiovascular events (18, 30). Studies have shown that the composition and richness of gut microbiota were changed in hypertension patients, and transplantation of feces from hypertensive subjects could induce hypertension status in germ-free mice (26). In addition, antibiotics treatment contributes to dysbiosis of gut microbiota, alteration of bacteria-produced short-chain fatty acids, and an increase in the blood pressure in the experimental animal model (31). Prominently, a recent study has proven that the impairment of the intestinal barrier was due to cirrhosis and not hypertension

TABLE 4 | Logistic regression analyses of risk of impaired intestinal barrier due to hypertension-related factors.

	OR	95% CI	*P*-value
Elevated DAO			
Duration ≥20 years	5.92	1.22–28.78	0.028
Poor DBP control	8.93	1.65–48.35	0.011
Cardiac complication	12.00	1.39–103.44	0.024
Renal complication	8.01	1.17–54.69	0.034
Use of multiple antihypertensive medications	3.61	1.36–9.58	0.010
Elevated D-lactate			
Use of multiple antihypertensive medications	3.24	1.31–7.98	0.011

Adjusted for gender, age, body mass index, diabetes, liver disease, history of smoking, alcohol consumption, Helicobacter pylori infection, cardiovascular risk, hypertension duration, blood pressure control, hypertensive complications, and use of multiple hypertension medications. CI, confidence interval; DAO, diamine oxidase; DBP, diastolic blood pressure; LPS, lipopolysaccharide; OR, odds ratio.

TABLE 5 | Intestinal barrier functions in patients with good or poor control of blood pressure.

	Good SBP control ($n = 67$)	Poor SBP control ($n = 39$)	*P*-value ($n = 83$)	Good DBP control ($n = 23$)	Poor DBP control	*P*-value
Elevated DAO	20 (29.85)	10 (25.64)	0.643	20 (24.10)	10 (43.48)	0.068
Elevated LPS	13 (19.40)	11 (28.21)	0.296	19 (22.89)	5 (21.74)	0.907
Elevated D-lactate	45 (61.16)	31 (79.49)	0.174	61 (73.49)	15 (65.22)	0.436

Data are presented as n (%). DAO, Diamine oxidase; DBP, diastolic blood pressure; LPS, lipopolysaccharide; SBP, systolic blood pressure.

itself. Farnesoid x receptor agonists can protect barrier function and thereby reduce gut bacterial translocation to host circulation in mice models (32). These studies provide the possibility of prevention for hypertension through a novel gastrointestinal barrier pathway. To be mentioned, the mosaic history indicates hypertension has resulted from multiple reasons, including genes, the immune system, the endocrine system, and the environment (33). The gut and gut microbiota, one of the biggest organs and "the forgotten organ" (34), might be underestimated in hypertension and hypertension-related organ damage.

The enzyme DAO is mainly expressed in intestinal mucosa and usually has a low presence in blood. The amount of DAO is positively associated with the permeability of the intestinal barrier (35). Previous study has shown increased activity of DAO in SHRs, and the increase of BP might be related to degradation of putrescine by DAO (36). Another study connected heart function with the gastrointestinal tract, showing that the plasma level of DAO was significantly elevated after cardiopulmonary resuscitation (CPR) in porcines (37). To the best of knowledge, our present study is the first study in human that shows that increased DAO in circulation is positively associated with hypertension (**Table 2**).

Our results show that impaired intestinal barrier is associated with multiple hypertension-related factors and complications (**Table 4**). Intestinal barrier injury in long-term hypertension (>20 years) might be a result of organ failure or even a direct complication of hypertension (7, 38). DBP is a risk factor for multiple cardiovascular diseases; similarly (39, 40), our results showed that higher DBP was a risk factor for small intestinal mucosal injury. Moreover, poor DBP control may indicate that patients might have increased vascular stiffness or arteriosclerosis, which can decrease intestinal perfusion; interestingly, the lack of perfusion after CPR may induce a decrease of DAO and impaired intestinal integrity (37). The present study also suggests that hypertension-related renal and cardiac complications are risk factors for intestinal mucosa impairment. Accumulation of toxins in the blood and urea in the intestine disrupts intestinal tight junction proteins, decreases epithelial barrier function, impairs gut homeostasis, and triggers intestinal disorders in chronic kidney diseases (7, 41). In addition, heart failure leads to severe congestion and disordered microcirculation in the gut (6). These hemodynamic alterations lead to intestinal epithelial edema and dysfunction due to increased hypoxia (42).

In conclusion, the present study indicates that hypertension is associated with biomarkers of intestinal barrier impairment, especially in patients with long hypertension duration, poor BP control, cardiac and renal complications, and the use of multiple antihypertensive medications. Further studies are required to determine the precise mechanism of the intestinal barrier, serum biomarkers, and the gut microbiome in hypertension and, finally, to gain insights into diagnosis or therapy for hypertensive patients.

There are several limitations to the present study. First, the results were generated from a single-center study. Second, due to the retrospective nature of our study, some confirmatory examinations, such as endoscopic and mucosal pathologic examinations, were not available for most patients. Serum markers only indirectly reflect intestinal barrier function. Finally, more cases of participants as well as mechanism studies are required to generate a confirmatory conclusion.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was performed in accordance with the Declaration of Helsinki and with the approval of the Ethical Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University. Given that this was a retrospective study, informed consent from the research subjects was waived.

AUTHOR CONTRIBUTIONS

CL, DL, and PX designed the study and carried out the data collection. H-JZ and X-XH designed the study. All authors wrote the paper, read, and approved the final 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/fmed.2020.543698/full#supplementary-material

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The Association Between ABO Blood Group and Preeclampsia: A Systematic Review and Meta-Analysis

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Objective: This meta-analysis comprehensively evaluated the association between ABO blood group and the risk of preeclampsia (PE).

Design: Systematic review and meta-analysis.

Data sources: PubMed, Web of Science, and ScienceDirect databases from their inception to September 23, 2020.

Methods: Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were obtained through random-effects and fixed-effects models according to heterogeneity. Meta-regression analysis was applied to explore the source of heterogeneity. We conducted a subgroup analysis by the publication year, study design, state, and Newcastle-Ottawa Scale (NOS) score. In addition, we calculated the rate of each ABO blood group in PE by total pooled effects.

Results: A total of 12 articles with 714,153 patients were included in our analysis. Compared with people without PE (control group), the O blood group presented a lower risk of PE (OR 0.95, 95% CI 0.93–0.97). The AB (OR 1.46, 95% CI 1.12–1.91) blood group presented a higher risk. However, the total pooled OR and 95% CI for the A (OR 1.02, 95% CI 0.90–1.16) and B (OR 1.02, 95% CI 0.98–1.05) blood groups were not significant. The funnel plot and linear regression equation showed that there was no publication bias for the O, A, or B blood groups (all $P > 0.05$). However, the funnel plot and linear regression equation for the AB blood group were obviously asymmetric ($P < 0.05$), and the publication bias persisted even after the trim-and-fill method was applied ($P < 0.05$). Multivariable meta-regression analysis did not find a specific source of heterogeneity. The A blood group showed an association with early-onset PE (OR 0.53, 95% CI 0.33–0.83), and the other blood groups showed no significant differences. In PE, the rates of the O, A, B, and AB blood groups decreased gradually (0.39, 0.33, 0.19, 0.07).

Conclusion: These findings suggest that pregnant women with AB blood group are more likely to develop PE, and more attention should be paid to AB blood group whose blood pressure is high but not sufficient to diagnose PE.

Systematic Review Registration: Prospero CRD42021227930.

Keywords: ABO blood group, preeclampsia, pooled odds ratios, confidence intervals, systematic review, meta-analysis

INTRODUCTION

Preeclampsia (PE) is a common complication during pregnancy that affects 5–8% of pregnant women (1, 2). PE is associated with a variety of short-term and long-term complications in mothers and infants, such as placental abruption, cardiovascular disease, renal disease, metabolic disorders, fetal growth restriction (FGR), and preterm birth (3–5). After 20 weeks of gestation, women with systolic BP $\geq$140 mmHg or diastolic BP $\geq$90 mmHg on two occasions with or without proteinuria and renal, liver, lung, or neurological organ dysfunction were considered to have PE (5, 6). PE can be categorized as early onset (<34 weeks of gestation) or late onset ($\geq$34 weeks of gestation) (7). In addition, PE can be classified as mild or severe PE depending on the severity of the condition (diagnostic criteria for severe PE are shown in Appendix S1 in **Supplementary Material**) (8, 9). Risk factors associated with the development of PE have been reported, including previous history of PE, history of abnormal blood pressure, history of gestational diabetes mellitus, multiple pregnancy, and nulliparity (10, 11). Additionally compared with pregnant women without PE, mounting evidence suggests that lower placental growth factor (PlGF) and higher soluble fms-like tyrosine kinase 1 (sFlt-1) levels of maternal blood during pregnancy are linked to PE. Thus, these factors and blood biomarkers may be used for risk prediction of PE before the appearance of the clinical syndrome (6, 12, 13).

In 1901, the ABO blood group system was first discovered and defined by Karl Landsteiner in Austria. It includes types A, B, AB, and O, which are defined according to the expression of agglutinins A and B (14). In recent years, an increasing number of studies on ABO blood groups have been conducted, and blood group has been reported to be associated with the development of many human diseases, such as thrombotic vascular diseases (15), gestational diabetes mellitus (GDM) (16), acute respiratory distress syndrome (ARDS) (17), cardiovascular disease (CVD) (18), gastric cancer (19), infectious diseases (20), and PE (21). Although, the ABO system has been studied for more than a century, its clinical biological significance remains ambiguous.

In 2008, one study evaluated the association between ABO blood group and vascular disease and indicated that non-O blood group was at higher risk for some vascular diseases compared with O blood group (21). In 2013, a systematic review and meta-analysis reported that the AB blood group was associated with the occurrence of PE (22). A systematic review from 2016 aiming to elucidate the association of ABO blood groups with pregnancy-related complications indicated that women with a non-O blood group have an increased risk of PE (23). However, the results of subsequent studies have been inconsistent. Two studies found that patients with blood group AB have a higher risk of PE (24, 25), but another three studies considered that there was no distinct association between ABO blood group and PE (26–28). These five studies included four case–control studies and one cross-sectional study. The largest study population was 17,564 individuals, and the smallest study population was 147 individuals. Hence, we conducted this meta-analysis to comprehensively evaluate the association between ABO blood group and the risk of PE. In addition, we calculated the specific rate of each ABO blood group in PE.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (29).

Literature Search

We searched for the relevant literature through the PubMed, Web of Science, and ScienceDirect databases from inception to September 23, 2020. The Population, Intervention, Comparator, Outcomes and Study designs (PICOS) principle was used to identify articles in the various databases (Appendix S2 in **Supplementary Material**). We restricted the language to English. We also tracked references to relevant articles. The details of the search process are shown in Appendix S3 in **Supplementary Material**. Two authors independently collected and integrated the data.

Eligibility Criteria

We selected articles on the basis of the database searches and applied EndNote X9 to remove duplicate articles. Then, we browsed the titles and abstracts to exclude unrelated articles. This meta-analysis followed the following inclusion criteria: (1) included data on ABO blood group for pregnant women; (2) included pregnant women with and without preeclampsia; (3) prospective and retrospective studies. Reviews, meta-analysis, articles lacking relevant data, letters, and abstracts were excluded.

Data Extraction and Study Quality Assessment

Two authors independently reviewed each study and decided whether it was eligible for inclusion in our meta-analysis, and if there was any disagreement, the corresponding author joined the discussion. We extracted the following data from the articles: first author name, year of publication, study design, state, and

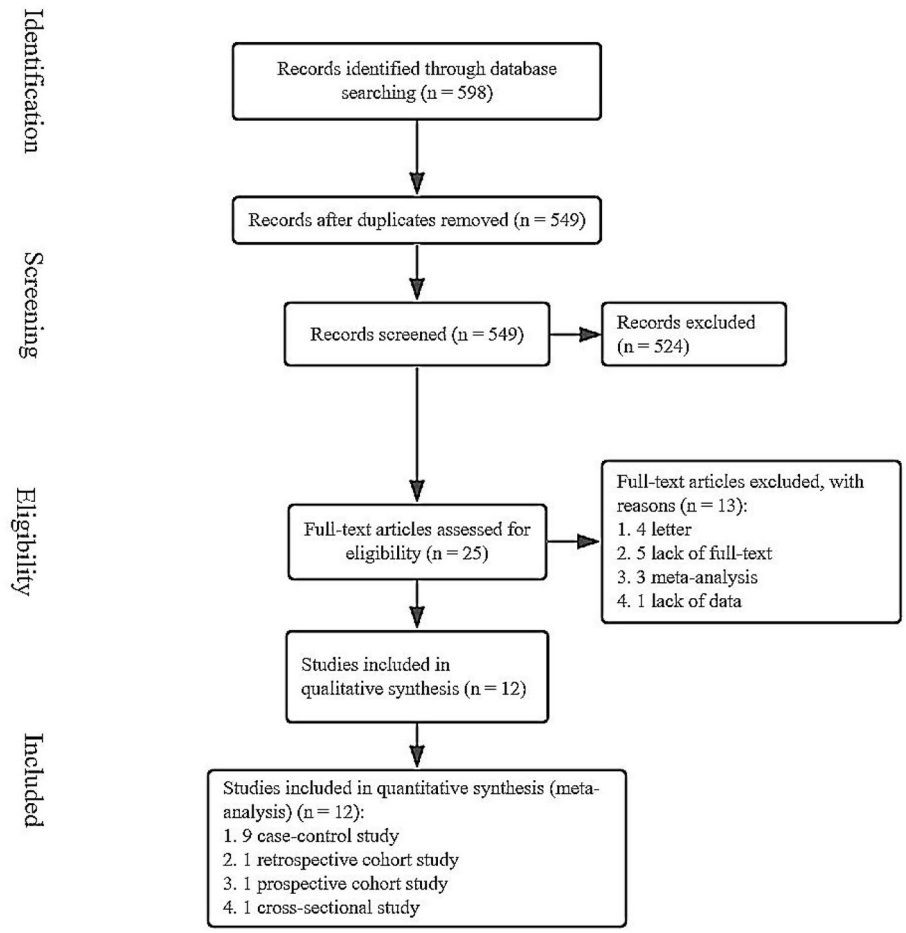

FIGURE 1 | A flow chart of screened studies on ABO blood group and PE.

conclusions. The extracted data provided sufficient information for the construction of 2 × 2 tables. The study quality assessment was based on the Newcastle–Ottawa Scale (NOS, Australia and Ottawa, Canada) (30). Using this protocol, the maximum score for each study was nine. Studies with a score ≥7 were regarded as high-quality articles (31). Subgroup analysis was based on the publication year (<2010, ≥2010), study design, state, and NOS score (<7, ≥7) to further evaluate the association between ABO blood group and the risk of PE. Meanwhile, we assessed the association of ABO blood group with mild or severe PE and early-onset or late-onset PE. In addition, we calculated the rate of ABO blood group in PE based on the included studies.

Statistical Analysis

All the data were analyzed *via* R version 3.6. Forest plots were constructed to obtain Pooled Odds Ratios (ORs) and 95% Confidence Intervals (95% CIs). If $I^2 < 50\%$ and $P_{heterogeneity} > 0.05$, the fixed-effects model was applied to calculate pooled effect estimates. If $I^2 \geq 50\%$ or $P_{heterogeneity} \leq 0.05$, the random-effects model was applied. We conducted leave-one-out sensitivity analysis by removing each study to explore the robustness of the included literature. Publication bias was evaluated by funnel plots and linear regression equations. If the funnel plots were obviously asymmetric, we further adjusted the data by the trim-and-fill method. In addition, the multivariable meta-regression analysis was conducted to explore the source of heterogeneity on the basis of publication year, NOS score, state, and study design. We pooled the rates of O, A, B, and AB blood group in PE as proportions with 95% CIs after log transformation. A cut-off value of $P < 0.05$ was defined as statistically significant.

RESULTS

Study Selection

We searched for the relevant literature through PubMed, Web of Science, and ScienceDirect databases from inception to September 23, 2020. A total of 598 studies were obtained (**Figure 1**). After removing duplicate articles, 549 articles remained. Then, irrelevant and data-deficient articles were eliminated by browsing the titles, abstracts, and full text. Finally, we included 12 articles in this meta-analysis (24–28, 32–38).

TABLE 1 | Characteristics of the included articles.

First author	Year	Country (state)	Study design	N	PE: Control*	O (PE: control)	A (PE: control)	B (PE: control)	AB (PE: control)	Conclusions
Okoye HC	2020	Nigeria (Africa)	Cross-sectional	147	66: 81	46: 49	12: –	7: –	1: –	No effect of ABO blood types on the risk of PE
Mahasub N	2020	Thailand (Asia)	Case–control	690	230: 460	72: 164	53: 99	88: 171	17: 26	No effect of ABO blood types on the risk of PE
Burgess A	2019	Pennsylvania (North America)	Case–control	511	252: 259	106: 122	95: 100	38: 32	13: 5	AB blood group increased the risk of PE
Aghasadeghi F	2017	Iran (Asia)	Case–control	331	121: 210	61: 93	28: 63	26: 46	6: 8	No effect of ABO blood types on the risk of PE
Avci D	2016	Turkey (Asia)	Case–control	17,564	250: 17,314	69: 5,423	104: 7,756	46: 2,819	31: 1,316	AB blood group increased the risk of PE
Phaloprakarn C	2013	Thailand (Asia)	Case–control	5,320	350: 4,970	105: 1,851	100: 1,053	113: 1,719	32: 347	A and AB blood group increased the risk of PE
Lee BK	2012	Sweden (Europe)	Retrospective cohort	679,740	37,814: 641,926	13,881: 243,041	17,408: 291,453	4,430: 74,147	2,095: 33,285	Non-O blood group increased the risk of PE
Alpoim PN	2011	Brazil (South America)	Case–control	90	55: 35	17: 15	–	–	–	No effect of ABO blood types on the risk of PE
Hiltunen LM	2009	Finland (Europe)	Case–control	927	248: 679	72: 217	104: 294	40: 124	32: 44	AB blood group increased the risk of PE
Clark P	2008	Scotland (Europe)	Prospective cohort	3,985	66: 3,919	32: 2,055	–	–	–	No effect of ABO blood types on the risk of PE
Witsenburg C P	2005	Netherlands (Europe)	Case–control	308	36: 272	11: 111	–	–	–	No effect of ABO blood types on the risk of PE
Scott JR	1976	Iowa (North America)	Case–control	4,540	46: 4,494	22: 2,139	15: 1,705	7: 511	2: 139	No effect of ABO blood types on the risk of PE

**Control means pregnant women without preeclampsia (PE). –, No data are available in the article.*

Study Characteristics

The main characteristics of the included studies are shown in **Table 1**. This meta-analysis included 12 articles with 714,153 patients: nine case–control studies, one cross-sectional study, one retrospective cohort study, and one prospective cohort study. The publication dates of these articles ranged from 1976 to 2020. Among these articles, the study areas included Europe for four studies; Asia, four; North America, two; South America, one; and Africa, one. The smallest sample size was 90, and the largest sample size was 679,740. The conclusions of seven articles indicated that there was no effect of ABO blood group on the risk of PE. Four studies showed that AB blood group increased the risk of PE. One study indicated that non-O blood groups had significantly higher odds of PE. One study showed that the A blood group increased the risk of PE.

Total Pooled Effect

As shown in **Figure 2A**, the heterogeneity among the eligible articles was $I^2 = 18\%$ ($P = 0.26$), so we chose a fixed-effects model. The total pooled effect showed that the O blood group presented as a protective factor against PE (OR 0.95, 95% CI 0.93–0.97). At the same time, we calculated the outcomes for A, B, and AB blood groups. The AB blood group presented a high risk of PE in the random-effects model, respectively (OR 1.46, 95% CI 1.12–1.91, $I^2 = 62\%$, $P_{heterogeneity} = 0.01$, **Figure 3A**). However, the total pooled OR and 95% CI showed no significance of the A blood group in the random-effects model (OR_A 1.02, 95% CI_A 0.90–1.16, $I^2_A = 49\%$, $P_{heterogeneity} = 0.05$) and B blood group in the fixed-effect model (OR 1.02, 95% CI 0.98–1.05, $I^2 = 0\%$, $P_{heterogeneity} = 0.81$) (**Figures S1A, S2A**). Although, only some articles studied mild or severe PE and early-onset or late-onset PE, we analyzed them further. As **Figure S3** shows, regardless of mild or severe PE, there was no association between the ABO blood group and PE. However, the A blood group showed an association with early-onset PE, and the other blood groups showed no significance (OR 0.53, 95% CI 0.33–0.83, $I^2 = 0\%$, **Figure 4**).

Publication Bias and Sensitivity Analysis

The funnel plot and linear regression equation showed that there was no publication bias with respect to the effects of the O, A, and B blood group ($P_O = 0.59$, $P_A = 0.67$, $P_B = 0.90$) (**Figure 2B**, **Figures S1B, S2B**). The funnel plot of AB blood group was clearly asymmetrical (**Figure 3B**). We further conducted the trim-and-fill method; the funnel plot was symmetric, but publication bias still existed ($P < 0.05$, **Figure 3C**). As **Figure 2C** shows, when omitting one of these studies (28), the sensitivity analysis of the O blood group showed an OR of 0.95 (95% CI 0.93–0.97), nearly the same outcome as the total pooled effect (OR 0.95, 95% CI 0.93–0.97). Similarly, when omitting any one of the other studies, the outcomes showed that O blood group was a protective factor against PE. The sensitivity analysis of the AB blood group showed similar outcomes after omitting any one study (**Figure 3D**). The sensitivity analysis of the A and B blood groups showed that after omitting any one study, the effect of the A and B blood groups was not significant (**Figures S1C, S2C**).

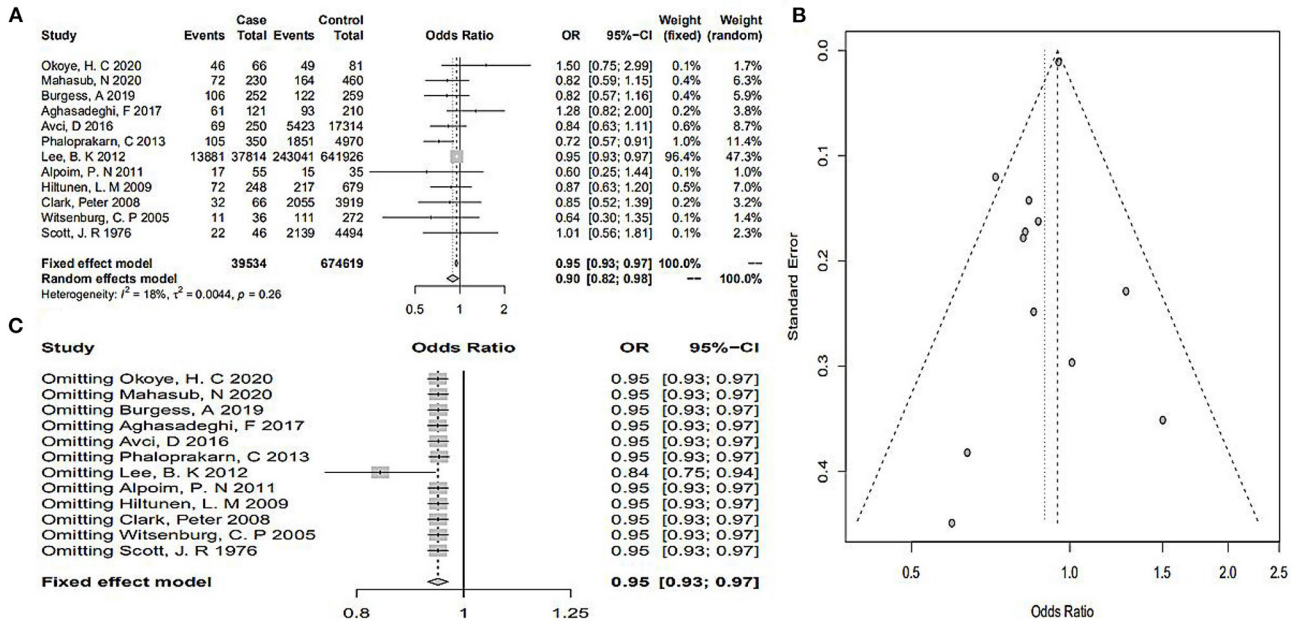

FIGURE 2 | (A) Forest plots of the risk of PE in the O blood group. **(B)** Funnel plot of the included studies for the O blood group. **(C)** Sensitivity analysis of the included studies for the O blood group.

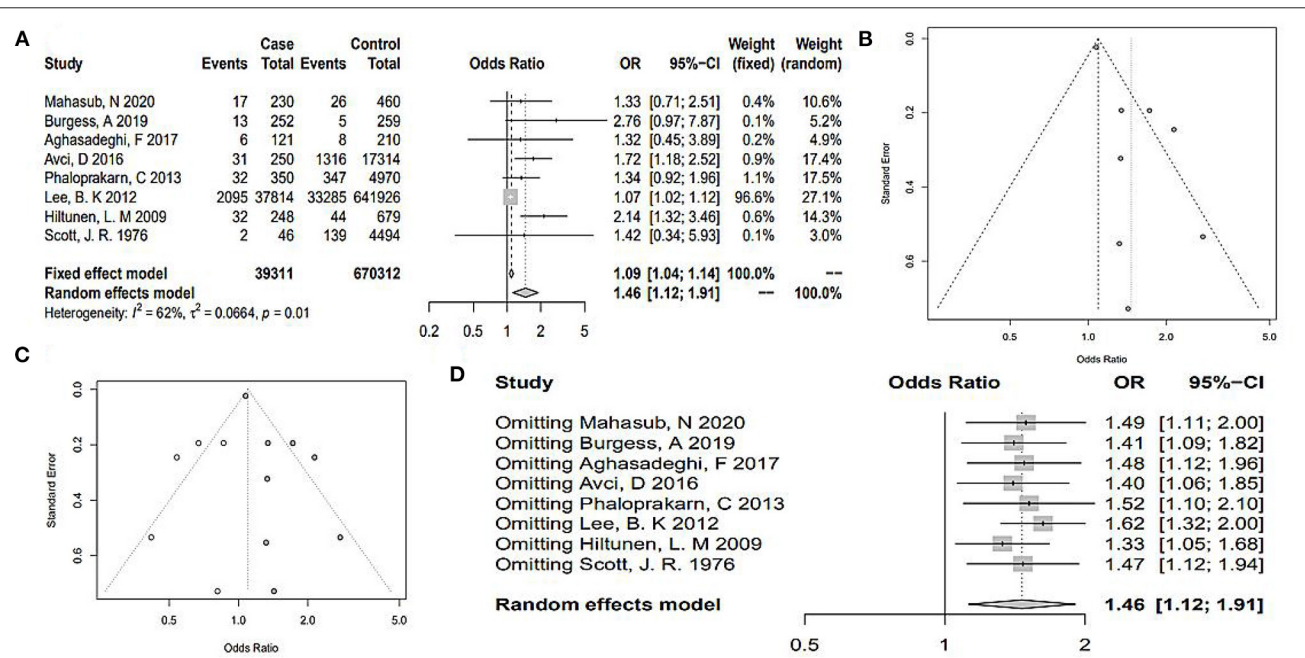

FIGURE 3 | (A) Forest plots of the risk of PE in the AB blood group. **(B)** Funnel plot of the included studies for the AB blood group. **(C)** Funnel plot of the included studies for the AB blood group after trim-and-fill method. **(D)** Sensitivity analysis of the included studies for the AB blood group.

Multivariable Meta-Regression Analysis

In the total pooled effect, heterogeneity of the AB blood group was I^2 = 62.0% (P < 0.05, **Figure 3A**). Thus, we conducted multivariable meta-regression analysis on the basis of publication year, NOS score, state, and study design. The results confirmed that these factors showed no significant effect on the heterogeneity (all P > 0.05, **Table 2**).

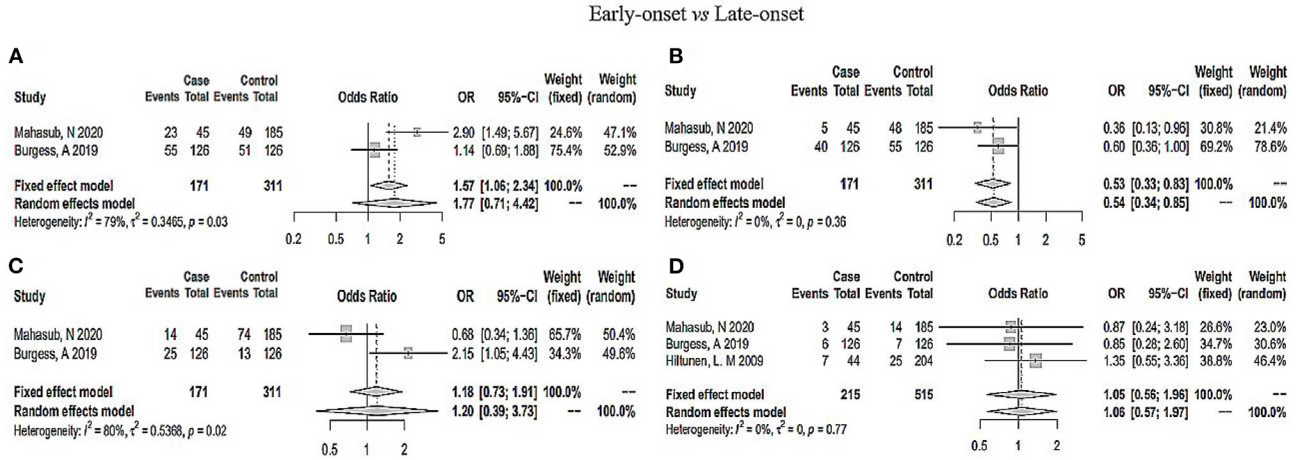

FIGURE 4 | Analysis of early-onset (case) and late-onset (control) PE in ABO blood group. **(A)** O blood group; **(B)** A blood group; **(C)** B blood group; **(D)** AB blood group.

TABLE 2 | Results of meta-regression analysis.

Study-level variables	Coefficient (95% CI)	*P*-value
Publication year	(−0.03, 0.05)	0.6
NOS score	(−0.59, 0.30)	0.53
State	(−0.26, 0.91)	0.28
Study design	(−31.91, 14.40)	0.46

NOS, Newcastle–Ottawa Scale.

Subgroup Analysis

Subgroup analysis was based on the study design, state, NOS score (<7, ≥7) and publication year (<2010, ≥2010) to further evaluate the association between ABO blood group and the risk of PE. As shown in **Table 3**, the outcomes in the O blood group were almost the same. When publication year <2010 and studies performed in America, the outcomes showed no significance (all $P > 0.05$). Subgroup analysis of cross-sectional study design and studies performed in Africa, which included only one study each, showed no significance. The outcome for European region of AB blood group was not significant for PE ($N_{Europe} = 2$, OR_{Europe} 1.45, 95% CI_{Europe} 0.74–2.84) (**Table 4**). The subgroup analysis of the A blood group was somewhat inconsistent and showed no significance (**Table S1**). Only the outcomes of cohort study, NOS score ≥ 7 and European region showed significant differences ($N_{cohort\ study} = 1$, $OR_{cohort\ study}$ 1.03, 95% $CI_{cohort\ study}$ 1.00–1.05; $N_{Europe} = 2$, OR_{Europe} 1.03, 95% CI_{Europe} 1.01–1.05; $N_{NOS\ score\ \geq 7} = 3$, $OR_{NOS\ score\ \geq 7}$ 1.03, 95% $CI_{NOS\ score\ \geq 7}$ 1.01–1.05). The subgroup analysis of the B blood group was almost consistent (**Table S2**).

Rates of ABO Blood Group in PE

The rates of the O, A, B, and AB blood groups were further analyzed by forest plots. As shown in **Figure 5**, we can see that the rate of the O blood group was 0.39 (95% CI 0.33–0.44, $I^2 =$ 90%). In PE, the rates of the A, B, and AB blood group decreased gradually (0.33, 0.19, and 0.07).

DISCUSSION

Our systematic review and meta-analysis comprehensively explored the association between ABO blood group and PE. Twelve articles comprising 714,153 patients were included. On the basis of previous studies and the outcomes we obtained, the present study demonstrated that compared with the control group, the O blood group presented as a protective factor for PE. Conversely, the AB blood group aggravated the risk of PE, and the A and B blood groups showed no significant effect on the risk of PE. Notably, we found that the A blood group showed an association with early-onset PE. In addition, we further calculated the specific incidences of the ABO blood groups in PE. The rate of the O blood group in PE was 0.39 (95% CI 0.33–0.44, $I^2 = 90\%$), and the rates of the A, B, and AB blood groups were 0.33, 0.19, and 0.07, respectively.

ABO blood group antigens exist on many kinds of cells of the human body; in addition to common red blood cells, these antigens are also expressed on vascular endothelial cells and neuronal cells (39). Existing studies found that ABO blood group status is correlated with many diseases, such as CVD, ARDS, GDM, and PE (16–18, 27, 28). Nevertheless, the association between PE and ABO blood group has been controversial. In 1976, an article published in *JAMA* studied 23 patients with PE, 23 patients with eclampsia, and 4,494 controls and suggested that there was no association between ABO blood group and PE (controls vs. PE: O blood group, 47.6 vs. 47.8%; A blood group, 37.9 vs. 32.6%; B blood group, 11.4 vs. 15.2%; AB blood group, 3.1 vs. 4.3%; all $P > 0.05$) (32). Studies performed in 2005 and 2008 arrived at the same conclusion. A meta-analysis also concluded that non-O blood groups are more susceptible to certain vascular diseases than O blood group (21). In 2009, for the first time, a population-based nested case–control study indicated that AB

TABLE 3 | Subgroup analysis of the risk of PE in O blood group.

Subgroup	Studies (*N*)	PE: control	O (PE: control)	I^2	OR (95% CI)
Study design					
Case–control study	9	1,588: 28,693	535: 10,135	0%	0.82 (0.73–0.93)
Cohort study	2	37,880: 645,845	13,913: 245,096	0%	0.95 (0.93–0.97)
Cross-sectional study	1	66: 81	46: 49	–	1.50 (0.75–2.99)
State					
Asia	4	951: 22,954	307: 7,531	39%	0.82 (0.71–0.95)
Europe	4	38,164: 646,796	13,996: 245,424	0%	0.95 (0.93–0.97)
America	3	353: 4,788	145: 2,276	0%	0.83 (0.63–1.10)
Africa	1	66: 81	46: 49	–	1.50 (0.75–2.99)
NOS score					
<7	8	1,176: 31,473	423: 11,809	0%	0.82 (0.72–0.94)
≥7	4	38,358: 643,146	14,071: 243,471	0%	0.95 (0.93–0.97)
Publication year					
<2010	4	396: 9,364	137: 4,522	0	0.86 (0.68–1.08)
≥2010	8	39,138: 665,255	14,357: 250,758	41%	0.95 (0.93–0.97)

NOS, Newcastle–Ottawa Scale; PE, preeclampsia.

TABLE 4 | Subgroup analysis of the risk of PE in AB blood group.

Subgroup	Studies (*N*)	PE: control	AB (PE: control)	I^2	OR (95% CI)
Study design					
Case–control study	7	1,497: 28,386	133: 1,885	0%	1.63 (1.32–2.00)
Cohort study	1	37,814: 641,926	2,095: 33,285	–	1.07 (1.02–1.12)
State					
Asia	4	951: 22,954	86: 1,697	0%	1.47 (1.15–1.87)
Europe	2	38,062: 642,605	2,127: 33,329	87%	1.45 (0.74–2.84)
America	2	298: 4,753	15: 144	0%	2.27 (1.01–5.13)
NOS score					
<7	5	1,019: 27,247	2,144: 33,355	0%	1.07 (1.03–1.12)
≥7	3	38,292: 643,065	84: 1,815	0%	1.68 (1.34–2.09)
Publication year					
<2010	2	294: 5,173	34: 183	0%	2.06 (1.31–3.23)
≥2010	6	39,017: 665,139	2,194: 34,987	53%	1.34 (1.04–1.72)

NOS, Newcastle–Ottawa Scale; PE, preeclampsia.

blood group increased the risk of PE (controls vs. PE: O blood group, 32.0 vs. 29.0%, $P = 0.4$; A blood group, 43.3 vs. 41.9%, $P = 0.7$; B blood group, 18.3 vs. 16.1%, $P = 0.5$; AB blood group, 6.5 vs. 12.9%, $P = 0.002$) (35). This outcome was consistent with ours. Subsequently, Alpoim et al. studied the association between severe PE (sPE) and ABO and indicated that there was no effect of ABO blood group on the risk of PE. In 2012, the team of Lee conducted a cohort study of 641,926 pregnant women and used two models for systematic analysis. After adjusting model 1 (age, country of origin, calendar year, smoking, and RhD status), women in blood group AB had an increased risk of PE (OR 1.10, 95% CI 1.04–1.16, $P < 0.001$) and an even higher increase in risk for sPE (OR 1.18, 95% CI 1.07–1.30, $P < 0.001$). The same outcomes were also obtained in the A and B blood groups. Similar outcomes were obtained from model 2, which adjusted for the model 1 covariates and for BMI, diabetes, and hypertension. For example, women in the AB blood group had an increased risk of PE and sPE (OR 1.12, 95% CI 1.05–1.21, $P < 0.001$; OR 1.20, 95% CI 1.08–1.35, $P < 0.001$). In summary, the outcomes showed that patients with non-O blood groups had an increased risk of PE (37). Furthermore, in 2013, a systematic review and meta-analysis that included only two eligible articles reported that the AB blood group was associated with the occurrence of PE (OR 2.42, 95% CI 1.63–3.58, $P < 0.0001$) (22). However, the results of subsequent studies are also inconsistent. A systematic review from 2016 aimed to elucidate the association of ABO blood groups with

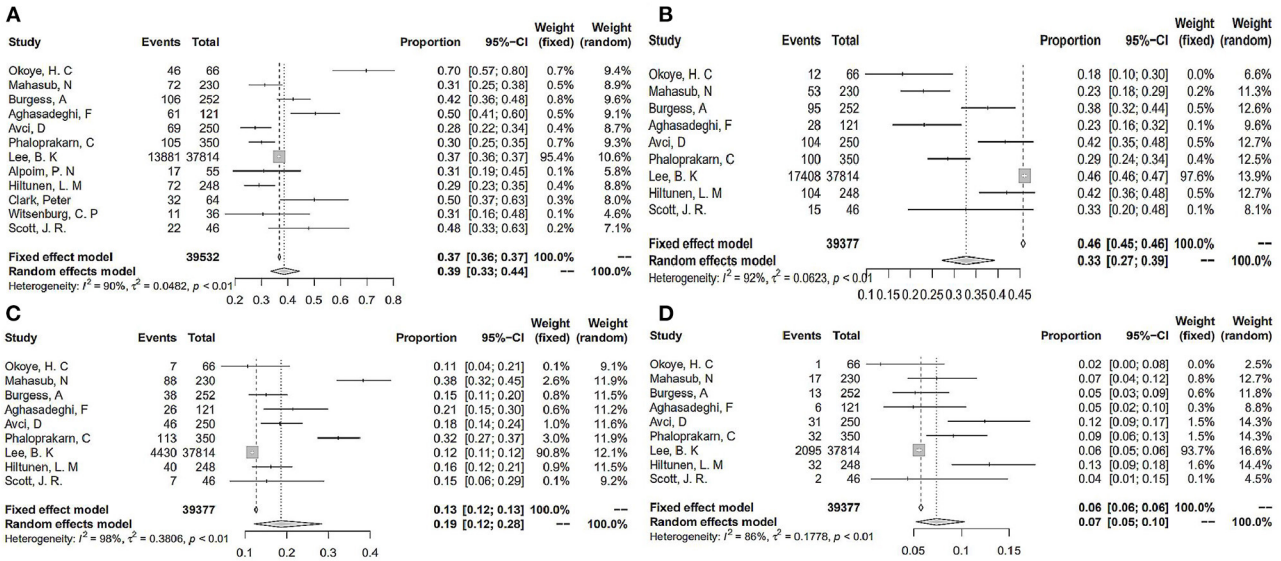

FIGURE 5 | The rates of ABO blood group in PE. **(A)** O blood group; **(B)** A blood group; **(C)** B blood group; **(D)** AB blood group.

pregnancy-related complications, and the results indicated that women with A or AB blood group had an increased risk of PE (O blood group, OR 0.77, 95% CI 0.67–0.88; A blood group, OR 1.78, 95% CI 1.04–3.07; AB blood group, OR 1.94, 95% CI 1.20–3.13) (23). However, the results of subsequent studies have been inconsistent. Two studies found that patients with blood group AB have a higher risk for PE (24, 25), but another three studies considered that there was no distinct association between ABO blood group and PE (26–28). The conclusion of our analysis indicated that the O blood group is a protective factor against PE. Conversely, the blood group AB aggravated the risk of PE, while the A and B blood groups showed no significant effect on the risk of PE. Notably, we found that the A blood group showed an association with early-onset PE. In addition, we further calculated the specific rate of each ABO blood group in PE, and the rates of the O, A, B, and AB blood groups decreased gradually (0.39, 0.33, 0.19, 0.07).

The strengths of our study include that different blood groups were analyzed and that subgroup analysis was carried out in detail. Furthermore, we evaluated both mild and severe PE and both early-onset and late-onset PE. Both funnel plots and linear regression equations were used to calculate publication bias. Multivariable meta-regression analysis on the basis of subgroups was also conducted to explore the source of heterogeneity. In addition, the rates of O, non-O, A, B, and AB blood groups were further specifically analyzed though total pooled effects. Undoubtedly, there are also some limitations in this study. First, only 12 articles were included, and the limited number of studies may influence the outcomes. We restricted the language of studies to English. In addition, in the meta-analysis of 2016, we were unable to find the full text of all included studies. PE is a complex physiological and pathological process, and many factors will affect the occurrence and development of PE (e.g., genetic factors, diet, and environment). It is obviously insufficient to use only the ABO blood group as a factor to predict PE, and all the potential risk factors may act as confounding factors in research outcomes (40–44). Although, the relationship between the ABO blood group system and disease has been studied for a long time, the mechanism of how the ABO blood group system causes and affects disease is not clear. Studies have found that placental protein 13 produced by pregnant women may be associated with the onset of PE by binding to β-galactosides (such as *N*-acetylgalactosamine, galactose, and fucose) at the end of ABO blood group antigens. However, the study on placental protein 13 is not conclusive, but a potential possibility. ABO blood group system has a high degree of polymorphism and it is difficult to simulate ABO blood group antigen in animal models, making it difficult to explore the relationship between ABO blood group and the pathogenesis of PE (45, 46). With the development of molecular biology techniques, transgenic techniques, and bioanalytical tools, we expect to discover how the ABO blood group system causes and affects disease.

CONCLUSION

In conclusion, the O blood group is a protective factor against PE. Conversely, the AB blood group aggravates the risk of PE, and the A and B blood groups have no significant effect on the risk of PE. In addition, the A blood group showed an association with early-onset PE. These findings suggested that clinicians should pay more attention to pregnant women with blood group AB whose blood pressure is high but not sufficient to diagnose PE.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

TL and YW: study design, data extration, statistical analysis, and manuscript writing. LW, ZL, CL, and WL: study design, data extraction, and verification. KX and HD: study design, statistical analysis, manuscript editing and reviewing, and funding. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.665069/full#supplementary-material

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Admission Systolic Blood Pressure and In-hospital Mortality in Acute Type A Aortic Dissection: A Retrospective Observational Study

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Background: Evidence between admission systolic blood pressure (SBP) and in-hospital deaths in acute type A aortic dissection (AAD) patients is inadequate. Here, we examined the relationship between SBP and in-hospital deaths in AAD patients.

Methods: 703 AAD patients were enrolled from January 2014 to December 2018. The independent and dependent variables targeted were admission SBP and in-hospital deaths, respectively. Gender, age, body mass index (BMI), chronic renal insufficiency, smoking, hypertension, diabetes, laboratory indicators, and management were used as covariates.

Results: The 703 participants had a mean age of 50.48 ± 11.35. About 76.24% of the participants were male. After adjusting for confounders, there was a negative correlation between AAD patients' admission SBP and in-hospital deaths (OR = 0.88, 95%CI 0.80–0.96). Consequently, a non-linear relationship of point 120 (mmHg) was detected between admission SBP and in-hospital deaths for AAD patients. Confidence intervals and effect sizes of the right (SBP >120 mmHg) and left (SBP ≤120 mmHg) sides of the inflection point were 0.96 (0.85–1.09) and 0.67 (0.51–0.88), respectively. The change in the male population and non-diabetes people was more pronounced according to subgroup analysis.

Conclusions: Correlation between admission SBP and in-hospital mortality of AAD patients is non-linear. SBP negatively correlated with in-hospital mortality when ≤120 mmHg.

Keywords: systolic blood pressure, SBP, aortic dissection, AAD, in-hospital mortality

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INTRODUCTION

Numerous studies have identified blood pressure as a key determinant of adverse events in cardiovascular disease patients (1, 2). Various studies have observed the J-curve phenomenon amid blood pressure serial levels and adverse cardiovascular events like in-hospital mortality (3, 4). Many observational studies show that admission systolic blood pressure (SBP) is associated with the risk of death in acute cardiovascular conditions like acute heart failure (5) and

cardiogenic shock (6, 7). Additionally, admission SBP is integrated into most danger scoring models in patients with acute coronary syndromes (8). Conversely, in-hospital deaths in patients with acute type A aortic dissection (AAD) are unclear in relation to SBP at admission. Here, we examined the relationship between SBP admission levels and in-hospital mortality among unselected consecutive AAD patients after adjusting for potential confounding factors.

METHODS AND PARTICIPANTS

Study Design

This retrospective, observational study used baseline admission SBP as independent variable and all-cause in-hospital death as dependent variable.

Study Population

We non-selectively and consecutively collected data for all participants at the Second Xiangya Hospital of Central South University, Changsha, Hunan, China. Anonymous data were compiled from the electronic hospital medical record system. Ethical approval for the study was provided by the hospital's institutional review board. Informed consent was waived because the study was retrospective.

The study involves 703 in-patients treated at the hospital from January 2014 to December 2018. Diagnosis was mainly based on 2014 ESC guidelines on the treatment and diagnosis of aortic ailments. Any dissection that involved the ascending aorta with presentation within 14 days of symptom onset was defined as AAD. The diagnosis of AAD was confirmed by imaging like Computed tomography (CT) or Magnetic resonance imaging (MRI). Inclusion criteria were hospital admission for acute type A aortic dissection patients within $\leq$14 days after symptoms onset. The following were used as exclusion criteria: (1) unfinished blood pressure tests, (2) presence of intramural hematoma, which a haematoma develops in the media of the aortic wall in the absence of an false lumen and intimal tear. Intramural haematoma is diagnosed in the presence of a circular or crescent-shaped thickening of more than 5 mm of the aortic wall in the absence of detectable blood flow, (3) presence of symptoms for $>$14 days.

Variables

Admission SBP for all AAD participants was measured at baseline. In-hospital mortality was described as all-cause death during admission. Study covariates involved general information, demographic data, blood biochemistry, medical imaging examination and treatment variables that can affect admission SBP, or in-hospital mortality. Variables for the construction of the fully adjusted model were: (1) continuous variables (age, BMI, time to presentation, aortic diameter, triglyceride (TG), high-density lipoprotein (HDL), ejection fraction (EF), low-density lipoprotein (LDL), creatinine (Cr), total cholesterol (TC), and obtained at baseline), and (2) categorical variables (including smoking, gender, diabetes, Marfan syndrome, bicuspid aortic valve, hypertension, stroke, atherosclerosis, aortic regurgitation, chronic renal insufficiency (CRI), abdominal vessel involvement, arch vessel involvement, symptom, and management.

Missing Data Addressing

We performed multiple multivariable imputations to address missing data in order to maximize statistical power and minimize bias. The data analysis had no covariates with missing data. In addition, five imputed datasets with chained equations were created using MICE software package (9). Sensitivity analysis found no significant differences between the generated complete data and raw data. Thus, all multivariable analyses results based on the imputed datasets were combined with Rubin's rules.

Statistical Analysis

Continuous variables are shown as mean $\pm$ SD (normal distribution) or medium (25th, 75th) [skewed distribution]. Categorical variables are shown as percentage. Kruskal Wallis H test (skewed distribution), chi-squared test (categorical variables) or ANOVA (One way) were used to analyze normally distributed data, particularly variations between different admission systolic blood pressure groups (Quartile). To investigate whether admission systolic blood pressure correlated with in-hospital mortality in certain members, statistical analyses were done in three key steps. Step 1: Multivariate and univariate regression (linear) models engaged. Three additional models were constructed. A crude model without covariates adjustment was made. Model I was adjusted only for sociodemographic data. The second model was made by adding the covariates as shown in **Table 1** to the first model. Step 2 addressed non-linearity in admission SBP and in-hospital mortality. Fitting of an additive-generalized model and penalized spline method (smooth curve) was done. In case any detection of non-linearity was observed, the point of inflection was calculated using a recursive algorithm and a linear two-piece regression constructed. This was done on the inflection point for both sides. For the likelihood log-ratio test, the best fit model was checked on the values of P. Step 3: a stratified linear regression model was used for subgroup analyses. First, continuous variable were changed to categorical variables as stated in the clinical quartile (cut point) and an interaction test was done. A test on the likelihood ratio followed the checks done on the modification of effect for those of indicators on the subgroup. A sensitivity study was used to confirm the stoutness of data analysis that converted admission SBP to a categorical variable and the trend's *p value* calculated. The aim was to detect the likelihood of non-linearity and to affirm SBP admission results as a continuous variable. Survival curves were constructed using Kaplan–Meier analysis and parallels with the test on log-rank. EmpowerStats (http://www.empowerstats.com, X&Y Inc Solutions, Boston, MA) and R (http://www.r-project.org) were used for statistical analyses. $P = <0.05$ (two-sided) was considered statistically significant.

TABLE 1 | Basline characteristics of the patients ($N = 703$).

Characteristic	Systolic blood pressure (mmHg) (Quarter)				*P*-value
	Q1 (64–125)	Q2 (126–144)	Q3 (145–164)	Q4 (165–233)	
No. of patients	210	163	156	174	
Age (years, mean ± sd)	50.31 ± 12.10	52.63 ± 10.71	49.42 ± 11.88	49.63 ± 10.29	0.041
Gender (female)	52 (24.76%)	41 (25.15%)	32 (20.51%)	42 (24.14%)	0.750
BMI (Kg/m^2, mean ± sd)	23.76 ± 3.58	25.16 ± 4.44	25.72 ± 4.66	26.56 ± 4.44	<0.001
Smoking	57 (27.14%)	42 (25.77%)	53 (33.97%)	45 (25.86%)	0.304
Hypertension	112 (53.33%)	99 (60.74%)	119 (76.28%)	148 (85.06%)	<0.001
Diabetes	8 (3.81%)	5 (3.07%)	4 (2.56%)	5 (2.87%)	0.913
Marfan syndrome	10 (4.76%)	3 (1.84%)	6 (3.85%)	1 (0.57%)	0.066
Bicuspid aortic valve	3 (1.43%)	3 (1.84%)	1 (0.64%)	1 (0.57%)	0.636
CRI	2 (0.95%)	5 (3.07%)	1 (0.64%)	10 (5.75%)	0.008
Stroke	7 (3.33%)	5 (3.07%)	4 (2.56%)	8 (4.60%)	0.766
Atherosclerosis	16 (7.62%)	17 (10.43%)	8 (5.13%)	7 (4.02%)	0.094
Time to presentation (h, median [Q1–Q3])	15.00 (9.00–36.75)	24.00 (13.00–48.50)	20.00 (10.50–48.00)	18.00 (10.00–36.00)	0.160
SBP (mmHg, mean ± sd)	106.70 ± 14.30	135.14 ± 5.52	154.63 ± 5.45	182.75 ± 15.72	<0.001
DBP (mmHg, mean ± sd)	62.05 ± 13.04	74.22 ± 13.02	81.24 ± 13.62	97.06 ± 17.32	<0.001
Aortic diameter (mm)	46.50 ± 11.06	47.41 ± 11.61	45.23 ± 10.07	42.73 ± 7.59	<0.001
Aortic regurgitation	99 (47.14%)	80 (49.08%)	63 (40.38%)	72 (41.38%)	0.293
Abdominal vessel involvement	52 (24.76%)	40 (24.54%)	48 (30.77%)	43 (24.71%)	0.505
Arch vessel involvement	64 (30.48%)	49 (30.06%)	55 (35.26%)	53 (30.46%)	0.714
EF value (%)	63.98 ± 10.08	65.13 ± 7.83	64.81 ± 8.26	66.43 ± 5.38	0.066
Symptom					0.062
Chest pain	171 (81.43%)	135 (82.82%)	131 (83.97%)	144 (82.76%)	
Back pain	5 (2.38%)	7 (4.29%)	2 (1.28%)	8 (4.60%)	
Abdominal pain	7 (3.33%)	4 (2.45%)	3 (1.92%)	11 (6.32%)	
Syncope	10 (4.76%)	3 (1.84%)	2 (1.28%)	3 (1.72%)	
Cr (umol/L)	116.37 ± 85.08	113.92 ± 112.81	98.81 ± 83.35	145.95 ± 201.93	0.009
TG (mmol/L)	1.63 ± 0.95	1.52 ± 0.91	1.56 ± 0.90	1.59 ± 0.95	0.679
TC (mmol/L)	3.72 ± 0.92	3.81 ± 0.78	3.90 ± 0.94	4.16 ± 0.94	<0.001
HDL (mmol/L)	1.07 ± 0.30	1.13 ± 0.31	1.21 ± 0.42	1.23 ± 0.35	<0.001
LDL (mmol/L)	1.89 ± 0.83	1.89 ± 0.73	2.02 ± 0.87	2.18 ± 0.83	0.002
Management					0.494
Medical	75 (35.71%)	48 (29.45%)	48 (30.77%)	48 (27.59%)	
Endovascular	11 (5.24%)	14 (8.59%)	8 (5.13%)	10 (5.75%)	
Surgical	124 (59.05%)	101 (61.96%)	100 (64.10%)	116 (66.67%)	
Mortality (overall)					0.048
Survivor	124 (59.05%)	112 (68.71%)	108 (69.23%)	124 (71.26%)	
Non-survivor	86 (40.95%)	51 (31.29%)	48 (30.77%)	50 (28.74%)	
Mortality (operation)					0.076
Survivor	115 (85.19%)	106 (92.17%)	101 (93.52%)	117 (92.86%)	
Non-survivor	20 (14.81%)	9 (7.83%)	7 (6.48%)	9 (7.14%)	

BMI, body mass index; SBP, systolic blood pressure; DBP, diastole blood pressure; Cr, creatinine; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRI, chronic renal insufficiency; EF, ejection fraction.

RESULTS

Characteristics of Selected Patients at Baseline

Based on exclusion and inclusion criteria, 703 participants were included (**Figure 1**). The baseline characteristics of these selected participants are shown in **Table 1** in reference to the quartile admission SBP. The participant's average age was 50.48 ± 11.35 years and 76.24% of them were male. No statistically significant differences were observed for smoking, gender, Marfan syndrome, diabetes, bicuspid aortic valve, stroke, atherosclerosis, time to presentation, aortic regurgitation, abdominal vessel involvement, arch vessel involvement, EF value, symptom, TG, and management among different admission

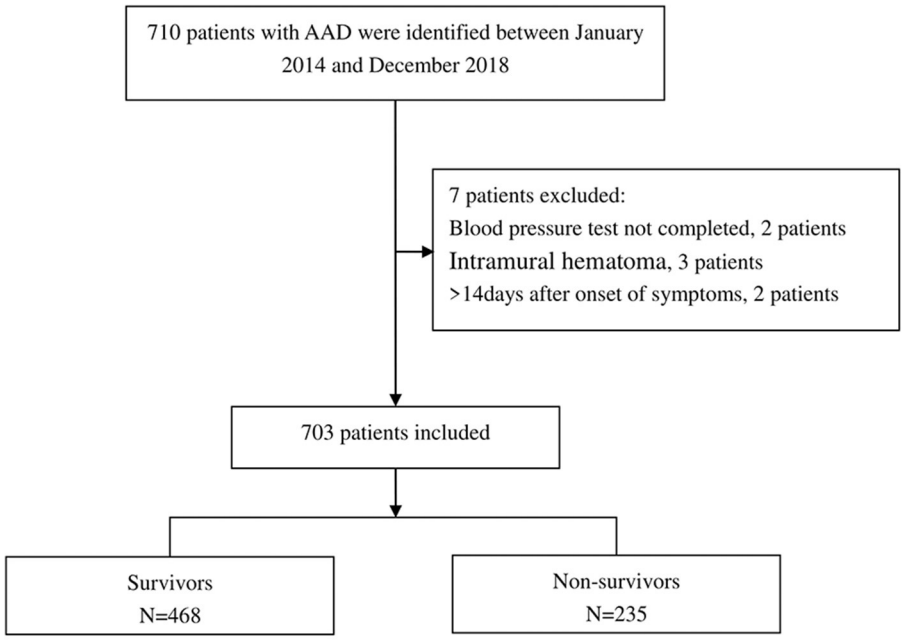

FIGURE 1 | Flow chart of patient enrollment.

SBP clusters (all *p values* = >0.05). Contributors with the uppermost group of admission SBP (Q4) had higher values in BMI, DBP, Cr, TC, HDL, LDL, hypertension, and CRI relative to the other groups. Similar patterns were observed for age and aortic diameter in Q2 groups, and mortality in Q1 groups. **Supplementary Tables 1, 2** show the causes of death in each quartile of operation (endovascular and surgical) patients and the rates of in-hospital complications for each quartile of medical management patients, respectively.

Univariate Analysis

Univariate analyses results (**Table 2**) revealed that gender (0.97, 0.67–1.40), BMI (1.00, 0.97–1.04), smoking (0.83, 0.58–1.18), hypertension (1.32, 0.94–1.86), diabetes (1.39, 0.59–3.31), mafan syndrome (1.34, 0.54–3.32), bicuspid aortic valve (0.66, 0.13–3.30), CRI (2.56, 0.99–6.56), stroke (2.04, 0.90–4.62), time to presentation (1.00, 0.99–1.00), aortic diameter (1.00, 0.99–1.02), aortic regurgitation (0.88, 0.64–1.21), abdominal vessel involvement (0.78, 0.54–1.13), arch vessel involvement (0.89, 0.63–1.25), EF value (0.99, 0.97–1.01), back pain (0.72, 0.28–1.87), abdominal pain (0.61, 0.24–1.54), syncope (1.22, 0.47–3.20), TG (1.16, 0.98–1.36), TC (1.04, 0.87–1.23), and LDL (0.83, 0.68–1.01) were not concomitant with the outcome variable. Additionally, SBP (0.91, 0.86–0.96), DBP (0.98, 0.97–0.99), HDL (0.50, 0.30–0.84), surgical (0.02, 0.01–0.03) and endovascular (0.01, 0.00–0.04) were negatively correlated with the outcome variable. Contrary to this, univariate analysis showed that age (1.02, 1.01–1.04), atherosclerosis (2.10, 1.17–3.79) and Cr (1.00, 1.00–1.00) correlated with the outcome variable.

Results of the Unadjusted and Adjusted Model

Three models were created in this experiment to examine the autonomous effects of admission SBP on in-hospital mortality after modifying for possible confounders. The effect values (OR) and 95% confidence intervals for these three equations are shown in **Table 3**. In the non-adjusted model (crude model), for every 10 mmHg rise in admission SBP, in-hospital death reduced by 9% (0.91, 95% CI 0.86–0.96). In the minimum-adjusted model (model I), admission SBP was greater by 10 mmHg and in-hospital mortality reduced by 9% (0.91, 95% CI 0.86–0.96). In the fully adjusted model (model II) (adjusted covariates are shown in **Table 1**, except DBP), for each additional 10 mmHg of admission SBP, in-hospital mortality reduced by 12% (0.88, 95% CI 0.80–0.96). We also converted admission SBP from a continuous variable to a categorical variable (Quartile). The P for trend of admission SBP with categorical variables in the fully adjusted model was constant with the result with admission SBP as a constant variable. However, when the admission SBP enters the fully-adjusted model as a categorical variable, the trend of the effective value in the different admission SBP group is non-equidistant. Based on this non-equidistant changes in effect size, there may be a non-linear relationship between in-hospital mortality and SBP admission.

The Non-linearity Results Between In-hospital Mortality and Admission SBP

The current study examined the non-linear correlation between in-hospital mortality and admission SBP (**Table 4**, **Figure 2**). The smooth curve outcome revealed that the relationship

TABLE 2 | Univariate analysis for in-hospital mortality.

	Statistics	OR (95%CI)	*P*-value
Age (years)	50.48 ± 11.35	1.02 (1.01, 1.04)	<0.001
Gender (female)	167 (23.76%)	0.97 (0.67, 1.40)	0.877
BMI (Kg/m^2)	25.21 ± 4.38	1.00 (0.97, 1.04)	0.817
Smoking	197 (28.02%)	0.83 (0.58, 1.18)	0.298
Hypertension	478 (67.99%)	1.32 (0.94, 1.86)	0.115
Diabetes	22 (3.13%)	1.39 (0.59, 3.31)	0.452
Marfan syndrome	20 (2.84%)	1.34 (0.54, 3.32)	0.529
Bicuspid aortic valve	8 (1.14%)	0.66 (0.13, 3.30)	0.614
CRI	18 (2.56%)	2.56 (0.99, 6.56)	0.051
Stroke	24 (3.41%)	2.04 (0.90, 4.62)	0.086
Atherosclerosis	48 (6.83%)	2.10 (1.17, 3.79)	0.013
Time to presentation (h, median [Q1–Q3])	20.00 (10.00–48.00)	1.00 (0.99, 1.00)	0.149
SBP(per 10 mmHg)	14.28 ± 3.11	0.91 (0.86, 0.96)	<0.001
DBP (mmHg)	77.80 ± 19.40	0.98 (0.97, 0.99)	<0.001
Aortic diameter (mm)	45.46 ± 10.32	1.00 (0.99, 1.02)	0.621
Aortic regurgitation	314 (44.67%)	0.88 (0.64, 1.21)	0.425
Abdominal vessel involvement	183 (26.03%)	0.78 (0.54, 1.13)	0.192
Arch vessel involvement	221 (31.44%)	0.89 (0.63, 1.25)	0.505
EF value (%)	65.07 ± 8.14	0.99 (0.97, 1.01)	0.345
Symptom			
Chest pain	581 (82.65%)	Ref	
Back pain	22 (3.13%)	0.72 (0.28, 1.87)	0.499
Abdominal pain	25 (3.56%)	0.61 (0.24, 1.54)	0.293
Syncope	18 (2.56%)	1.22 (0.47, 3.20)	0.684
Cr (umol/L)	119.23 ± 130.21	1.00 (1.00, 1.00)	0.003
TG (mmol/L)	1.58 ± 0.93	1.16 (0.98, 1.36)	0.087
TC (mmol/L)	3.89 ± 0.91	1.04 (0.87, 1.23)	0.678
HDL (mmol/L)	1.16 ± 0.35	0.50 (0.30, 0.84)	0.008
LDL (mmol/L)	1.99 ± 0.83	0.83 (0.68, 1.01)	0.057
Management			
Medical	219 (31.15%)	Ref	
Endovascular	43 (6.12%)	0.01 (0.00, 0.04)	<0.001
Surgical	441 (62.73%)	0.02 (0.01, 0.03)	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastole blood pressure; Cr, creatinine; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRI, chronic renal insufficiency; EF, ejection fraction.

TABLE 3 | Relationship between systolic blood pressure and in-hospital mortality in different models.

Exposure	Crude Model (OR, 95%CI, *P*)	Model I (OR, 95%CI, *P*)	Model II (OR, 95%CI, *P*)
SBP (mmHg, per 10 increments)	0.91 (0.86, 0.96) <0.001	0.91 (0.86, 0.96) <0.001	0.88 (0.80, 0.96) 0.005
SBP (mmHg) (quarter)			
Q1	Ref	Ref	Ref
Q2	0.66 (0.43, 1.01) 0.055	0.61 (0.40, 0.95) 0.029	0.60 (0.30, 1.21) 0.156
Q3	0.64 (0.41, 0.99) 0.046	0.65 (0.42, 1.01) 0.053	0.47 (0.22, 1.00) 0.050
Q3	0.58 (0.38, 0.89) 0.013	0.59 (0.38, 0.91) 0.016	0.44 (0.21, 0.94) 0.035
P for trend	0.012	0.018	0.025

Crude Model adjusted for none. Model I adjusted for age and gender. Model II adjusted for age, gender, BMI, smoking, hypertension, diabetes, Marfan syndrome, Bicuspid aortic valve, CRI, stroke, atherosclerosis, time to presentation, aortic diameter, aortic regurgitation, abdominal vessel involvement, arch vessel involvement, EF value, symptom, Cr, TG, TC, HDL, LDL, and management. BMI, body mass index; SBP, systolic blood pressure; Cr, creatinine; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRI, chronic renal insufficiency; EF, ejection fraction.

TABLE 4 | The results of the two-piecewise linear model (SBP per 10 increments).

	Mortality (OR, 95%CI)	*P*-value
Fitting model by standard linear regression	0.88 (0.80, 0.96)	0.005
Fitting model by two-piecewise linear regression		
Inflection point of SBP	120	
≤120	0.67 (0.51, 0.88)	0.004
>120	0.96 (0.85, 1.09)	0.554
P for log-likelihood ratio test	0.039	

Adjusted: age, gender, BMI, smoking, hypertension, diabetes, Marfan syndrome, Bicuspid aortic valve, CRI, stroke, atherosclerosis, time to presentation, aortic diameter, aortic regurgitation, abdominal vessel involvement, arch vessel involvement, EF value, symptom, Cr, TG, TC, HDL, LDL, and management. BMI, body mass index; SBP, systolic blood pressure; Cr, creatinine; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRI, chronic renal insufficiency; EF, ejection fraction.

between in-hospital mortality and admission SBP was non-linear (after amending for covariates presented in **Table 1** excepted DBP). We fit the association between in-hospital mortality and admission SBP using linear regression model and two-piecewise linear regression model, respectively. The *p-value* for the log-likelihood ratio test was <0.05. This result indicates dual piecewise linear regression was more appropriate for fitting the association between admission SBP and in-hospital mortality since it perfectly represents association between admission SBP and in-hospital mortality. The premeditated inflection point was 120 (mmHg) through two-piecewise linear regression and recursive algorithm. On the left side of the inflection point (SBP ≤120 mmHg), effect size and 95% CI was 0.67 and 0.51–0.88, respectively (SBP per 10 increments). On the right side of the inflection point (SBP >120 mmHg), effect size and 95% CI was 0.96 0.85–1.09, correspondingly (SBP per 10 increments).

Subgroup Analysis

We used gender, age, smoking, BMI, hypertension, diabetes, Marfan syndrome, bicuspid aortic valve, CRI, stroke, atherosclerosis, time to presentation, aortic diameter, aortic regurgitation, abdominal vessel involvement, arch vessel involvement, EF value, symptom, and management as the stratification variables to detect the development of effect sizes in these variables (**Table 5**). We observed that the deviation in the male population is more pronounced (p for interaction =

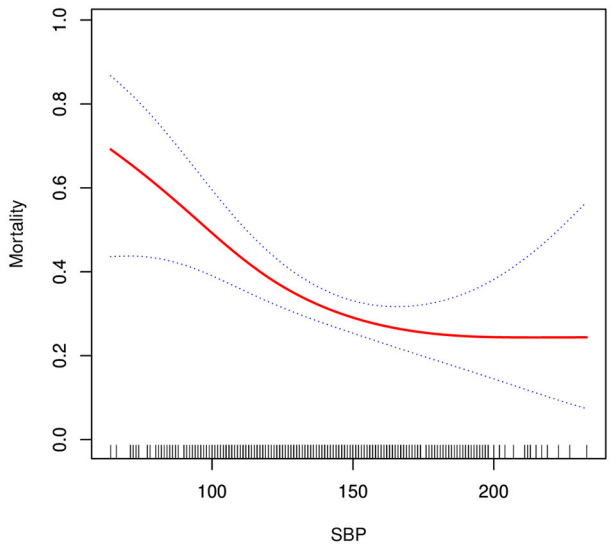

FIGURE 2 | Association between systolic blood pressure and in-hospital mortality. A non-linear association between systolic blood pressure and in-hospital mortality was found ($P = 0.009$) in a generalized additive model (GAM). The solid red line represents the smooth curve fit between variables. Blue bands represent the 95% confidence interval from the fit. All adjusted for age, gender, BMI, smoking, hypertension, diabetes, Marfan syndrome, Bicuspid aortic valve, CRI, stroke, atherosclerosis, time to presentation, aortic diameter, aortic regurgitation, abdominal vessel involvement, arch vessel involvement, EF value, symptom, Cr, TG, TC, HDL, LDL, and management.

0.036, 0.88 with male vs. 1.00 with female). A similar trend was observed in non-diabetics (p for interaction = 0.020, 0.90 with non-diabetics vs. 1.37 with diabetics).

DISCUSSION

In the fully adjusted model, we found that admission SBP negatively correlated with in-hospital mortality after fine-tuning other covariates. The model-based effect sizes can be interpreted as that a 10 mmHg rise in admission SBP is associated with 12% lower odds of in-hospital mortality. We also found non-linearity between admission SBP and in-hospital mortality. On the left side of the inflection point (SBP ≤120 mmHg), risk of in-hospital deaths in AAD patients was condensed by 33% for each extra 10 mmHg of admission SBP. On the right side of the inflection point (SBP > 120 mmHg), this relationship could not be observed [0.96 (95%CI 0.85–1.09), $p = 0.554$]. Moreover, subgroup analysis identified a stronger association between admission SBP and in-hospital mortality in males and non-diabetics.

In hypertension patients, lowering blood pressure decreases risk of cardiovascular events and death (10, 11), but the best target blood pressure is uncertain (12, 13). Large, randomized trials did not find benefit when blood pressure targets were <140/90 mmHg (14, 15). Additionally, several *post-hoc* analyses have demonstrated that the advantage of lowering blood pressure treatment might even be reversed below a certain threshold, which is called non-linear or J-curve phenomenon (16, 17).

TABLE 5 | Results of subgroup analysis and interaction analysis (SBP per 10 increments).

Characteristic	No.	OR	95%CI Low	95%CI High	*P* (interaction)
Age (years)					0.682
<60	536	0.90	0.85	0.96	
≥60	167	0.93	0.83	1.03	
Gender					0.036*
Male	536	0.88	0.83	0.93	
Female	167	1.00	0.90	1.11	
BMI (Kg/m^2)					0.920
<18.5	22	0.98	0.68	1.41	
≥18.5, <23	199	0.91	0.82	1.01	
≥23	482	0.90	0.85	0.96	
Smoking					0.483
no	506	0.92	0.86	0.98	
yes	197	0.88	0.79	0.98	
Hypertension					0.186
no	225	0.95	0.85	1.05	
yes	478	0.87	0.82	0.93	
Diabetes					0.020*
no	681	0.90	0.85	0.95	
yes	22	1.37	0.94	2.01	
Marfan syndrome					0.059
no	683	0.90	0.86	0.95	
yes	20	1.34	0.87	2.08	
Bicuspid aortic valve					0.928
no	695	0.91	0.86	0.96	
yes	8	0.85	0.47	1.55	
CRI					0.273
no	685	0.91	0.86	0.96	
yes	18	0.76	0.55	1.06	
Stroke					0.679
no	679	0.90	0.86	0.95	
yes	24	0.96	0.74	1.23	
Atherosclerosis					0.142
no	655	0.92	0.87	0.97	
yes	48	0.77	0.61	0.98	
Time to presentation (h)					0.656
Low (1.00–14.00)	256	0.90	0.84	0.97	
Middle (15.00–58.00)	254	0.86	0.78	0.95	
High (59.00–288.00)	193	0.92	0.78	1.09	
Aortic diameter (mm)					0.227
<35	67	0.82	0.67	1.00	
≥35	495	0.93	0.87	0.99	
Aortic regurgitation					0.155
no	389	0.88	0.82	0.94	
yes	314	0.95	0.88	1.03	
Abdominal vessel involvement					0.870

(Continued)

TABLE 5 | Continued

Characteristic	No.	OR	95%CI Low	95%CI High	*P* (interaction)
no	520	0.91	0.86	0.97	
yes	183	0.90	0.81	1.01	
Arch vessel involvement					0.757
no	482	0.91	0.86	0.97	
yes	221	0.90	0.82	0.99	
EF value (%)					0.551
<50	25	0.83	0.59	1.17	
≥50	528	0.92	0.86	0.98	
Symptom					0.115
Chest pain	581	0.91	0.86	0.96	
Back pain	22	0.67	0.45	0.99	
Abdominal pain	25	0.95	0.71	1.27	
Syncope	18	0.55	0.29	1.06	
Management					0.302
Medical	219	0.95	0.84	1.07	
Endovascular	43	1.08	0.71	1.63	
Surgical	441	0.85	0.76	0.95	

BMI, body mass index; CRI, chronic renal insufficiency; EF, ejection fraction.

A series of studies have associated blood pressure with in-hospital mortality of AAD patients (18, 19). However, they did not perform non-linearity and subgroup analyses. Although Bossone et al. (20) found the relationship between in-hospital mortality and SBP in AAD patients to be non-linear, they did not elaborate on this. Consequently, the impact of this study was the innovation of a J-shaped curve and threshold effect on the link between admission SBP and in-hospital deaths in AAD patients.

Subgroup analyses are very important for scientific studies (21). They help us to a better understanding of the independent relationship between the admission of in-hospital deaths and SBP for AAD patients. In this study, we used gender, age, smoking, hypertension, BMI, diabetes, bicuspid aortic valve, Marfan syndrome, CRI, stroke, atherosclerosis, time to presentation, aortic diameter, aortic regurgitation, abdominal vessel involvement, arch vessel involvement, EF value, symptom, and management as stratification variables, of which interactions were observed in male and non-diabetes patients.

The following are the clinical values of this experiment: (1) to the best of our knowledge, this is the first report of the threshold effect between SBP admission and in-hospital death in AAD patients, (2) our findings may guide future studies on models (diagnostic and predictive) of in-hospital death rates in AAD patients. However, the improvement of research results is needed for clinical treatment decisions.

There are certain strengths in this study. (1) Non-linearity is higher, offering room for exploration; (2) As a result of observational study, strict statistical adjustments were used to reduce residual confounders; (3) Target independent variables were handled equally as continuous and categorical variables. Such an approach can decrease contingency in data analysis and heighten the strength of results; (4) the effect modifier factor analysis improves data use and produces stable conclusions in diverse subgroups in this study.

This study has some limitations. First, our discoveries are based on a Chinese population, reducing the generalizability of our findings. Second, patients with little or high SBP may have died before getting to hospital, lowering the prevalence of sicker patients. Third, blood pressure pharmacologic management in AAD patients was done by physicians in accordance with recent guidelines but this was not protocol-driven. Our current data cannot prove whether this factor will affect patient outcomes. Lastly, pre-hospital medication and emotion were not available, which may affect blood pressure.

CONCLUSIONS

The relationship between admission SBP and in-hospital mortality is not linear. At ≤120 mmHg, SBP correlation to in-hospital mortality is negative.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Second Xiangyang Hospital of Central South University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The manuscript writing and collection of patient information was done by GY. Data collection was done by WP, HH, XL, YZ, and XP. The patients' general indices were analyzed and interpreted by XC. The final manuscript was read and approved by all authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.542212/full#supplementary-material

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ORIGINAL RESEARCH
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The Non-linear Relationship Between Normal Range Systolic Blood Pressure and Cardiovascular or All-Cause Mortality Among Elderly Population

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Purpose: The aim was to explore the association of normal range SBP with cardiovascular and all-cause mortality in older adults without hypertension.

Methods: Participants aged ≥ 65 years without hypertension and those had an SBP level between 90 and 129 mmHg were included from the National Health and Nutrition Examination Survey (1999–2014). SBP was categorized into: 90–99, 100–109, 110–119, and 120–129 mmHg. Multivariate Cox regression was performed with hazard ratio (HR) and 95% confidence interval (CI).

Results: Of the 1,074 participants, 584 were men (54.38%). Compared with participants with SBP level ranged 110 to 119 mmHg, the HRs for all-cause mortality risk was 1.83 (95% CI: 1.04, 3.23) for SBP level ranged 90 to 99 mm Hg, 0.87 (95% CI: 0.54, 1.41) for SBP level ranged 100 to 109 mmHg, and 1.30 (95% CI: 0.96, 1.75) for SBP level ranged 120 to 129 mmHg (P for trend = 0.448), and the HR for cardiovascular mortality risk was 3.30 (95% CI: 0.87, 12.54) for SBP level ranged 90 to 99 mmHg, 0.35(95% CI: 0.08, 1.56) for SBP level ranged 100 to 109 mmHg, and 1.75 (95% CI: 0.78, 3.94) for SBP level ranged 120 to 129 mm Hg (P for trend = 0.349) after confounders were adjusted.

Conclusion: These were a nonlinear association of normal range SBP level with all-cause and cardiovascular death in older adults.

Keywords: normal blood pressure, systolic blood pressure, elderly population, cardiovascular mortality, all-cause mortality

INTRODUCTION

Hypertension is one of the most common chronic diseases and remains the leading cause of death in worldwide (1). Hypertension is generally defined as having a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg, and prehypertension was a SBP of 120–139 mmHg and/or a DBP of 80-89 mmHg (2–5). In addition, prehypertension was further divided into low (120–129/80–84 mmHg) and high (130–139/80–89 mmHg) prehypertension,

respectively (6). Several previous meta-analyses demonstrated the increased risk for cardiovascular diseases (CVD) in people with low-range prehypertension, and a higher risk for mortality despite adjusting for cardiovascular risk factors (7–10). Furthermore, a recent study showed an increment of the risk of incident CVD with increasing SBP levels in persons without hypertension nor other traditional atherosclerotic cardiovascular disease risk factors (11). However, previous studies were mainly conducted among young and middle-aged population, but the evidence for older adults aged ≥ 65 years is lacking. Importantly, in 2017, the definition of hypertension has been adjusted to 130/80 mm Hg with a SBP/DBP by the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guidelines (12). These changes were largely driven by the increasing importance of hypertension control in preventing CVD (12, 13). Importantly, among elderly population free of hypertension, the association of 2017 ACC/AHA elevated hypertension (120–129/80mmHg) and normal blood pressure (<120/80 mmHg) with the risk of mortality were still unclear. To address the knowledge gap, the aim of the present study was to explore the association of SBP level with cardiovascular and all-cause mortality in elderly population without hypertension.

METHODS

Study Population

All participants were included from the 1999–2014 National Health and Nutrition Examination Surveys (NHANES). NHANES was an ongoing nationally representative study with a series of stratified, multistage probability surveys on United States civilian, non-institutionalized population, which was conducted by the National Center for Health Statistics of the Center for Disease Control and Prevention (14, 15). We enrolled subjects aged ≥ 65 years old. However, participants aged < 65 years, with missing data on follow-up, blood pressure, blood lipid, height and weight, past medical history, education level, marital status and smoking status at baseline were excluded. In addition, participants with hypertension and SBP < 90 mmHg were also excluded. Finally, a total of 1,074 participants were included for data analysis (**Figure 1**). The survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention. All participants have provided written informed consent.

Blood Pressure Measurement

Details of blood pressure measurement was described previously (15, 16). In brief, it was measured by a trained physician using a mercury sphygmomanometer [W. A. Baum Co. Inc (1050), Copiague, New York, USA] and an appropriately sized cuff. Three consecutive blood pressure readings were obtained from the same arm. SBP and diastolic blood pressure (DBP) were defined as the average value of three blood pressure measurements. Hypertension was defined as a previous diagnosis by a physician, and/or SBP/DPB ≥130/80 mmHg, and/or currently taking antihypertensive medications according to the 2017 ACC/AHA hypertension guideline (12). SBP level ranged from 90 to 129 mmHg was considered normal range. Participants

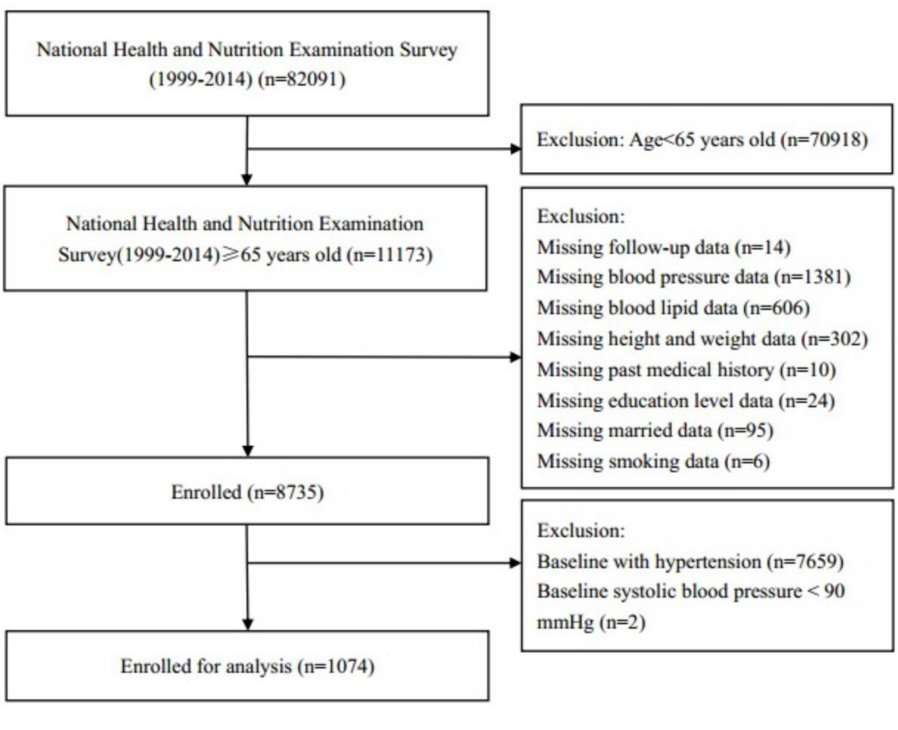

FIGURE 1 | Research flow chart.

were divided into four groups according to baseline SBP: 90–99, 100–109, 110–119, and 120–129 mmHg.

Covariate Assessment

Data from questionnaires and physical examination were obtained according to a standardized procedure. Age, sex, race, marital status, smoking status, educational level, and history of comorbidities (including hypertension, diabetes, CVD and cancer) were self-reported during in-person interview. Medication history was obtained from self-report and the questions on prescribed medications. Other covariates included height, weight, total cholesterol, high-density lipoprotein cholesterol were also assessed. Body mass index (BMI) was defined as mass (kg) divided by the square of height (m^2). Diabetes was defined as having a history of diabetes, or taking hypoglycemic medications currently, or fasting blood glucose

TABLE 1 | Demographic and clinical characteristics according to normal systolic blood pressure levels.

		Systolic blood pressure, mmHg				
	Total	**90–99**	**100–109**	**110–119**	**120–129**	***P*-value**
Number	1074	41	162	401	470	
Age, years	72.20 ± 5.62	72.02 ± 5.33	71.86 ± 5.51	71.76 ± 5.49	72.71 ± 5.76	0.074
Sex, *n* (%)						0.774
Male	584 (54.38)	20 (48.78)	85 (52.47)	224 (55.86)	255 (54.26)	
Female	490 (45.62)	21 (51.22)	77 (47.53)	177 (44.14)	215 (45.74)	
Race, *n* (%)						0.593
Non-white	396 (36.87)	11 (26.83)	60 (37.04)	148 (36.91)	177 (37.66)	
White	678 (63.13)	30 (73.17)	102 (62.96)	253 (63.09)	293 (62.34)	
Marital status, *n*(%)						0.813
Married	415 (38.64)	16 (39.02)	68 (41.98)	151 (37.66)	180 (38.30)	
Other	659 (61.36)	25 (60.98)	94 (58.02)	250 (62.34)	290 (61.70)	
Education level, *n* (%)						0.226
Less than high school	346 (32.22)	11 (26.83)	44 (27.16)	126 (31.42)	165 (35.11)	
High school or above	728 (67.78)	30 (73.17)	118 (72.84)	275 (68.58)	305 (64.89)	
Smoking, *n* (%)						0.595
No	487 (45.34)	19 (46.34)	76 (46.91)	171 (42.64)	221 (47.02)	
Yes	587 (54.66)	22 (53.66)	86 (53.09)	230 (57.36)	249 (52.98)	
Body mass index, kg/m^2	26.40 ± 4.79	25.03 ± 5.22	25.69 ± 5.06	26.58 ± 4.75	26.61 ± 4.66	0.038
Systolic blood pressure, mmHg	117.18 ± 8.47	95.86 ± 2.50	105.84 ± 2.79	115.07 ± 2.94	124.74 ± 2.92	<0.001
Diastolic blood pressure, mmHg	63.21 ± 11.53	53.64 ± 13.65	60.17 ± 12.01	63.31 ± 10.66	65.02 ± 11.28	<0.001
Total cholesterol, mg/dl	203.68 ± 39.41	215.44 ± 48.47	198.57 ± 38.88	201.32 ± 36.87	206.43 ± 40.52	0.018
HDL cholesterol, mg/dl	56.17 ± 16.49	62.98 ± 19.84	58.03 ± 14.96	54.81 ± 16.01	56.09 ± 16.93	0.008
Comorbidities, *n* (%)						
Diabetes						0.293
No	913 (85.01)	37 (90.24)	140 (86.42)	347 (86.53)	389 (82.77)	
Yes	161 (14.99)	4 (9.76)	22 (13.58)	54 (13.47)	81 (17.23)	
Cardiovascular disease						0.835
No	969 (90.22)	37 (90.24)	143 (88.27)	364 (90.77)	425 (90.43)	
Yes	105 (9.78)	4 (9.76)	19 (11.73)	37 (9.23)	45 (9.57)	
Cancer						0.521
No	839 (78.12)	29 (70.73)	123 (75.93)	319 (79.55)	368 (78.30)	
Yes	235 (21.88)	12 (29.27)	39 (24.07)	82 (20.45)	102 (21.70)	
Outcomes, *n* (%)						
Cardiovascular disease mortality						0.158
No	1027 (95.62)	38 (92.68)	159 (98.15)	386 (96.26)	444 (94.47)	
Yes	47 (4.38)	3 (7.32)	3 (1.85)	15 (3.74)	26 (5.53)	
All-cause mortality						<0.001
No	794 (73.93)	25 (60.98)	131 (80.86)	313 (78.05)	325 (69.15)	
Yes	280 (26.07)	16 (39.02)	31 (19.14)	88 (21.95)	145 (30.85)	

n, number; HDL, high density lipoprotein.
Values are mean ± standardized differences or n (%).

level ≥ 7.0 mmol/l (126 mg/dl), or hemoglobin A1c (HbA1C) level ≥ 6.5% (17). Further details of data collection can be found in https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Outcomes

Outcomes of this study mainly were all-cause and cardiovascular mortality as obtained from a publicly available dataset of the NHANES. The database captured the vital status and cause of death of survey subjects from baseline to 31 December 2015 which came first (16). Cardiovascular mortality was defined according to the International Classification of Diseases, 10th Edition, Clinical Modification System codes (I00–I09, I11, I13, I20–I51, and I60–I69) derived from death-certificate data.

Statistical Analysis

Baseline characteristics are presented as mean ± standard deviation (continuous variables) or percentage (categorical variables) as appropriate. We compared baseline characteristics among participants according to SBP level using Chi-square for categorical variables, and Analysis of Variance for continuous

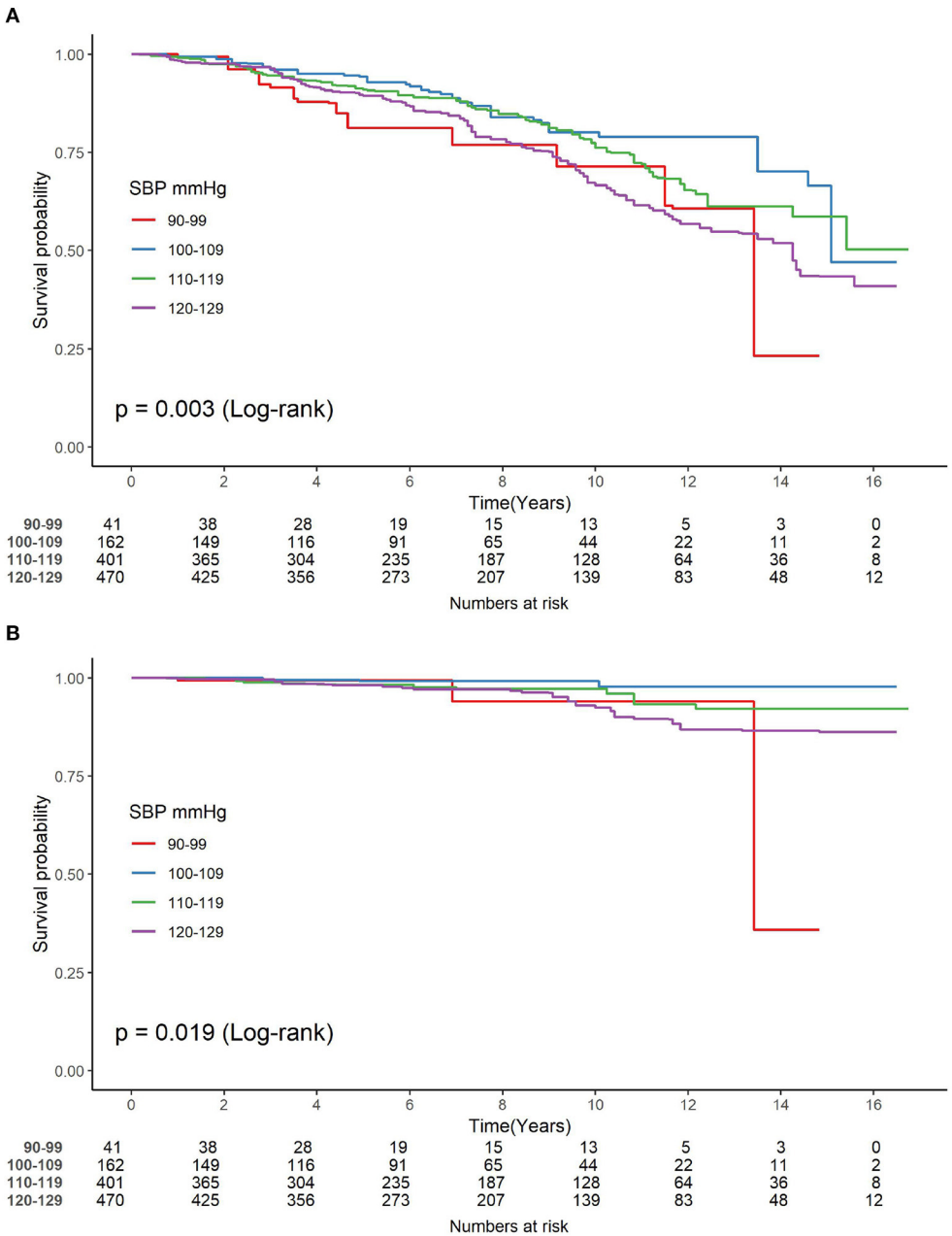

FIGURE 2 | (A,B) Kaplan-Meier analysis for the incidence of mortality among groups of different normal systolic blood pressure level. SBP, systolic blood pressure.

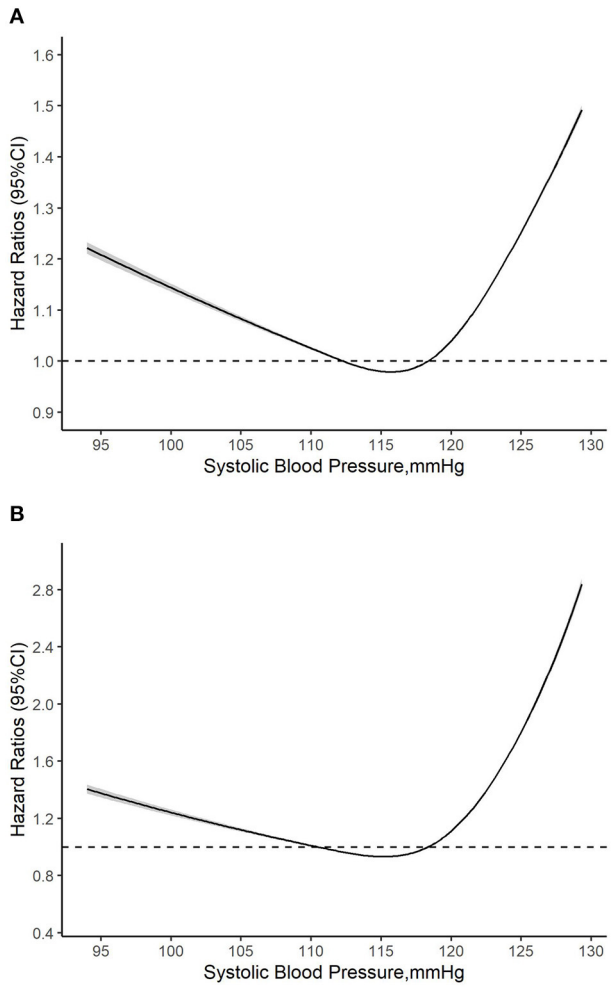

FIGURE 3 | (A,B) Multivariate adjusted restricted cubic curve for the relationship between normal systolic blood pressure and mortality. HR, hazard ratio; CI, confidence interval. Age, sex, race, marital status, education level, smoking, body mass index, diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, and comorbidities (diabetes, cardiovascular disease, and cancer) were all adjusted.

variables, respectively. Standardized Kaplan-Meier curves were used for survival analysis, and log-rank test was used to compare the differences in survival rate by SBP levels. The relationship between SBP levels and all-cause or cardiovascular mortality was examined by using Cox proportional hazards regression models, and hazard ratios (HRs) and 95% confidence interval (CI) were calculated. Model I only included SBP, and Model II was additionally adjusted for age, race, and sex. Model III was further adjusted for marital status, education level, smoking status, body mass index, DBP, total cholesterol, high density lipoprotein cholesterol, and pre-existing comorbidities (diabetes, cardiovascular disease, and cancer). Subgroup analysis were conducted according to body mass index (< 25 or ≥ 25 kg/m^2), sex (male and female), diabetes (yes and no), and race (White and non-White). Their interactions between diabetes and prehypertension status with all-cause and cardiovascular mortality were also tested. Given the inherent nature of multiple complex survey designs, we accounted for sample weight for each participant in the NHANES dataset. We used svydesign function in R to account for sampling weights, as well as the stratification and clustering. A 2-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

The baseline demographic characteristics were presented in **Table 1**. The study population included 1,074 subjects [584 (54.38%) male], average age was 72.20 ± 5.62 years. Participants with higher SBP level also had higher BMI, total cholesterol and DBP. However, there were no significant differences in age, sex, race, marital status, education level, smoking status, and comorbidities among SBP groups.

The Relationship Between Systolic Blood Pressure and Mortality

During a median follow-up of 89.41 months, 47 (4.38%) cases of cardiovascular and 280 (26.07%) cases of all-cause mortality were observed, respectively. In addition, among all the 1,074 participants, there were 16 (39.02%), 31 (19.14%), 88 (21.95%) and 145 (30.85%) cases of all-cause mortality occurred ranging from 90–99 mmHg for SBP, 100–109 mmHg, 110–119 mmHg to 120–129 mmHg ($P < 0.001$), and 3 (7.32%), 3 (1.85%), 15 (3.74%), 26 (5.53%) cases of cardiovascular mortality occurred, respectively, among the above four groups ($P = 0.158$). **Figure 2** showed the Kaplan-Meier mortality rate by the groups according to SBP level. The log-rank test revealed that there was a significant difference among each group of SBP in all-cause mortality (**Figure 2A**) and cardiovascular mortality (**Figure 2B**).

As shown in **Figure 3**, the multivariate restrictive cubic curves showed that SBP has a non-linear relationship with all-cause (**Figure 3A**) and cardiovascular (**Figure 3B**) mortality, respectively. In addition, the risk of mortality may be the lowest when the SBP range from 110 to 119 mmHg. As shown in **Table 2**, when SBP was treated as a continuous variable, SBP has no obvious relationship with all-cause and cardiovascular mortality regardless of confounder adjustments (all $P > 0.05$). However, when SBP was referred as a categorical variable, compared with participants with an SBP level of 110 to 119 mmHg, there seemed to be a significantly higher risk for all-cause mortality among participants with an SBP level of 90 to 99 mmHg (HR, 1.56; 95% CI, 0.86, 2.82) and 120 to 129 mmHg (HR, 1.36; 95% CI, 1.03, 1.80) (P for trend = 0.113) in Model I. In Model III where age, sex, race, marital status, education level, smoking, body mass index, DBP, total cholesterol, high density lipoprotein cholesterol, and comorbidities (diabetes, CVD, and cancer) were adjusted, similar increment of all-cause mortality risk was observed among participants with an SBP level of 90

TABLE 2 | Multivariate Cox regression analysis of normal systolic blood pressure with mortality.

	Number	Model I HR (95%CI), *P*-value	Model II HR (95%CI), *P*-value	Model III HR (95%CI), *P*-value
All-cause mortality				
SBP (per 10 mmHg increment)	1074	1.16(0.98,1.38)0.085	1.06(0.87,1.29)0.576	1.09(0.89,1.35)0.402
Each 10 mmHg increase in participants with SBP < 115 mmHg	410	1.02(0.68,1.54)0.923	0.91(0.62,1.35)0.645	1.02(0.67,1.57)0.923
Each 10 mmHg increase in participants with SBP ≥ 115 mmHg	664	1.60(1.18,2.16)0.002	1.58(1.15,2.19)0.005	1.61(1.14,2.29)0.008
SBP group, mmHg				
90–99	41	1.56(0.86,2.82)0.145	2.01(1.10,3.64)0.022	1.83(1.04,3.23)0.037
100–109	162	0.81(0.50,1.29)0.367	0.89(0.56,1.43)0.636	0.87(0.54,1.41)0.581
110–119	401	1.0	1.0	1.0
120–129	470	1.36(1.03,1.8)0.031	1.27(0.96,1.68)0.089	1.30(0.96,1.75)0.086
P for trend		0.113	0.592	0.448
Cardiovascular mortality				
SBP (per 10 mmHg increment)	1074	1.09(0.88,1.34)0.449	1.25(0.71,2.23)0.441	1.36(0.79,2.35)0.269
Each 10 mmHg increase in participants with SBP < 115 mmHg	378	0.78(0.22,2.76)0.703	0.58(0.20,1.7)0.324	0.70(0.25,1.97)0.499
Each 10 mmHg increase in participants with SBP ≥ 115 mmHg	696	2.31(1.02,5.25)0.045	2.36(1.06,5.27)0.036	2.71(1.07,6.88)0.036
SBP group, mmHg				
90–99	41	2.54(0.64,10.05)0.185	3.18(0.78,13.02)0.107	3.30(0.87,12.54)0.080
100–109	162	0.35(0.08,1.48)0.152	0.38(0.09,1.64)0.194	0.35(0.08,1.56)0.170
110–119	401	1.0	1.0	1.0
120–129	470	1.58(0.69,3.59)0.277	1.57(0.73,3.36)0.245	1.75(0.78,3.94)0.176
P for trend		0.418	0.544	0.349

SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval.
Model I adjust for none.
Model II adjust for age, sex, and race.
Model III adjust for age, sex, race, marital status, education level, smoking, body mass index, diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, and comorbidities (diabetes, cardiovascular disease, and cancer).

to 99 mmHg (HR, 1.83; 95% CI, 1.04, 3.23; $P = 0.037$) and 120 to 129 mmHg (HR, 1.30; 95% CI, 0.96, 1.75; $P = 0.086$) (P for trend = 0.448). As for cardiovascular mortality, all-cause mortality risk was also seemed to be higher among participants with an SBP level of 90 to 99 mmHg (HR, 3.30; 95% CI, 0.87, 12.54; $P = 0.080$) and 120 to 129 mmHg (HR, 1.75; 95% CI, 0.78, 3.94; $P = 0.176$), but the association did not reach statistical significance.

Subgroup Analysis

The result of subgroup analysis was shown in **Table 3**. Compared to the reference group (SBP: 110–119 mmHg), participants with the level of SBP 90–99 mmHg had a higher risk of all-cause mortality among female population compared to male population (HR: 3.01 vs. 1.58), non-White population compared to White population (HR: 3.08 vs. 1.89), for people with BMI ≥ 25 compared to BMI< 25 kg/m^2 (HR: 3.12 vs. 1.09) and those without diabetes compared to those with diabetes (HR: 2.23 vs. 0.67). Similar results were also found in participants with the level of SBP was 120–129 mmHg. When the level of SBP was 90–99 mmHg, and compared to the reference group, we only found the risk for cardiovascular mortality might be higher in women, White population, without diabetes and people with BMI < 25 kg/m^2 (all $P < 0.05$). However, when the level of SBP was 120–129 mmHg, and compared to the reference group, we only found the risk for cardiovascular mortality might be higher in people with BMI ≥ 25 kg/m^2 (HR, 2.93; 95% CI, 1.19, 7.21; $P = 0.019$). In addition, we found that only BMI interacted significantly with the association between SBP and cardiovascular mortality (P for interaction = 0.012), while there were no interaction between sex, race, diabetes status and cardiovascular and all-cause mortality (all P-interaction > 0.05).

DISCUSSION

The main findings from the present study of older individuals with normal blood pressure were (1) when SBP <115 mmHg, as SBP decreased, the risk of mortality gradually increased, and when SBP ≥115 mmHg the risk of mortality gradually increased with SBP level. The appropriate SBP level is probably 110–120 mmHg. (2) The risk for cardiovascular mortality was increased at a SBP ≥ 115 mmHg. (3) Although SBP was in the normal range, relatively higher or lower SBP levels have a higher risk of mortality in women and population with overweight or obesity. (4) The relationship between normal SBP and all-cause mortality was differed by sex, race, BMI, and the history of diabetes. (5) The SBP level in the normal range might have dose-response relationship with all-cause and cardiovascular mortality.

Our findings were consistent with a prior meta-analysis of individual data for one million adults in 61 prospective studies, which demonstrated that usual SBP ≥115 mm Hg might significantly elevate the risk for all-cause and cardiovascular

TABLE 3 | Subgroups analyses of normal systolic blood pressure with mortality.

		Systolic blood pressure, mmHg Hazard ratios (95%CI), *P*-value				
Characteristic	**Number**	**90–99**	**100–109**	**110–119**	**120–129**	***P*-interaction**
All-cause mortality						
Sex						0.578
Male	584	1.58(0.76,3.27)0.219	0.65(0.38,1.10)0.108	1.0	1.01(0.69,1.47)0.972	
Female	490	3.01(1.31,6.94)0.010	1.45(0.56,3.75)0.446	1.0	1.88(0.98,3.62)0.059	
Race						0.721
Non-white	396	3.08(0.78,12.07)0.107	0.97(0.40,2.35)0.943	1.0	1.90(0.96,3.76)0.066	
White	678	1.89(1.03,3.45)0.039	0.91(0.53,1.56)0.732	1.0	1.27(0.91,1.77)0.157	
Body mass index, kg/m^2						0.560
<25	456	1.09(0.49,2.41)0.837	0.62(0.31,1.21)0.161	1.0	1.14(0.74,1.77)0.558	
≥25	618	3.12(1.46,6.68)0.003	1.14(0.53,2.45)0.744	1.0	1.52(1.01,2.28)0.046	
Diabetes						0.082
No	913	2.23(1.22,4.08)0.009	0.84(0.46,1.52)0.564	1.0	1.45(1.04,2.03)0.029	
Yes	161	0.67(0.11,4.15)0.669	1.10(0.4,2.97)0.857	1.0	0.86(0.31,2.41)0.771	
Cardiovascular mortality						
Sex						0.605
Male	584	1.49(0.19,11.89)0.709	0.37(0.07,1.99)0.248	1.0	1.59(0.58,4.34)0.364	
Female	490	18.7(2.16,161.92)0.008	0.38(0.04,3.22)0.372	1.0	2.37(0.54,10.28)0.251	
Race						0.731
Non-white	396	0.00 (0.00, Inf) 0.999	0.67(0.05,8.24)0.754	1.0	0.92(0.22,3.77)0.909	
White	678	4.81(1.05,22.09)0.043	0.47(0.09,2.53)0.381	1.0	2.52(0.96,6.58)0.059	
Body mass index, kg/m^2						0.012
<25	456	7.40(1.36,40.14)0.02	0.95(0.11,8.1)0.964	1.0	1.21(0.32,4.49)0.778	
≥25	618	1.15(0.11,12.33)0.908	0.00 (0.00, Inf) 0.997	1.0	2.93(1.19,7.21)0.019	
Diabetes						0.662
No	913	6.31(1.56,25.5)0.01	0.57(0.11,2.96)0.506	1.0	2.25(0.93,5.44)0.073	
Yes	161	0.66(0.04,11.12)0.774	0.00 (0.00, Inf) 0.999	1.0	3.04(0.59,15.57)0.182	

CI, confidence interval.

When analyzing a subgroup variable, age, sex, race, marital status, education level, smoking, body mass index, diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, and comorbidities (diabetes, cardiovascular disease, and cancer) were all adjusted except the variable itself.

mortality (18). However, some studies have found that when SBP (120–139 mmHg) did not significantly increase the risk of death among elder population (19–21). Although we found that SBP >115 mmHg in the elderly might increase the mortality risk for older adults, it was still unclear whether blood pressure treatment should be initiated earlier. Currently, a large number of hypertension guidelines recommend pharmacological treatment to be initiated when SBP/DBP ≥140/90 mm Hg in population with aged ≥ 65 years, and if tolerable, the SBP can be reduced to <130 mm Hg (1, 3, 4). The post-analysis of the Felodipine Event Reduction (FEVER) trial found that when the average blood pressure level after treatment was lower than 120/70 mmHg, the risk of stroke, cardiac events and total death were the lowest (22). SBP intervention trial (SPRINT) also demonstrated that targeting a SBP of <120 mmHg compared to <140 mmHg could significantly result in the lower rates of fatal and non-fatal major cardiovascular events and all-cause mortality (23).However, for patients with type 2 diabetes, targeting a SBP of <120 mm Hg, as compared with <140 mm Hg, did not reduce the rate of a composite outcome of fatal and non-fatal major cardiovascular events (24). Therefore, more studies on blood pressure management among elderly may be needed in the future, which may help to refine the SBP target (<120 mmHg) for older adults in line with the results from SPRINT, JATOS, VALISH trials. Besides, our finding might suggest a lower blood pressure threshold to define hypertension in elderly people.

In addition, subgroup analysis showed that the relationship between normal SBP and all-cause mortality was differed by sex, race, overweight/obesity, and diabetes. A previous meta-analysis also showed a sex difference in the relationship between SBP and death in elder population (18). Among ambulatory adults aged 75 years or older, treating to an SBP target of <120 mm Hg compared with an SBP target of <140 mm Hg has resulted in significantly lower rates of fatal and non-fatal major cardiovascular events and death from any cause (25). We found that SBP of 120–129 mm Hg might increase risk for all-cause mortality among subjects without diabetes, but SBP <120 mm Hg did not, and this observation was similar to previous studies (24, 26). We also found that older adults with BMI ≥ 25 kg/m^2 with a SBP of 120–129 mm Hg significantly increased the risk

of all-cause and cardiovascular mortality. For the elderly with overweight or obesity, they might benefit more by having SBP < 120 mm Hg.

To cautiously interpret our findings, some limitations of the present study should be noted. First, the small sample size might limit the generalizability of findings. Second, SBP was only measured once at baseline. Third, multiple covariates self-reported, therefore recall bias was possible. Fourth, this study did not fully consider the residual confounding effects, for example, atherosclerotic cardiovascular disease score and physical activity and diet. Fifth, we only explored the association of SBP with mortality, but not with adverse CVD events. Sixth, in this study, very few participants aged ≥g80 years, and there was no relevant data on frail, disability indices, and dementia/cognitive decline. Another limitation is that the cardiovascular event rate was low in a long follow-up, which is possible that the participants are normotensive at the beginning of study, therefore they have a lower risk of CVD over the years. Despite this issue, the direction of association between SBP and CVD mortality agrees with our overall findings. Besides, the present study had several strengths. On the one hand, NHANES have a rigorous and standardized study protocol, and have an extensive quality control procedure in data collection. On the other hand, the long period of follow up and the inclusion of multiple ethnic groups made this result reliable. Besides, this is one of the few studies to explore the relationship between SBP and all-cause and cardiovascular mortality in elderly normotensive subjects over such a long-term, prospective follow-up.

CONCLUSIONS

In conclusion, SBP might have a dose-response relationship with all-cause and cardiovascular mortality in older normotensive population. Despite having normal range of SBP, low SBP (90 to 99 mmHg) or elevated SBP (120 to 129 mmHg) might increase the risk of all-cause mortality for older adults. The blood pressure management of the elderly population should be individualized, and more attention needed to be paid to the elderly individuals without hypertension.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Centers for Disease Control and Prevention. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Using Latent Class Analysis to Identify Different Risk Patterns for Patients With Masked Hypertension

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Background: There is controversy whether masked hypertension (MHT) requires additional intervention. The aim of this study is to evaluate whether MHT accompanied with high-risk metabolic syndrome (MetS), as the subphenotype, will have a different prognosis from low-risk MetS.

Methods: We applied latent class analysis to identify subphenotypes of MHT, using the clinical and biological information collected from High-risk Cardiovascular Factor Screening and Chronic Disease Management Programme. We modeled the data, examined the relationship between subphenotypes and clinical outcomes, and further explored the impact of antihypertensive medication.

Results: We included a total of 140 patients with MHT for analysis. The latent class model showed that the two-class (high/low-risk MetS) model was most suitable for MHT classification. The high-risk MetS subphenotype was characterized by larger waist circumference, lower HDL-C, higher fasting blood glucose and triglycerides, and prevalence of diabetes. After four years of follow-up, participants in subphenotype 1 had a higher non-major adverse cardiovascular event (MACE) survival probability than those in subphenotype 2 ($P = 0.016$). There was no interaction between different subphenotypes and the use of antihypertensive medications affecting the occurrence of MACE.

Conclusions: We have identified two subphenotypes in MHT that have different metabolic characteristics and prognosis, which could give a clue to the importance of tracing the clinical correlation between MHT and metabolic risk factors. For patients with MHT and high-risk MetS, antihypertensive therapy may be insufficient.

Keywords: masked hypertension, metabolic risk factor, community-based study, latent class analysis, risk patterns

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INTRODUCTION

Masked hypertension (MHT) is characterized by office readings suggesting normal BP but out-of-office readings, such as ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring, being consistently above normal (1). Meta-analysis and recent studies have shown that the risk of cardiovascular events in MHT patients is higher than in normotensive patients, whose risk is close to that of patients with persistent hypertension (2–4). With the presence of metabolic

abnormalities and hypertension-mediated organ damage, the cardiovascular risk level in MHT patients might be high (5, 6). The latest arterial hypertension guideline points out that avoiding bad habits in daily life are recommended as the management for MHT to reduce cardiovascular risk (Class I, Level C), but there still lacks risk stratification of MHT to guide treatment (1).

Metabolic syndrome (MetS), as a special "disease state" resulting from an excess of stored and/or circulating energy, is associated with elevations in blood pressure (BP) (7). Although it is generally recognized that metabolic abnormalities are heterogeneous in common chronic diseases (such as diabetes and hypertension), and there is evidence that diabetic patients with different metabolic subphenotypes have different prognoses (8, 9), it is still unknown whether MHT with high-risk MetS is regarded as a subphenotype and whether it has a worse prognosis than low-risk MetS.

Latent class analysis (LCA), a well-proven statistical technique that uses mixed modeling to find the best-fit model for different populations based on baseline data classification, has been used widely to identify subphenotypes of many diseases (10). In this study, we assume that there are different subphenotypes of MHT patients, and distinguish MHT patients based on high or low-risk MetS in an LCA model to identify latent classes and observe their natural prognosis.

MATERIALS AND METHODS

This study was performed in accordance with the principles of the Helsinki Declaration II and approved by the Ethics Committee of Guangdong Provincial People's Hospital. All participants were informed and their consent to participate in this study was obtained.

Study Population

This study was designed as a prospective cohort study consecutively enrolling MHT patients who had participated in the High-Risk Cardiovascular Factor Screening and Chronic Disease Management Programme, a project that organized by the Guangdong Provincial People's Hospital and implemented by community hospitals in Dongguan, in 2012. A follow-up registration system was established to collect data. The inclusion criteria in this study were: (1) aged 30–75; (2) diagnosed with MHT by the ABPM test; (3) left ventricular ejection fraction (Simpson's) >50%. The exclusion criteria were patients with a history of (1) secondary hypertension; (2) antihypertensive drugs used or stopped taking antihypertensive drugs for more than 2 weeks; (3) angina or myocardial infarction; (4) myocarditis; (5) stroke; (6) chronic kidney disease; and (7) autoimmune disease or tumor.

All experimental data were collected from the database of the medical center and recorded by two authors (Fu and Hu).

Blood Pressure and Measurement

Office BP measurements in the clinic were conducted by experienced community doctors and nurses using a calibrated OMRON Upper Arm Electronic Sphygmomanometer (Model HBP1100U). After the study participants took a seat and rested for at least 5 min, the cuff blood pressure measurement obtained three consecutive readings that were averaged for analysis. ABPM was performed uniformly using the verified and qualified TM2430 Oscillometric Ambulatory Blood Pressure Monitor from A&D Company, Limited. Each participant's blood pressure was monitored for 24 h, every 20 min during the waking period and every 30 min during the sleep period. Unqualified data (including <70% success rate of blood pressure measurement or <20 readings during the waking period or <7 readings during the sleep period) were repeated.

LDL-cholesterol, HDL-cholesterol (HDL-C), triglycerides, total cholesterol and fasting blood glucose were detected using a Beckman AU5800 spectrophotometer via colorimetry. Waist circumference was measured with tape measure positioned at the level of the umbilicus when the participants stood with their feet 25–30 cm apart and at the end of the exhalation. Diabetes status was based on previous history. Smoking was defined as any previous smoking (yes/no). Alcohol consumption was defined as alcohol consumption >3 times a week (yes/no). Antihypertensive drug use was recorded according to self-report.

Assessment of Masked Hypertension

MHT is defined as office blood pressure (average of 3 readings) <140/90 mmHg, but ambulatory blood pressure over a 24 h period with average blood pressure ≥130/80 mmHg and/or daytime (waking period) average blood pressure ≥135/85 mmHg and/or nighttime (sleeping period) average blood pressure ≥120/70 mmHg. Otherwise, patients are non-hypertensive, according to the 2013 European Society of Hypertension criteria (11).

Long-Term Outcomes

Patients were interviewed by phone every 3 months and face-to-face every 6 months to see whether they had had any major adverse cardiovascular event (MACE), including cardiac death, stroke, or coronary heart disease (CHD). Cardiac death was defined as cardiac-caused death on the patient's death certificate. The definition of stroke was the development of neurological dysfunction symptoms and objective findings that last more than 24 h. Coronary heart disease was defined as coronary artery stenosis confirmed by coronary digital subtraction angiography equal to or more than 70%.

All patients completed a follow-up period of 48 months, and the follow-up data of patients were reviewed and evaluated in 2017. All interviews were conducted by a cardiologist, and the follow-up information was obtained from the narration of the patient or immediate relatives and further confirmed by the electronic medical record at the hospital if the patient had had a MACE.

Statistical Analysis

In the latent class analysis model, baseline clinical data and biomarker concentrations were regarded as category-defining variables without consideration of clinical outcomes. The selection of clinical variables referred to the diagnostic criteria of metabolic syndrome, including waist circumference, HDL-C, triglycerides, fasting blood glucose, and diabetes status, in order

to discriminate high/low-risk MetS. For the sake of maintaining the consistency of the direction of the variables, we converted HDL-C to 1/HDL-C, which tends to be classified as high-risk MetS when it is higher.

We first listed the clinical characteristics and laboratory data of the study population. Next, we selected waist circumference, triglycerides, HDL-C, fasting blood glucose, and diabetes status as variables to fit a series of latent class models using the depmixS4 R package (12). The model selection criterion was based on the Bayesian information criterion, log likelihood ratio test, and the size of the smallest class. The latent class model is estimated using the full-information maximum likelihood method, which allows the full use of data from all patients. Then, we identified significant differences between the groups by using the *t* test (Class = 2) or variance analysis (Class > 2) for normally distributed data, the Mann-Whitney U test (Class = 2) or Kruskal-Wallis H test (Class > 2) for skewed distribution data, and the chi-square test or Fisher's exact test for categorical variables. After that, the Kaplan-Meier method was used to describe and confirm the cumulative incidence of MACE, and the log-rank test was conducted to compare between groups. Sensitivity analysis was conducted after excluding those with diabetes status since it had a certain increased cardiovascular risk. Comparisons where $P < 0.05$ (two-sided) were considered to be statistically significant. All of the analyses were performed with Stata 15.0, R, and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA).

RESULTS

Selection of Optimal Latent Class Model

The flowchart of our study was presented in **Figure 1**. A total of 140 MHT patients were included in the study. Baseline clinical characteristics and laboratory tests of the patients are shown in **Supplementary Table 1**. The LCA showed that the *p*-value testing was significant for the two/three/four-class (**Table 1**). The value of Bayesian Information Criteria were lowest in three-class mode, but this model produced a class with only 28 participants. Although the reduction of the Bayesian information standard guided us to add additional classes to the model, considering our research purpose (high/low-risk classification) and the small number of participants in the three-class model, the two-class model was considered to be the best fit for the participants (**Figure 2**). In order to distinguish different groups conveniently, we referred to them as Class 1 and Class 2. The average latent class probabilities for the most likely class in the Class 1 were 0.93 and 0.97 for Class 2. The classification probability of 43 (82.7%) Class 1 patients and 81 (92.0%) Class 2 patients was >0.9, indicating that the model has strong grade differentiation.

Population Characteristics of Different Classes

Table 2 lists the comparisons of all the variables involved in the classification. No significant difference were found in demographic spectrum and health behavior, including age, sex, smoking and alcohol consumption. Except for diabetes status, differences of classified variables were statistically significant, which again verified the reliability of the two-class model. Class 1 had a larger waist circumference, lower HDL-C, higher fasting blood glucose and triglycerides, and prevalence of diabetes, which was in line with the original intention of the high-risk MetS we set.

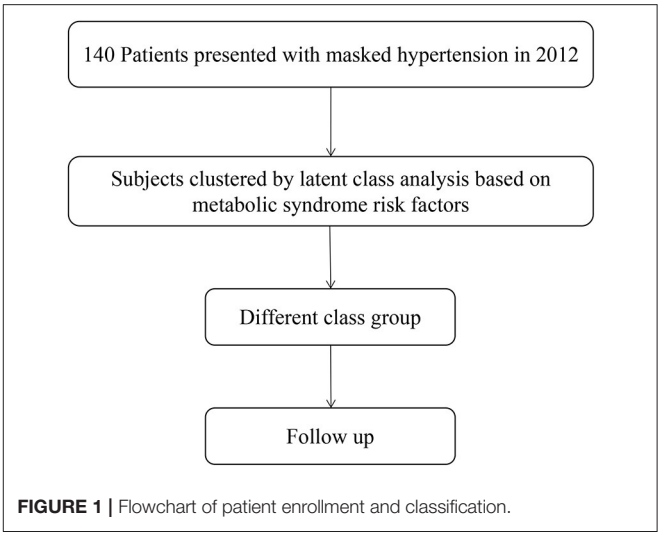

FIGURE 1 | Flowchart of patient enrollment and classification.

Prognoses of Different Classes

For the purpose of determining whether these two categories have different natural prognoses, we did the survival analysis based on the 48-month follow-up information. **Figure 3** illustrates the composition of the outcome, where a total of five people in Class 1 had MACE, of which two had stroke and three had CHD, while one case in Class 2 had CHD. There was no occurrence of cardiac death in either class. As shown in **Figure 4**, overall MACE-free survival at 48 months was 90.4% in Class 1 and 98.9% in Class 2 (Log-rank test: $P = 0.016$). Sensitivity analysis also suggested that after excluding those patients with diabetic status ($n = 21$), the natural prognosis of difference classes still significant (Log-rank test: $P = 0.009$, **Supplementary Figure 1**). Furthermore, in order to clarify whether inter-class differences existed in the prognosis after blood pressure-lowering medications, we tested the interaction. The result suggested that there was no statistically significant interaction between different subphenotypes and blood pressure-lowering drug use (**Supplementary Table 2**).

DISCUSSION

Our findings suggested that in MHT patients, there are two different classes that have various clinical features, pathophysiological characteristics, and natural prognoses, meeting the necessary criteria for defining subphenotypes. Although we have recognized the heterogeneity of many chronic diseases in the past, there is currently no clinical cohort study for MHT to clarify its potential classification and further guide effective countermeasures. In our study, there was a significant correlation between subphenotypes and clinical results, which

TABLE 1 | Summary of latent class model identification and fit statistics.

Class	Bayesian information criteria	Number of individuals per class				*P*-value
		1	2	3	4	
2-class	2112.58	52	88	–	–	<0.001
3-class	294.23	28	76	36	–	<0.001
4-class	367.07	38	38	36	28	<0.001

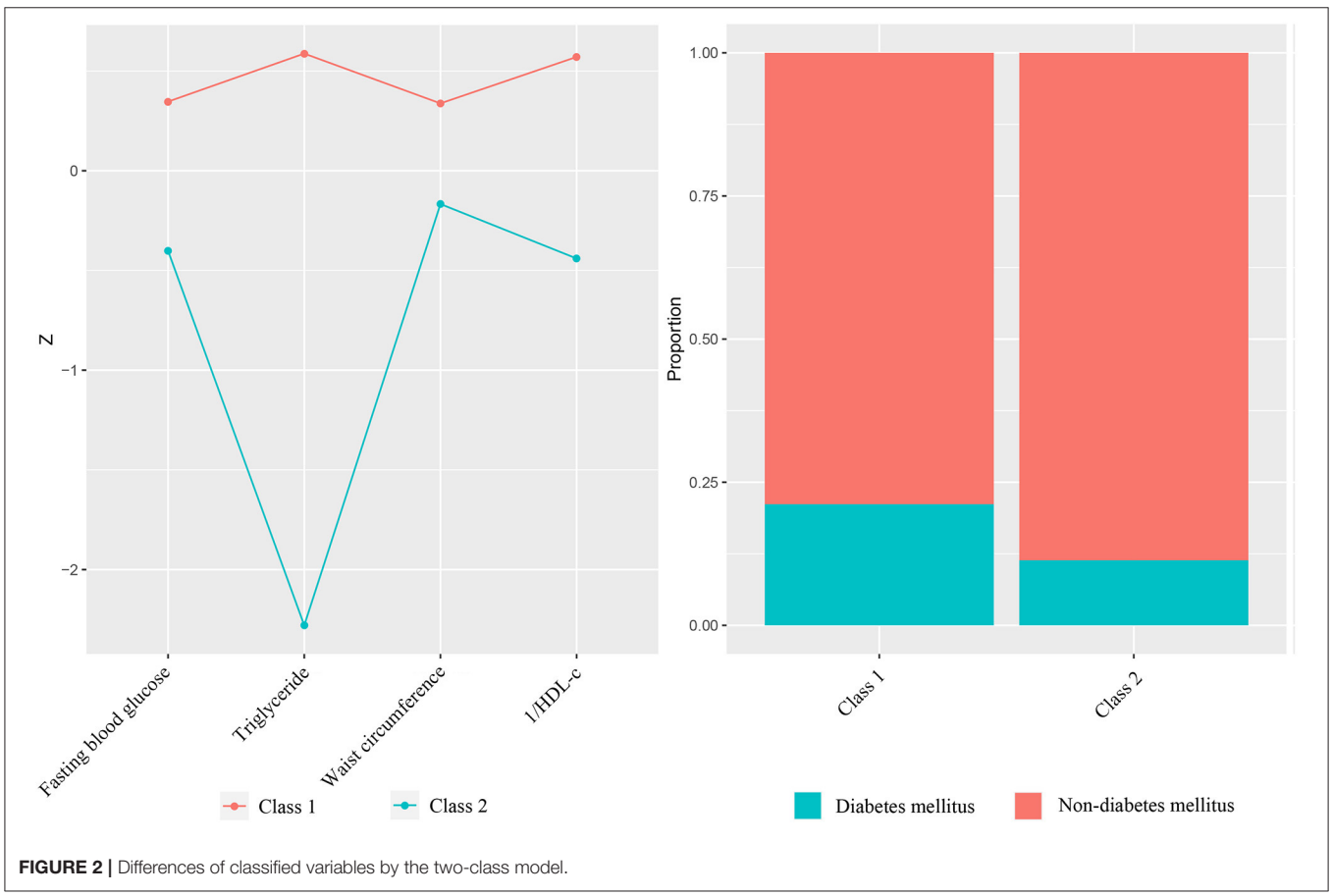

FIGURE 2 | Differences of classified variables by the two-class model.

indicated that the identification of these two subphenotypes may be crucial for future MHT clinical interventions.

The demographic characteristics of the classes reflected the uniformity of allocation, while the MetS-associated classified variables discriminated between the high- and low-risk MetS subphenotypes. Overall, phenotype 1, as an identification group, described the patients with larger waist circumference, less HDL-C, higher fasting blood glucose, triglycerides, and prevalence of diabetes. In contrast, phenotype 2 showed characteristics opposite to phenotype 1 and belonged to low-risk MetS patients. What is interesting is that the natural classification of all participants was in line with the diagnostic criteria of MetS, which was a reasonable clustering method and corresponded with clinical practice. In LCA, the best-fit model was based on a given number of categories. Although the *P* value of the log likelihood ratio test was significant among the two/three/four-class in our research, considering the population distribution, posterior probability of allocation, and especially the original intention of our research design, the two-class model was finally adopted.

Clustering of cardiac metabolic risk factors in adults is known as "metabolic syndrome," a concept that is useful in both clinical and research fields. The mechanisms of the relationship between metabolic risk factors and elevated blood pressure are still unclear. A cross-sectional study conducted by Afsar indicated that the prevalence of MetS was increased in patients with MHT more than in normotensive individuals, and it was highest in patients with persistent hypertension (13). The Ohasama Study conducted a population-based survey of 395 people and reported that elevated blood pressure was

TABLE 2 | Baseline characteristics of the study population post classification.

	Class 1	Class 2	*P*-value
N	52	88	
Age	60 ± 9	58 ± 8	0.399
Male	27 (51.92%)	33 (37.50%)	0.096
Waist, cm	86.13 ± 8.28	81.68 ± 9.90	0.007
Diabetes	11 (21.15%)	10 (11.36%)	0.117
Smoking	14 (26.92%)	16 (18.18%)	0.223
Alcohol consumption	1 (1.92%)	2 (2.27%)	0.890
1/HDL-C, mg/dL	0.02 ± 0.01	0.02 ± 0.00	<0.001
Fasting blood glucose, mmol/L	5.86 ± 1.65	4.95 ± 0.84	<0.001
Triglyceride, mg/dL	263.32 ± 181.88	93.33 ± 27.70	<0.001
Waist, cm (Z score)	0.29 ± 0.87	−0.17 ± 1.04	0.007
1/HDL-C, mg/dL (Z score)	0.59 ± 1.04	−0.35 ± 0.80	<0.001
Fasting blood glucose, mg/dL (Z score)	0.45 ± 1.29	−0.26 ± 0.66	<0.001
Triglyceride, mg/dL (Z score)	0.77 ± 1.31	−0.45 ± 0.20	<0.001

Values are shown as mean ± SD or n (%). HDL-C, high-density lipoprotein cholesterol.

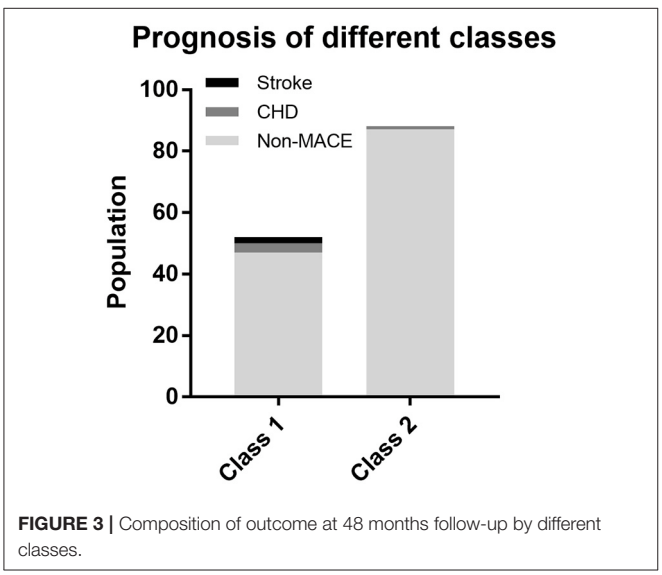

FIGURE 3 | Composition of outcome at 48 months follow-up by different classes.

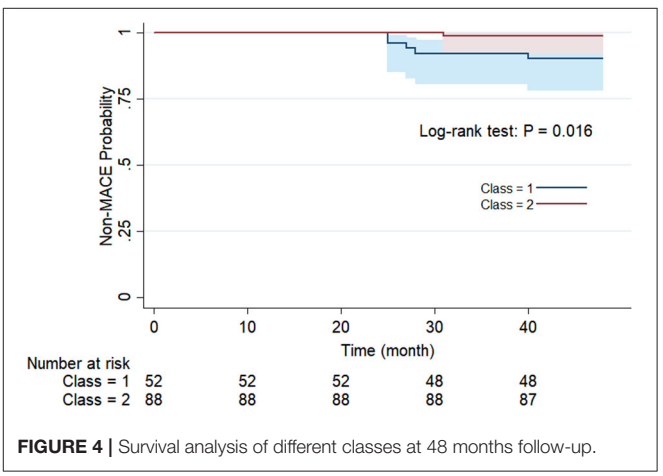

FIGURE 4 | Survival analysis of different classes at 48 months follow-up.

significantly associated with clustering of metabolic risk factors (14). Furthermore, a systematic review suggested that patients with MetS have a higher risk of non-dipping blood pressure than patients without MetS (15). These discoveries increased the possibility that metabolic risk factors may contribute to the occurrence of hypertension. In terms of specific metabolic factors, Mancia et al. confirmed that serum glucose has been associated with the development of hypertension, and also proposed that MHT associated with metabolic risk factors is likely to worsen hypertension, thereby contributing to a poor prognosis (16). Kenny et al. emphasized the importance of waist circumference and proposed that patients with MHT were more likely to have metabolic syndrome and high-normal office blood pressure compared with normotensive people (17). Another study also showed that diabetes status and insulin levels are related to elevated blood pressure (18). Although the pathogenesis of the pathophysiological relationship between metabolic risk factors and elevated blood pressure has not been well clarified, we already know that being overweight will not only lead to abnormal structure and function of many organs and systems in the body, but will also increase all-cause mortality, including cardiovascular disease (19, 20). A tendency to obesity or existing abdominal obesity can activate the renin-angiotensin-aldosterone system, causing expression of inflammatory factors and free radicals and increased arterial resistance, which may be the cause of secondary dyslipidemia, elevated fasting plasma glucose, insulin resistance, and high blood pressure (18). In recent years, epicardial adipose tissue has received widespread attention. It is also related to hypertension, which also illustrates the inherent correlation between MetS-related lipid metabolism abnormalities and the occurrence of atherosclerotic hypertension (21). In summary, most studies support the suggestion that elevated blood pressure is a secondary change of metabolic

disorders. That is, some insidious cases of hypertension may be derived from early metabolic disorders. Therefore, our research divided MHT into high/low-risk MetS categories, to distinguish those cases of MHT driven by metabolic disorders. Our results agreed with the conclusions of previous studies.

In addition to the methodological advantages of latent category analysis, another strength of our study was the four-year follow-up of the two classes of patients. The follow-up information was provided by dozens of community hospitals where every enrolled patient had completed their follow-up interviews. The results showed that more MACE occurred in Class 1; in particular, there were increased incidences of stroke and CHD. A large cohort study which recruited more than 2 million people found an obvious dose-response relationship between cumulative exposure to metabolic disorders and stroke, as people with three metabolic factors had a 24% increased risk of stroke (22). As for CHD, a Mendelian randomization study suggested that the loci associated with the direct action of HDL-C and triglycerides appeared to have location- and mechanism-specific causality on coronary artery disease (23). All of this evidence from the genetic level and high-quality population studies help explain why the incidence of coronary heart disease and stroke in Class 1 (high-risk MetS) is higher than in Class 2 (24).

The impact of subphenotype on medication choice is also of concern, so we conducted an interaction analysis, using data on the use of antihypertensive drugs. The results indicated that there was no significant difference in subphenotype between antihypertensive treatment and the occurrence of MACE, which may be due to the reason that antihypertensive drugs did not address the problem of metabolic disorders. As a kind of antihypertensive drugs, mineralocorticoid receptor antagonists are considered to be clinically valuable treatments for metabolic disorders in hypertensive patients. This is because obesity, as the center of MetS, stimulates the secretion of mineralocorticoid which is associated with an increased risk of insulin resistance, metabolic syndrome, and diabetes (25). Mineralocorticoid receptor antagonists can not only lower blood pressure, but also improve insulin sensitivity, relieve oxidative stress and reduce the inflammatory response of MetS, which could eventually prevent the occurrence of cardiovascular disease (26). In our study, however, since there was a small percentage of patient who took mineralocorticoid receptor antagonists, the protective effect on cardiovascular disease may not be well manifested. From this point of view, on the basis of lowering blood pressure, the management of metabolic disorders are needed to be considered in MHT patient with high-risk MetS.

This study has some limitations. First, our research was performed on a small sample within a single city; thus, generalization of the conclusions must be limited. Second, the boundary settings of the categorical variables were based on the characteristics of the population; that is, no specific cut off values were defined for the boundaries, which may render the variables impractical as clinical tools. However, what is worth mentioning is that compared with subphenotype discrimination of other diseases, the number of categorical variables used in this study was relatively few. Third, although these metabolic risk factors are valuable for prognosis, rapid developments in metabolic genetics and novel molecular markers may facilitate more comprehensive identification of subphenotypes.

CONCLUSION

Classification based on metabolic risk factors suggests that MHT contains different subphenotypes and has different prognoses, prompting a need for future large-scale cohort studies to further elucidate these subphenotypes. In addition to antihypertensive treatment, the management of metabolic disorder in MHT populations may be also considered in the future.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Guangdong Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MF and XH prepared and wrote the manuscript. SY and SS performed the data analysis. YZha and YF contributed to the acquisition of the data. QG reviewed and made critical revisions to the manuscript. YZho and HD contributed to the ideas and approved the final version of the manuscript. All authors have read and approved the final 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/fcvm.2021.680083/full#supplementary-material

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frontiers in Medicine

ORIGINAL RESEARCH
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Long-Term Effects of Financial Incentives for General Practitioners on Quality Indicators in the Treatment of Patients With Diabetes Mellitus in Primary Care—A Follow-Up Analysis of a Cluster Randomized Parallel Controlled Trial

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Background: The effect of financial incentives on the quality of primary care is of high interest, and so is its sustainability after financial incentives are withdrawn.

Objective: To assess both long-term effects and sustainability of financial incentives for general practitioners (GPs) in the treatment of patients with diabetes mellitus based on quality indicators (QIs) calculated from routine data from electronic medical records.

Design/Participants: Randomized controlled trial using routine data from electronic medical records of patients with diabetes mellitus of Swiss GPs.

Intervention: During the study period of 24 months, all GPs received bimonthly feedback reports with information on their actual treatment as reflected in QIs. In the intervention group, the reports were combined with financial incentives for quality improvement. The incentive was stopped after 12 months.

Measurements: Proportion of patients meeting the process QI of annual HbA1c measurements and the clinical QI of blood pressure levels below 140/85 mmHg.

Results: A total of 71 GPs from 43 different practices were included along with 3,854 of their patients with diabetes mellitus. Throughout the study, the proportion of patients with annual HbA1c measurements was stable in the intervention group (78.8–78.9%) and decreased slightly in the control group (81.5–80.2%) [odds ratio (OR): 1.21; 95% CI: 1.04–1.42, $p < 0.05$]. The proportion of patients achieving blood pressure levels below 140/85 mmHg decreased in the control group (51.2–47.2%) and increased in the intervention group (49.7–51.9%) (OR: 1.18; 95% CI: 1.04–1.35, $p < 0.05$) where it peaked at 54.9% after 18 months and decreased steadily over the last 6 months.

Conclusion: After the withdrawal of financial incentives for the GPs after 12 months, some QIs still improved, indicating that 1 year might be too short to observe the full effect of such interventions. The decrease in QI achievement rates after 18 months suggests that the positive effects of time-limited financial incentives eventually wane.

Keywords: quality indicators—healthcare, hypertension management, diabetes management and control, pay for performance (P4P), financial incentive, primary care, chronic conditions and diseases

INTRODUCTION

Improving the quality of care for the chronically ill, especially in patients with diabetes mellitus, is an important issue in all industrialized countries (1). At the level of healthcare providers, various strategies such as audit and feedback, clinical education, clinical reminders, or financial incentives have been pursued to narrow the gap between actual and optimal care (2). Financial incentives for healthcare providers, also called pay for performance (P4P) strategies when combined with quality indicators (QIs), have been studied in different settings. However, evidence concerning their effect on the quality of care, especially in ambulatory settings, is still inconclusive and little information is available from randomized controlled trials.

Not only the immediate effect of financial incentives is of interest but also further developments after their removal. Financial incentives often diminish when performance approaches the achievable maximum or when the financial resources are directed to quality-improvement efforts in other clinical areas. With limited resources available, the sustainability of improvements in quality of care is crucial for the long-term effectiveness of financial incentives. Former analyses in the United Kingdom and the United States of America showed conflicting evidence, with results ranging from declining performance to sustained performance levels (3–7).

In Switzerland, no real-life data on the P4P approach exists, and the use of QIs, especially in primary care, has been marginal. With this cluster-randomized parallel controlled trial, we aimed to test whether financial incentives are more effective than evidence-based educational feedback reports in the increasing proportion of patients with diabetes mellitus meeting specific QIs. Results directly after the intervention phase (12 months) indicated a little effect on directly incentivized QIs (8). With this analysis, we aimed to assess the long-term effects and sustainability of financial incentives after their removal.

METHODS

Study Design and Participants

We conducted a follow-up analysis of a cluster-randomized parallel controlled trial in Swiss primary care using data from the FIRE database (family medicine international classification of primary care (ICPC) research using electronic medical records) (9). General practitioners (GPs) who participate in the FIRE project periodically contribute anonymized data from their electronic medical records (EMRs) to the steadily growing database holding the following components: administrative information, vital signs, laboratory values, medication data, and diagnostic codes according to the ICPC-2 classification scheme (10). At the start of recruitment in June 2018, more than 400 GPs participated in the FIRE project, and records from more than 500,000 patients and 5 million consultations were available.

In June 2018, all eligible GPs received an invitation to participate in the study [for the detailed eligibility criteria regarding data availability and data quality, see Meier et al. (8)]. We included all patients listed in the EMRs from all participating GPs with a diagnosis of diabetes mellitus who met at least one of the following criteria: (1) ICPC-2-code T89 (insulin-dependent diabetes mellitus) or T90 (insulin-independent diabetes mellitus). (2) Antidiabetic medication according to the anatomical therapeutic chemical classification system (A10A, A10B, and A10X) (11). Patients with diabetes mellitus were only eligible if they were diagnosed at least 4 months before the QI assessment and had at least one consultation within the last 12 months. During the study period, patients with newly identified diabetes mellitus were included, whereas patients without consultation within the last 12 months or reported dead were excluded from the analysis. For the flowchart of the study, see **Figure 1**.

According to the local Ethics Committee of the Canton of Zurich, the project did not fall under the scope of the law on human research and therefore did not require ethical approval (BASEC-Nr. Req-2017-00797). The trial was registered in the ISRCTN registry (identifier: ISRCTN13305645), and the study protocol has been published (12).

Intervention

During the intervention and follow-up phase, GPs in both study groups received bimonthly diabetes feedback reports, containing information on their patients with diabetes mellitus (age, gender, and body mass index), the proportion of patients with at least one HbA1c measurement within the previous 12 months, and the proportion of patients with blood pressure measurements and achieving the target blood pressure level. The reports were generated from each participating GP's own EMR data to provide an individualized overview of his performance. In their key messages, the reports addressed various issues in the treatment of patients with diabetes mellitus, such as the management of cardiovascular risk or the prevention of disease-related complications. An example of the report can be found in **Supplementary Material 1**. The intervention group was informed, after randomization, that they would receive a financial incentive of 75 Swiss francs per percentage point improvement in the reported QIs after the intervention period (see **Table 1** for

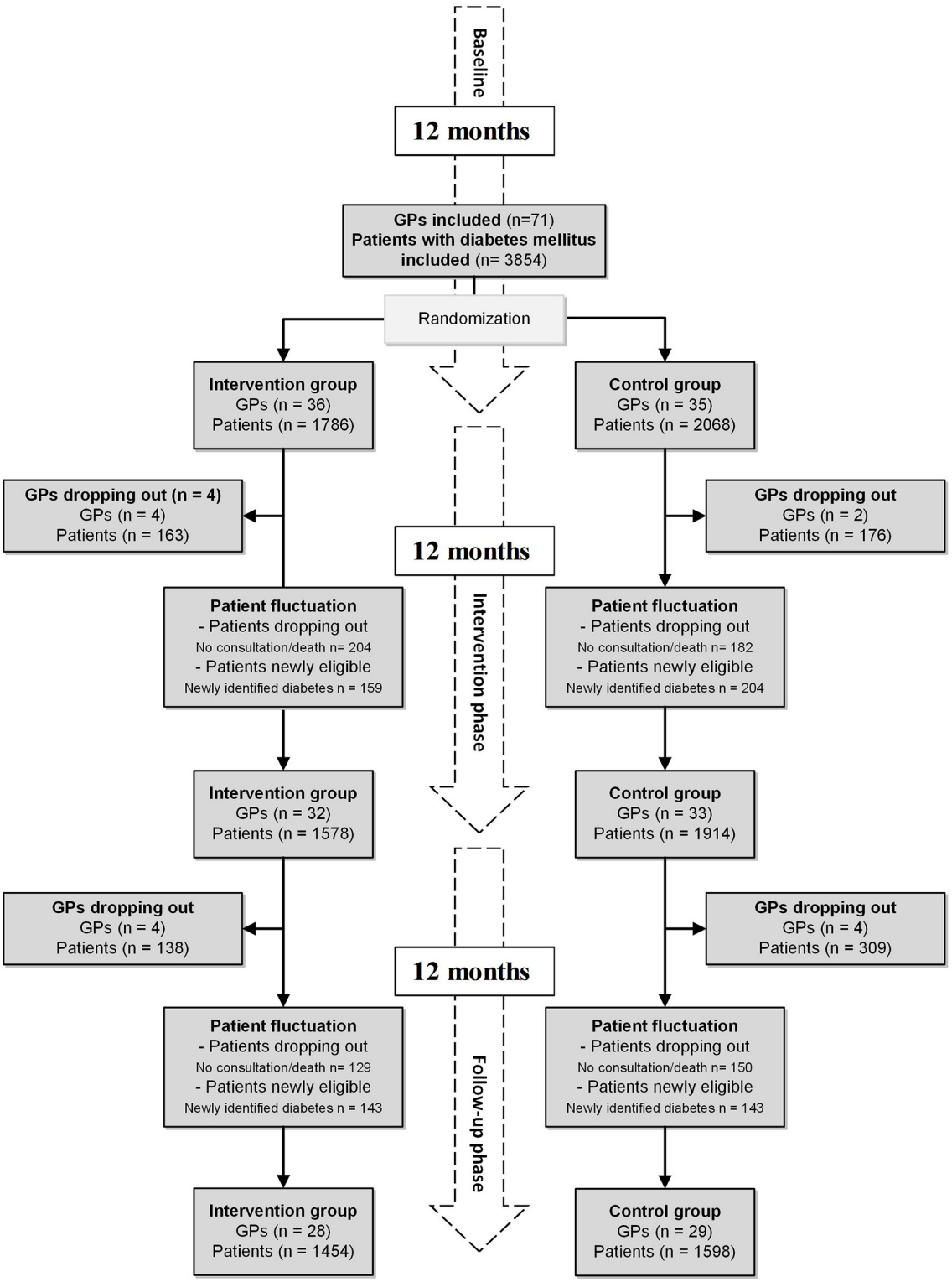

FIGURE 1 | Flowchart of the study, including dropouts of GPs and patient fluctuation. Financial incentives were stopped after the intervention phase. GP, general practitioner.

TABLE 1 | Quality indicators are used to assess primary and secondary outcomes.

Type	Subject	Description
Incentivized QIs		
Clinical QI	Blood pressure	Last blood pressure measurement <140/85 mmHg in the preceding 12 months.
Process QI	HbA1c	At least one measurement of HbA1c in the preceding 12 months.
Non-incentivized QIs		
Process QI	Blood pressure	At least one blood pressure measurement in the preceding 12 months.
Clinical QI	HbA1c	HbA1c level <7.5% in the preceding 12 months.
Process QI	Cholesterol	At least one cholesterol measurement in the preceding 12 months.
Clinical QI	Cholesterol	Total cholesterol <5 mmol/l in the preceding 12 months.

QI, quality indicator.

incentivized QI description). Simulations beforehand had shown that this incentive could add up to a significant financial amount for the GPs concerning their incomes. The control group was blinded for the financial incentive of the intervention group. The financial incentive was the only difference between the two groups.

Outcomes

Primary outcome: Between-group differences in the proportions of patients meeting incentivized QIs after 24 months (**Table 1**).

Secondary outcome: Between-group differences in the proportions of patients meeting non-incentivized QIs after 24 months (**Table 1**).

We assessed the proportions of patients meeting QIs at baseline and every 2 months until the trial was terminated after 24 months.

Randomization and Sample Size

We cluster-randomized at the practice level to minimize contamination between the groups. Randomization was constrained by the proportion of patients meeting clinical QIs at baseline per practice, the number of participating GPs per practice, GP network participation, and the number of patients with diabetes mellitus per practice. More details on the randomization and the sample size calculation can be found in Meier et al. (8).

Sensitivity Analysis

We also assessed the performance of GPs who were part of the FIRE project but had refused to participate in the randomized controlled trial. The analysis was carried out retrospectively for the same time points as in the randomized controlled trial. With this analysis, we aimed to investigate whether independent changes in the proportion of patients meeting the QIs occurred and whether receiving educational feedback alone had any effect.

Statistical Methods

We reported categorical data as frequencies and percentages, continuous variables as means with SDs, or medians with interquartile ranges (IQRs), as appropriate. To assess the effect of the financial incentives, we used hierarchical multivariable logistic regression models, with practice and GPs nested within practices as random variables. Meeting a QI was the (Boolean) dependent variable, and independent variables were time and group allocation. To study whether the intervention effect varied over time, we added an interaction term between time and intervention to the model. Furthermore, we adjusted for the age and gender of the GPs and the number of patients with diabetes mellitus per GP. The same model was used for the sensitivity analysis, with the non-participating GPs as a third group allocation. To visualize trend and effect, we computed each GP's proportion of patients meeting the QIs, aggregated within group and time point, and computed means and the Wald-95% CIs.

RESULTS

Study Population

A total of 71 GPs gave consent to participate in our study. Randomization allocated 21 practices with 36 GPs to the intervention group and 22 practices with 35 GPs to the control group. Subsequently, all patients with diabetes mellitus were included, resulting in an intention to treat a population of 3,854 patients (the intervention group: 1,786 patients and the control group: 2,068 patients). In the 12 months intervention period, four GPs dropped out of the intervention group (163 patients) and two GPs dropped out of the control group (176 patients). Throughout the 12 months of follow-up, another four GPs dropped out of the intervention group (138 patients) and five GPs dropped out of the control group (309 patients) (**Figure 1**).

Information on reasons and dates of dropouts of GPs is available in **Supplementary Material 1** and **Table 1**. The patient fluctuation was caused by death, changes in eligibility status (no consultation within 12 months), or newly identified patients with diabetes mellitus. Of the initially included 3,189 patients, 2,742 (71.1%) were observed over the entire study period (**Figure 1**). The study ended as planned after 24 months.

At baseline, GPs had a median age of 52 years (IQR: 44–60), 72% were male and 91.5% worked in a group practice. The patients had a median age of 70 years (IQR: 60–78), 57% were male. Detailed information on the baseline characteristics of the study population is provided in Meier et al. (8). The numbers of measurements of BP, HbA1c, and cholesterol and also the respective clinical values at baseline and in the two study phases are given in **Table 2**.

The median incentive paid to the GPs in the intervention group was 637.50 Swiss francs (IQR: 300–1,200) (€: 603.0, IQR: 284–1,137).

Primary Outcomes

Throughout the study, the proportion for the process QI HbA1c was stable in the intervention group (intervention phase: 78.8–78.1%; follow-up phase 78.1–78.9%) and decreased slightly in

TABLE 2 | Numbers of measurements per patient, and clinical values of BP, HbA1c, and cholesterol over the entire study period.

	Group	Baseline 12 months	Intervention phase 12 months	Follow-up phase 12 months
BP measures [median (IQR)]	Intervention	3 [1–4]	3 [2–4]	3 [2–4]
	Control	2 [1–4]	2 [1–4]	2 [1–4]
Systolic BP [mmHg] [median (IQR)]	Intervention	137.5 [128.5–149.0]	136.8 [127.7–146.7]	135.6 [127.7–147.0]
	Control	134.0 [125.0–143.3]	134.0 [124.5–143.3]	135.0 [125.1–145.0]
Diastolic BP [mmHg] [median (IQR)]	Intervention	80.0 [73.9–86.0]	80.0 [73.6–85.0]	79.2 [73.3–85.0]
	Control	80.0 [73.3–85.0]	79.0 [73.0–85.0]	80.0 [74.0–85.0]
HbA1c measures [median (IQR)]	Intervention	2 [1–3]	2 [1–3]	2 [1–3]
	Control	3 [1–4]	2 [1–3]	2 [1–4]
HbA1c [%] [median (IQR)]	Intervention	6.8 [6.3–7.5]	6.8 [6.3–7.5]	6.9 [6.3–7.6]
	Control	6.8 [6.3–7.5]	6.8 [6.2–7.5]	6.8 [6.2–7.5]
Cholesterol measures [median (IQR)]	Intervention	1 [1–2]	1 [1–1]	1 [1–2]
	Control	1 [1–1]	1 [1–1]	1 [1–1]
Cholesterol [mmol/l] [median (IQR)]	Intervention	4.5 [3.8–5.3]	4.3 [3.7–5.4]	4.3 [3.6–5.2]
	Control	4.6 [3.8–5.4]	4.6 [3.8–5.4]	4.4 [3.7–5.2]

BP, blood pressure; IQR, interquartile range.

the control group (intervention phase: 81.5–81.9%; follow-up phase 81.9–80.2%). The proportion of patients achieving a blood pressure target levels below 140/85 mmHg increased in the intervention group (intervention phase: 49.7–52.5%; follow-up phase 52.5–51.9%) and decreased in the control group (intervention phase: 51.2–48.9%; follow-up phase 48.9–47.2%). For illustration, see **Figure 2**.

The odds ratio (OR) for the interactive effect of time and intervention over the entire study period was 1.21 (95% CI: 1.04–1.42, $p < 0.05$) for the process QI of HbA1c and 1.18 (95% CI: 1.04–1.35, $p < 0.05$) for the clinical QI of achieving a blood pressure target level below 140/85 mmHg (**Table 3**). The detailed results of the logistic regression and the estimated random effects of GPs and GPs nested in practices can be found in **Supplementary Material 1**; **Tables 2**, **3**.

Secondary Outcomes

After 24 months, the proportions of patients meeting the cholesterol process QI and the clinical QIs increased in the intervention and the control groups, the corresponding proportion for the HbA1c process QI was stable, whereas the proportion for the BP process QI decreased in the control group (**Figure 2**). The logistic regression analysis revealed a significant effect of financial incentives on the cholesterol process QI (OR: 1.21; 95% CI: 1.06–1.38, $p > 0.01$) (**Table 3**).

Sensitivity Analysis

For the sensitivity analysis, we included 25 GPs from 15 different practices with 1,341 patients with diabetes mellitus. Practice, GP, and patient characteristics were similar to the study population, whereas baseline proportions of patients meeting QIs were lower for non-participants regarding blood pressure and cholesterol QIs (**Figure 2**). The results of the logistic regressions showed that no factors besides the intervention did affect the outcomes during the study period (**Supplementary Material 1** and **Supplementary Table 4**) and that the educational feedback report had no effect.

DISCUSSION

In this follow-up analysis of our cluster randomized parallel controlled trial, we evaluated the long-term effect of financial incentives on treatment quality of patients with diabetes mellitus for 12 months beyond incentives were stopped, compared to educational feedback reports. Compared to the baseline levels, the intervention group achieved an improvement of 2% in the proportion of patients achieving the recommended blood pressure target levels, whereas the proportion of patients receiving annual HbA1c measurements remained stable.

The most relevant and significant effect of financial incentives could be observed on the proportion of patients achieving the recommended blood pressure target levels. In the intervention group, the proportion increased steadily from the beginning of the trial until 18 months after the start of the study (6 months after the financial incentives were stopped). During this period, a significant increase of about 5% was achieved, corresponding to a decrease in the median systolic blood pressure of about 2 mmHg. After this peak performance, the proportion decreased by ∼3% in the last 6 months of the study. In the control group, the proportion fell 3% over the entire study period.

Interestingly, and in contrast to the analysis performed directly after the intervention phase (8), we could now observe an effect of financial incentives. Surprising, although by no means inexplicable, was the delay in peak performance until 6 months after the intervention ended. A time window of 12 months seemed to be too short to observe a consistent reduction in blood pressure in all practices. Even though patients with diabetes mellitus are a frequently visiting patient cohort, it takes a certain amount of time before they are seen for their regular control consultations and changes in hypertension treatment show.

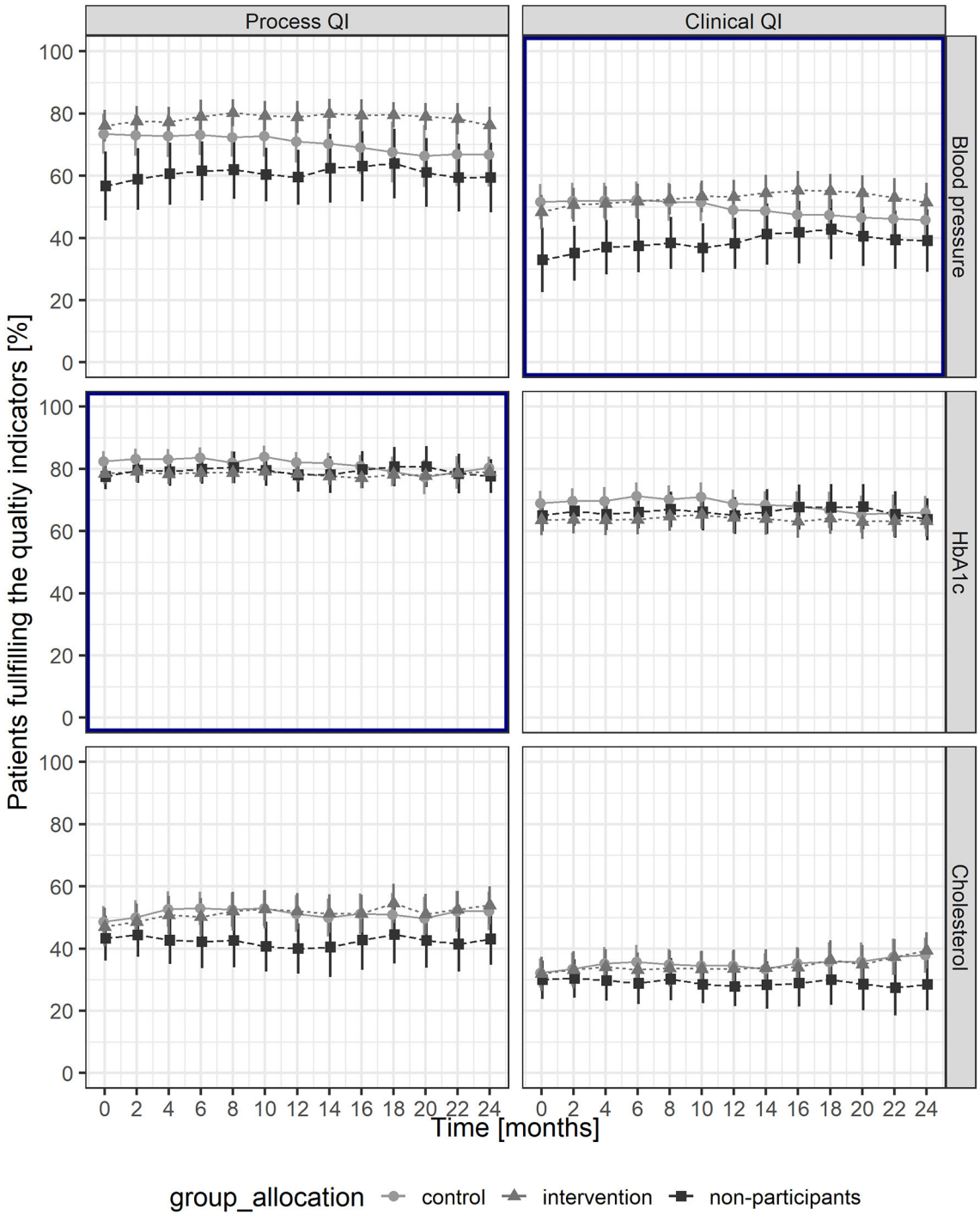

FIGURE 2 | Proportions of patients fulfilling the quality indicators throughout the study period, with mean and Wald-95% CI for each group. Bold frames indicate primary outcomes. QI, quality indicator.

The decline in the last 6 months of the follow-up phase reflects an essential challenge in implementing financial incentives, namely, the lack of sustainability of their effects. As other studies reported, a drop in performance after withdrawal of the incentives is common and can even reach pre-incentive levels (3–5). The mechanisms behind this decline following the removal of financial incentives are not yet fully elucidated. A potential explanation is that financial incentives, as external motivators,

TABLE 3 | Interactive effect of time and intervention over the entire study period of 24 months.

Type	Subject	OR	95% CI	*p*-value
Primary outcomes				
Clinical QI	Blood pressure	1.18	1.04–1.35	<0.05
Process QI	HbA1c	1.21	1.04–1.42	<0.05
Secondary outcomes				
Process QI	Blood pressure	1.14	0.97–1.34	0.11
Clinical QI	HbA1c	1.11	0.97–1.27	0.13
Process QI	Cholesterol	1.21	1.06–1.38	<0.01
Clinical QI	Cholesterol	1.10	0.96–1.26	0.17

The model is adjusted for the age and gender of the GPs and the number of patients with diabetes mellitus per GP.
QI, quality indicator; OR, odds ratio.

may crowd out intrinsic motivation; however, particularly in studies assessing health workers, the results are conflicting (13, 14).

The proportions of patients receiving annual HbA1c measurements were stable at ∼80% in both the intervention and control groups. However, the logistic regression, which took the interactive effect of time and intervention into account, revealed a significant difference between the intervention and control groups. We attribute this difference to a decrease in performance in the control group during the follow-up period, partially explainable by the COVID-19 pandemic in spring 2020 (around month 20 in the study period). For several weeks, GPs in Switzerland were only allowed to hold emergency consultations, which might have negatively impacted the care of patients with diabetes (15). Why this should affect only certain practices in the control group we cannot explain; however, shortly after the restrictions were lifted, previous levels were swiftly reached again in these affected practices. The lack of improvement in meeting the process QI of measuring HbA1c, for which rates of 80% were achieved, may be explained by a ceiling effect. This hypothesis gets support from our logistic regression models, which reveal a smaller variability of random effects on practice and GP levels for the QIs addressing HbA1c than for the other QIs. The assumption that a ceiling effect prevented further improvement above 80% is further supported by the fact that it is generally easier to improve process QIs than clinical QIs (16, 17).

In contrast to the results of the analyses immediately after the intervention phase, the spill-over effect of financial incentives on the process QI of measuring blood pressure values vanished (8). The effect on the process QI of measuring cholesterol, however, persisted. The evidence regarding spill-over effects on non-incentivized QIs and reporting of risk factors is inconclusive (18–21), and with care quality, in the control group and among the non-participants improving slightly we cannot fully exclude any study-independent effects.

Strengths and Limitations of This Study

To our knowledge, we conducted the first randomized controlled trial testing financial incentives for improved diabetes treatment in Europe. In general, studies to improve the quality of diabetes care are of high importance because of the high prevalence and burden of disease. We were able to implement a simple but effective intervention and blind the control group. In addition, we were able to compare the study results with another cohort not participating in the study. This study thus closes a gap, left by observational studies. Moreover, the baseline analysis showed that the patient population in this trial was highly comparable to other diabetes populations in Swiss primary care (22–24).

The EMR database from which the study draws may represent a potential limitation since such databases are known to be prone to missing data and data quality issues. These issues might not be apparent at baseline due to randomization. However, we cannot preclude that the increases in proportions of patients meeting process QIs are due to better data reporting rather than improved quality of care. This confounder is of particular concern in the case of the process QI of blood pressure measurement, as it is very likely that blood pressure values are not always reported in the dedicated field of the entry mask. However, these issues do not necessarily affect improvements in clinical QIs. A potential limitation is the risk of (self-) selection bias due to specific GPs participating or dropping out during the study. However, a dedicated subgroup analysis showed that GPs dropping out during the study were not different in performance from GPs remaining in the study. At last, information about the death of a patient is often missing in the FIRE database, since few GPs code it appropriately. To counteract this limitation, patients with no consultation within the last 12 months were excluded as losses of follow-up.

CONCLUSION

After the withdrawal of financial incentives for the GPs after 12 months, some QIs still improved, suggesting that 1 year might be too short to observe the full effect of such interventions. The decrease in QI achievement rates after 18 months suggests that the positive effects of time-limited financial incentives eventually wane.

DATA AVAILABILITY STATEMENT

The data are gathered within the ongoing FIRE project. The FIRE database can be accessed at any time by the scientific team of the institute. For external requests, access has to be requested from the head of the institute.

ETHICS STATEMENT

The local Ethics Committee of the Canton of Zurich waived approval, because the project is outside the scope of the law on human research (BASEC-Nr. Req-2017-00797).

AUTHOR CONTRIBUTIONS

RM: methodology, formal analysis, writing—original draft, review, and editing. CC: conceptualization, methodology,

writing—review and editing, and funding acquisition. FV: data curation, formal analysis, methodology, and writing—review and editing. LM: methodology and writing—review and editing. OS and TR: conceptualization, writing—review and editing, and funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.664510/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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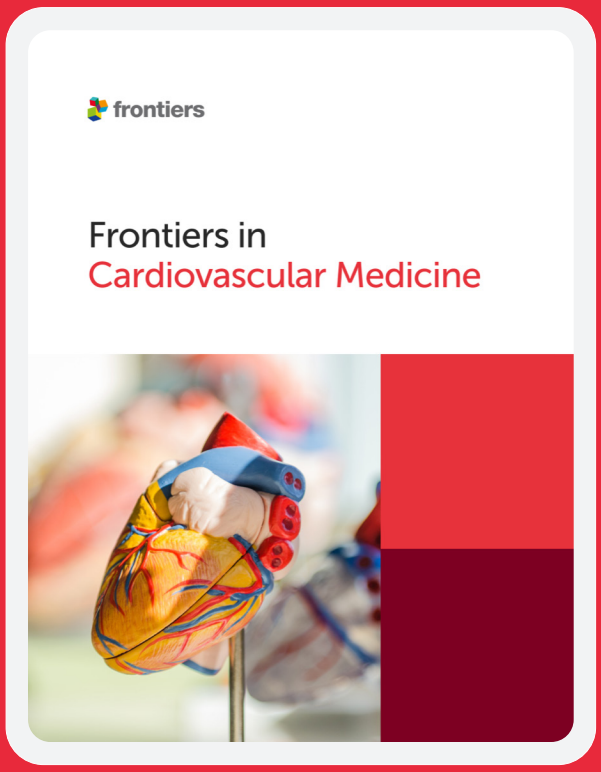

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