Co-existence of Hypertension and Pre-existing Cardiovascular Disease and Mortality in Patients on Continuous Ambulatory Peritoneal Dialysis

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Research article

Keywords: dialysis, mortality, hypertension, cardiovascular disease

Posted Date: June 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-34311/v1

Abstract

Background

Little is known about whether co-existence of hypertension (HTN) and pre-existing cardiovascular disease (CVD) has a more harmful effect on mortality compared with either comorbidity alone in patients on continuous ambulatory peritoneal dialysis (CAPD).

Methods

We conducted a retrospective study of 3073 incident Chinese patients on CAPD from five dialysis centers between January 1, 2005 and December 31, 2018 in a real-world setting. The primary and secondary outcomes were all-cause and CVD mortality. The association between interesting comorbidities and mortality was analyzed using Cox regression models and the Fine and Gray competing risk models.

Results

Over a median of 33.7 months of follow-up, 581 (18.6%) patients died, with 286 (9.3%) CVD mortality. The incidence of all-cause mortality was 32.2, 56.1, 74.4, and 131.0/1000 patient-years, and the incidence of CVD mortality was 15.0, 28.2, 34.7, and 69.6/1000 patient-years in the control group (those without either hypertension or CVD), HTN group, CVD group, and HTN plus CVD group respectively. After adjusting for the confounding factors, HTN plus CVD, CVD, and HTN groups had a higher risk of all-cause mortality (HR 3.98, 95% CI 3.07 to 5.17; HR 2.18, 95% CI 1.27 to 3.74; and HR 1.83, 95% CI 1.47 to 2.28) and CVD mortality (HR 4.68, 95% CI 3.27 to 6.69; HR 2.11, 95% CI 0.96 to 4.63; and HR 1.87, 95% CI 1.37 to 2.54), respectively, compared to the control group. Similar findings were observed using the Fine and Gray competing risk models. There was no significant interaction between HTN and CVD on all-cause and CVD mortality (β = 0.010, P = 0.973; β = 0.058, P = 0.892) in the study population.

Conclusions

Among CAPD patients, co-existence of HTN and pre-existing CVD at the start of CAPD had a more harmful effect on mortality compared to either HTN or pre-existing CVD alone, and pre-existing CVD may have also a more harmful effect on mortality than HTN.

Introduction

Although renal replacement therapy (RRT) has been significantly improved in recent decades, the overall prognosis of end stage renal disease (ESRD) remains poor, with only 11% of peritoneal dialysis patients surviving past 10 years [1]. Cardiovascular disease (CVD) accounts for approximately 50% of deaths in dialysis patients [2]. Dialysis patients have 10 to 30 times of CVD mortality than the general population,

even after adjusting for age, gender, and ethnicity [3]. Dialysis patients have a high prevalence of traditional CVD risk factors, such as hypertension (HTN), pre-existing CVD, diabetes mellitus, etc. The presence of HTN affects approximately 70.0% of Chinese patients on continuous ambulatory peritoneal dialysis (CAPD) [4, 5]. Elevated, lower or uncontrolled blood pressure (BP) is highly prevalent among dialysis patients and is associated with increased mortality in this population [6–8]. Meanwhile, chronic kidney disease (CKD) has been identified as an independent risk factor for CVD, resulting in twice as likely to develop CVD compared to the general population [9–11]. So, patients may have a higher prevalence of pre-existing CVD, when receiving RRT. Dialysis patients with pre-existing CVD have poorer survival compared to those without pre-existing CVD [12, 13]. Interestingly, among CAPD patients, we wonder whether co-existence of HTN and pre-existing CVD has a more harmful effect on mortality than HTN or pre-existing CVD alone, and pre-existing CVD is more strongly associated with mortality than HTN. The objective of this study was to evaluate (1) the association between the co-existence of HTN and pre-existing CVD at the start of dialysis and mortality, (2) the association between pre-existing CVD and HTN and mortality in CAPD patients.

Materials And Methods

Study Design and Population

We conducted a retrospective cohort study of 3073 incident CAPD patients from five PD centers of three provinces in China, between January 1, 2005, and December 31, 2018. The inclusion criteria were relatively broad, which implies that the patients may be reasonably representative for the CAPD population. On behalf of the real world setting of CAPD, no patient were excluded in this study. The study was approved by the Human Ethics Committee of each research center, consistent with the ethical principles of the Declaration of Helsinki.

Data Collection and Definitions

Data on demographics, comorbid conditions, medications, and laboratory values at the start of CAPD were abstracted from medical records by two trained investigators in each center using uniform and standardized data collection tools: demographic characteristics (age, sex, body mass index, systolic BP, diastolic BP, 24-hour urine volume, current smoking, and current alcohol consumption); comorbidities (diabetes mellitus, pre-existing CVD, HTN, hyperlipidemia); medications (calcium channel blockers, beta blockers, angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors [ACEI/ARBs], diuretics, statins, and aspirin); and laboratory variables (hemoglobin, serum albumin, serum uric acid, estimated glomerular filtration rate [eGFR], cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, high-sensitivity C-reactive protein [hs-CRP]). The diagnosis of HTN was defined as pre-dialysis systolic BP measurements >150 mmHg or diastolic BP > 85mmHg measured by ambulatory BP monitoring from medical records at the start of dialysis, or the use of antihypertensive medications [6]. The presence of CVD were defined as coronary heart disease, congestive heart failure, arrhythmias, cerebrovascular disease, or peripheral vascular disease. Current smoking was defined as at least one cigarette a day, and

current alcohol consumption defined as > 20 grams of ethanol a day [15]. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [16].

Outcomes and Follow-Up

The primary and secondary outcomes were all-cause and CVD mortality, respectively. If the patients died in any hospital, the exact cause of death was available by death certificates, and if the patients died outside a hospital, experts would meet a consensus on the cause of death, with a comprehensive consideration of recent health conditions provided by family members, and the medical history and descriptions from each dialysis center. Patients who died within three months from transferring to hemodialysis to death were considered to receive failure of CAPD therapy and not to be censored. All participants were conducted CAPD schedules in the light of International Standardized Peritoneal Dialysis Guidelines[17], and clinical nephrologists regularly adjusted the CAPD regimens according to patient's health conditions. All patients were followed up until CAPD cessation, death, the end of 8-year duration, or as of June 30, 2019. Transferring to hemodialysis with survival time of at least three months, renal transplantation, transferring to other centers, loss of follow-up, or still survival with a follow-up period of 8 years were considered to be censored.

Statistical Analysis

Variables with missing data before the data analysis were imputed using the missForest method, coping with different types of variables [18]. Incidence was calculated as number of events divided by total valid observational time at risk, scaled to episodes per 1000 years. Variables are presented as mean±standard deviation (SD) or median (interquartile range, IQR) or number (%). Patients were divided into four groups: control group (those without either HTN or pre-existing CVD), HTN group, CVD group, and HTN plus CVD group. Baseline variables were compared by the One-Way ANOVA or Kruskal-Wallis tests according to variable distribution (normality tested with Shapiro-Wilk test) for quantitative variables, and the chi-square test when appropriate for categorical variables among the groups. Multiple Logistic regression was conducted to evaluate the association between baseline variables and the co-existence of HTN and pre-existing CVD at baseline. The following factors were included in multiple Logistic regression: age, sex, body mass index, systolic BP, diastolic BP, current smoking, current alcohol consumption, 24-hour urine volume, diabetes mellitus, hyperlipidemia, hemoglobin, serum albumin, serum uric acid, eGFR, cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and hs-CRP. Medications were not included in the multiple Logistic regression because of the following reason: medications were usually used in those who had developed comorbidities, but not those comorbidity-free patients. If we enrolled medications into the multiple Logistic regression, the findings must showed that patients with the usage of medications are at higher risk for the presence of HTN plus and pre-existing CVD compared to those without the usage of medications, which was contradicted with clinical knowledge. Therefore, we did not included the usage of medications in multiple Logistic regression.

We used Kaplan-Meier curves to investigate the difference of cumulative mortality among four groups over the observational period. To analyze the association between comorbidities and mortality, we

constructed four Cox proportional hazards regression models adjusted for the following factors: Model 1, unadjusted; model 2, model 1 plus age, sex, body mass index, systolic BP, diastolic BP, current smoking, current alcohol consumption, 24-hour urine volume, diabetes mellitus, and hyperlipidemia; model 3, model 2 plus medications; model 4, model 3 plus hemoglobin, serum albumin, serum uric acid, eGFR, cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and hs-CRP. In addition, the association between comorbidities and mortality were also analyzed among subgroups of men, women, diabetes mellitus, non-diabetes mellitus, hyperlipidemia, and non-hyperlipidemia. The interaction between HTN and CVD on all-cause and CVD mortality was examined by performing a formal test of interaction.

Sensitivity Analysis

First, for all-cause mortality, hemodialysis or renal transplants were considered competing risks. When using hemodialysis or renal transplants as competing risks, we evaluated comorbidities and all-cause mortality using the Fine and Gray competing risk models, with adjusting for variables in the four Cox proportional hazards regression models. Similarly, for CVD mortality, non-CVD mortality, hemodialysis or renal transplants were considered competing risks. Second, for those adult patients with a short-term period of follow-up, the interesting outcomes may not be completely observed, with under-reporting of the incidence of mortality. For fully observing outcomes, we further analyzed the effect of comorbidities at the start of dialysis on mortality in those adult patients with at least 24-month period of follow-up.

The results of the Cox proportional hazards models and the Fine and Gray models were presented as the hazard ratio (HR) and the 95% confidence interval (CI). Statistical analyses were conducted by GraphPad Software 8.0 (GraphPad Prism Software Inc., San Diego, California) and the R package 3.6.0 (https://www.r-project.org/). The level of significance was set as 0.05 for all analyses.

Results

Patient Characteristics and comorbidities

All 3073 incident CAPD patients from five dialysis centers were included in the present study. All variables with less than 5% missing data were imputed before the data analysis, and there was no missing data for outcomes. Of 3073 with a median age of 49.0 (IQR 39.0-61.0), 1780 (57.9%) were men, 1987 (64.6%) had HTN, 431 (14.1%) had pre-existing CVD, and 567 (18.4%) had diabetes mellitus. All patients were divided into four group: HTN plus CVD group (n=370, 12.0%), CVD group (n=60, 2.0%), HTN (52.6%) group, and the control group (n=1027, 33.4%, Table 1). Compared to the control group, HTN plus CVD group tended to be elderly, with higher body mass index, systolic BP, hemoglobin, and cholesterol, but lower diastolic BP, as well as more likely to be current smoking, diabetes mellitus, hyperlipidemia, taking calcium channel blockers, beta blockers, diuretics, ACEI/ARBs, aspirin, and statins.

Co-existence of HTN plus pre-existing CVD at baseline and Related factors

We analyzed the factors associated with the co-existence of HTN and CVD at baseline using the multiple Logistic regression in the study population (Table 2). When adjusting for body mass index, diastolic BP, 24-hour urine volume, current alcohol consumption, serum albumin, serum uric acid, eGFR, cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and hs-CRP, we found that age, sex, systolic BP, current smoking, diabetes mellitus, hyperlipidemia, and hemoglobin were independently associated with the co-existence of HTN and pre-existing CVD.

Observational Period and Mortality

The median observational period was 33.7 (IQR 15.7-60.9) months. During this period, 571 (18.6%, 95% CI 17.1 to 20.0%) of 3073 patients died, with 286 (9.3%, 95% CI 8.2% to 10.4%) CVD mortality, 375 (12.2%, 95%CI 11.2% to 13.4%) transferring to hemodialysis, 159 (5.2%, 95% CI 4.5% to 6.0%) receiving renal transplants, 26 (0.8%, 95% CI 0.6% to 1.2%) transferring to other dialysis centers, and 106 (3.4%, 95% CI 2.8% to 4.1%) loss of follow-up. The number of all-cause mortality was 143 (38.6%, 95% CI 33.7% to 44.2%), 15 (25.0%, 95% CI 14.6% to 36.0%), 293 (18.1%, 95% CI 16.2% to 20.1%), and 120 (11.7%, 95% CI 9.7% to 13.5%) in the HTN plus CVD group, CVD group, HTN group, and control group, respectively. The number of CVD mortality was 76 (20.5%, 95% CI 16.5% to 25.0%), 7 (11.7%, 95% CI 4.8% to 21.1%), 147 (9.1%, 95% CI 7.7% to 10.6%), and 56 (5.5%, 95% CI 4.2% to 6.8%) in the HTN plus CVD group, CVD group, HTN group, and control group, respectively.

The incidence of all-cause mortality was 55.7/1000 patient-years in the study population, with 27.9/1000 patient-years of CVD mortality incidence (Table 3). The incidence of all-cause mortality was 131.0, 74.4, 56.1, and 32.2/1000 patient-years, and CVD mortality incidence was 69.6, 34.7, 28.2, and 15.0/1000 patient-years among the HTN plus CVD group, CVD group, HTN group, and control group, respectively.

Comorbidities and Mortality

Survival analysis found that the HTN plus CVD group had poorer cumulative survival (P<0.001) and CVD mortality-free survival (P=0.006) compared to the control group (Figure 1). The association between comorbidities and mortality was evaluated by the different Cox proportional hazards regression models (Table 4). When comparing to the control group, the HTN plus CVD group, CVD group and HTN group had 3.98 (95% CI 3.07 to 5.17), 2.18 (95%CI 1.27 to 3.74), and 1.83 (95%CI 1.47 to 2.28)-time risk of all-cause morality in the model 4, respectively. The HTN plus CVD group, CVD group and HTN group had 4.68 (95%CI 3.27 to 6.69), 2.11(95%CI 0.96 to 4.63), and 1.87 (95%CI 1.37 to 2.54)-time risk for CVD mortality compared to the control group in the model 4, respectively. Similar trends of the association between comorbidities and mortality were observed among subgroups of men, women, diabetes mellitus, non-diabetes mellitus, hyperlipidemia, and non-hyperlipidemia (Figure 2). There was no significant interaction between HTN and CVD on all-cause and CVD mortality (β=0.010, P=0.973; β=0.058, P=0.892) in the study population.

Sensitivity Analysis

When performing competing risk analyses with hemodialysis or renal transplants as the competing risk factors, the HTN plus CVD group, CVD group and HTN group had 3.00 (95% CI 2.19 to 4.11), 2.03 (95%CI 1.11 to 3.73), and 1.37 (95%CI 1.07 to 1.75)-time risk of all-cause morality compared to the control group, respectively, in the Fine and Gray model 4. Similarly, when using non-CVD mortality, hemodialysis or renal transplants as the competing risk factors, compared to the control group, the HTN plus CVD group, CVD group and HTN group had 3.17 (95% CI 2.03 to 4.97), 2.01 (95%CI 0.83 to 4.89), and 1.54 (95%CI 1.08 to 2.18)-time risk of all-cause morality, respectively, in the Fine and Gray model 4.

A total of 42 (1.4%) patients aged < 18 years at the start dialysis were excluded, with 6 deaths at the end study. By the end of study, 810 (26.3%) adult patients were follow up less than 24 months, and 282 (9.2%) adult patients survived for less than 24 months. The remaining 1939 (63.1%) adult patients were follow up for at least 24 months, with 283 (14.6%, 95% CI 12.9% to 16.1%) of all-cause mortality and 135 (7.0%, 95% CI 5.8% to 8.1%) of CVD mortality. We found that when comparing to the control group, the HTN plus CVD group, CVD group, and HTN group had 3.53 (95% CI 2.32 to 4.84), 1.73 (95% CI 1.01 to 2.97), and 1.46 (95% CI 1.17 to 1.81)-time risk of all-cause mortality, and 4.59 (95% CI 2.70 to 7.79), 1.93 (95% CI 0.88 to 4.28), and 1.58 (95% CI 1.15 to 2.16)-time risk of CVD mortality in the Cox regression model 4, respectively, among adult those with at least 24-month follow-up period.

Discussion

In our multi-center study of 3073 incident Chinese CAPD patients, the co-existence of HTN and pre-existing CVD at the start of dialysis were more strongly associated with all-cause and CVD mortality compared to either HTN or pre-existing CVD alone. Pre-existing CVD was also more strongly associated with all-cause and CVD mortality than hypertension. Similar trends were observed in the competing risk analysis, subgroups of men, women, diabetes mellitus, non-diabetes mellitus, hyperlipidemia, and non-hyperlipidemia patients, as well as those with at least 24-month period of follow up.

HTN is high prevalent and plays a significant role in the mortality of dialysis patients [19]. Previous observational studies over the past decade have confirmed the “U-shaped” or “reverse J-shaped” relationship between BP and mortality of dialysis patients [20-23]. On the contrary, a direct linear association between systolic BP outside the unit and all-cause mortality was observed (HR 1.26 for each 10mmHg higher systolic BP; 95% CI 1.14 to1.40) [24]. However, the relationship between HTN, as a comorbidity, and mortality of dialysis patients has received little attention. Meanwhile, the prevalence of CVD was 64.5% among patients aged > 65 years with chronic kidney disease, compared to 32.4% among those without CKD. Thus, dialysis patients may have a higher prevalence of pre-existing CVD, when receiving RRT, and have poorer survival. A study of 107,922 dialysis patients from the Unite States evaluated the association between the dialysis modality and mortality, with 26.0% of coronary artery disease of new ESRD patients [12]. The HR of death was significantly greater for patients with coronary artery disease compared with those without these conditions at ESRD onset CAD (HR 1.11, 95%CI 1.08 to 1.14). We previously conducted a study of 1068 Chinese CAPD patients, with 30.8% of pre-existing CVD patients. This reported that 7.0% of prior stroke CAPD patients (n=75) had 1.82-time risk of all-cause

mortality than those without this condition. However, to best of our knowledge, there has been no study focusing on the association between the co-existence of HTN and pre-existing CVD in dialysis patients. In the present study, we first reported that the co-existence of HTN and pre-existing CVD were more strongly associated with all-cause and CVD mortality compared to either HTN or pre-existing CVD alone in CAPD patients, with similar findings from the competing risk analysis. The 64.6% of prevalence of HTN in our study was slightly lower that those in these previous studies, in which the prevalence of HTN was 65.7% and 73.8% in Chinese CAPD patients [4, 5]. The 14.1% of prevalence of pre-existing CVD was mildly higher than 10.5% pre-existing CVD in one single study with 740 incident Chinese CAPD patients[5], but significantly lower than 30.3% in another single study with 985 incident Chinese CAPD patients [4]. In the study population, we found that when using those without either HTN or pre-existing CVD as a reference, patients with only pre-existing CVD had also more strongly associated with all-cause mortality (HR 2.18 vs. HR 1.83) and CVD mortality (HR 2.11 vs. HR 1.87) than those with only HTN. Among patients with at least 24-month survival time, patients with only pre-existing CVD had also more strongly associated with all-cause mortality (HR 1.73 vs. HR 1.46) and CVD mortality (HR 1.93 vs. HR 1.1.58) than those with only HTN, when comparing to those without either HTN or pre-existing CVD alone. Notably, the 2.18 of HR of pre-existing CVD for all-cause mortality was significantly higher than 1.11 of HR in the above-mentioned study with 2-year follow-up period [12], but slightly higher than 1.82 of HR in our previous study [13]. The disparities of these findings may be due to (1) different ethnicity; (2) different sample size; (3) different follow-up duration.

In the present study, baseline variables were unmatched among groups. Compared to patients with only HTN, those with HTN and pre-existing CVD were more likely to be elderly age, higher percentiles of current smoking, diabetes mellitus, and hyperlipidemia, higher levels of systolic BP, hemoglobin, and cholesterol. Elderly age, current smoking, and diabetes mellitus had an adverse effect on the prognosis of dialysis patients [25-28]. Patients with HTN and pre-existing CVD had higher percentiles of diabetes mellitus and hyperlipidemia than patients with only HTN, which contributed to higher percentiles of taking medications. Therefore, patients with HTN and pre-existing CVD had higher percentiles of taking calcium channel blockers, beta blockers, diuretics, ACEI/ARBs, aspirin, and statins. In summary, we should cautiously interpret our findings due to the significant difference of baseline variables among the study population.

Strengths of this study included a large sample size, population from five dialysis centers, and a detailed evaluation and adjustment for all-cause and CVD risk factors of real-world data. Several limitations should be considered. First, this was a retrospective study with potential unaccounted confounding factors and the selection biases. Although after adjusting for baseline variables, we did not draw conclusions about potential causal relationship between comorbidities and mortality. Nonetheless, changes of HRs among the model 2, 3, and 4 were less than 10%, suggesting three models we built were stable and reliable for predicting outcomes [29]. Second, one challenge was the definition of HTN. The optimal method to diagnose HTN in peritoneal dialysis patients is an area of controversy [30]. A recent study reported that similarly to the general populations, ambulatory BP monitoring is the gold standard method in management of HTN in peritoneal dialysis patients [6]. In our study, diagnosis of HTN mainly

based on the BP value measured by the ambulatory BP monitoring from their medical records, or the use of antihypertensive medications. Nonetheless, we did not analyzed the effect of changes of systolic BP and diastolic BP on the mortality in CAPD patients. Lastly, all eligible patients were from China, suggesting our findings may lack generalization to other ethnic populations.

In conclusion, the co-existence of HTN and pre-existing CVD at the start of CAPD had a more harmful effect on the subsequent risk of all-cause and CVD mortality than either HTN or pre-existing CVD alone, and pre-existing CVD was also more strongly associated with risk of all-cause and CVD mortality than HTN among CAPD patients. Our findings suggested that a combined assessment of HTN and pre-existing CVD compared with separate assessment of the two comorbidities further improved risk stratification of CAPD patients at risk of mortality.

List Of Abbreviations

CAPD, continuous ambulatory peritoneal dialysis; HTN, hypertension; CVD, cardiovascular disease; BP, blood pressure; ACEI/ARB, beta blockers, angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; HR, hazards ratio; CI, confidence index.

Declarations

Ethics approval and consent to participate

The study was consistent with the ethical principles of the Declaration of Helsinki and was approved by the Human Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University, Zhujiang Hospital of Southern Medical University, Jiujiang No. 1 People's Hospital, Affiliated Sixth People's Hospital, Shanghai Jiao Tong University, The First Affiliated Hospital of Zhengzhou University, and the First Affiliated Hospital of Nanchang University. Written informed consent was obtained from all participants.

Consent for publication

All authors have approved the submitted version. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No.

Authors' contributions

XY W, contributions to the conception, and drafted the work; XR F, the acquisition of data; FF P, the acquisition of data; YQ W, the acquisition of data; NS W, contributions to the conception and design of the work; Q, Z, analysis and interpretation of data; XJ Z, contributions to the conception and design of the work; XF W, contributions to the conception, design of the work, and revised it. All authors have read and approved the manuscript.

Acknowledgements

We express our gratitude to all patients who participated in the study.

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Tables

Table 1. The demographic characteristics, medications, and laboratory parameters at the start of dialysis therapy among four groups.

	Study population	Control group	HTN group	CVD group	HTN plus CVD group	P-value
ber	3073	1027	1616	60	370	
years	49.0 (39.0-61.0)	45.0 (34.0-56.0)	49.0 (39.0-60.0)	54.0 (44.0-64.0)	62.0 (52.0-70.0)	<0.001
stratification						<0.001
years	876 (28.5%)	403 (39.2%)	436 (27.0%)	12 (20.0%)	25 (6.8%)	
50 years	741 (24.1%)	253 (24.8%)	419 (25.9%)	15 (25.0%)	54 (14.6%)	
60 years	665 (21.7%)	202 (19.8%)	364 (22.5%)	12 (20.0%)	87 (23.5%)	
70 years	539 (17.6%)	125 (12.2%)	284 (17.6%)	14 (23.3%)	116 (31.4%)	
years	252 (8.2%)	43 (4.2%)	114 (7.1%)	7 (11.7%)	88 (23.8%)	
%	1780 (57.9%)	568 (55.3%)	957 (59.2%)	30 (50.0%)	225 (60.8%)	0.080
mass index, kg/m^2	22.6±7.3	22.0±7.8	22.9±7.6	20.9±5.4	23.2±3.5	<0.001
olic BP, Hg	149.8±25.7	143.1±26.1	153.2±24.5	135.9±26.8	154.6±25.6	<0.001
colic BP, Hg	87.5±15.8	85.3±15.8	89.6±15.6	84.4±15.7	84.5±15.3	<0.001
urine volume,	800(500-1200)	800 (440-1200)	800 (500-1200)	900 (400-1262)	800 (450-1200)	0.861
ent smoking,	310 (10.1%)	75 (7.3%)	184 (11.4%)	2 (3.3%)	49 (13.2%)	<0.001
ent alcohol umption, (%)	114 (3.7%)	34 (3.3%)	66 (4.1%)	1 (1.7%)	13 (3.5%)	0.608

etes mellitus,	567 (18.4%)	67 (6.5%)	318 (19.7%)	7 (11.7%)	175 (47.3%)	<0.001
erlipidemia	567 (18.4%)	140 (13.6%)	282 (17.5%)	20 (33.3%)	125 (33.8%)	<0.001
um channel kers (%)	2271 (73.9%)	608 (59.2%)	1311 (81.1%)	36 (60.0%)	315 (85.1%)	<0.001
blockers (%)	1255 (40.8%)	362 (35.2%)	695 (43.0%)	17 (28.3%)	181 (48.9%)	<0.001
etics (%)	205 (6.7%)	32 (3.1%)	123 (7.6%)	1 (1.7%)	49 (13.2%)	<0.001
E/ARBs (%)	1042 (33.9%)	293 (28.5%)	556 (34.4%)	19 (31.7%)	173 (46.8%)	<0.001
rin (%)	247 (8.0%)	30 (2.9%)	128 (7.9%)	3 (5.0%)	86 (23.2%)	<0.001
ns (%)	439 (14.3%)	73 (7.1%)	241 (14.9%)	12 (20.0%)	113 (30.5%)	<0.001
oglobin, g/dL	9.3±2.8	9.2±2.9	9.1±2.8	9.1±2.2	9.8±2.9	<0.001
m albumin,	3.5±0.6	3.5±0.6	3.5±0.5	3.4±0.7	3.5±0.6	0.750
m uric acid, dL	6.9±2.3	7.0±2.3	6.9±2.4	6.4±2.2	6.8±2.2	0.184
R, min/1.73 m^2	6.4 (4.7-8.3)	6.6 (4.7-8.5)	6.4 (4.7-8.2)	6.1 (4.6-8.4)	6.2 (4.7-8.2)	0.415
esterol, dL	151 (117-183)	146 (112-179)	153 (118-183)	157 (132-187)	157 (125-187)	0.045
yceride, dL	94 (57-153)	92 (62-149)	95 (53-156)	85 (32-158)	99 (59-153)	0.413
density rotein, mg/dL	40 (31-50)	39 (31-51)	40 (32-50)	41 (31-53)	38 (31-48)	0.525
density rotein, mg/dL	82 (48-117)	82 (54-118)	82 (4-116)	89 (37-120)	79 (30-116)	0.861
RP, mg/L	4.4 (1.9-	4.1 (1.8-	4.5 (2.1-	4.5 (1.7-	4.4 (1.9-	0.643

14.2)	12.5)	14.1)	20.1)	18.9)

Control group: patients without either HTN or pre-existing CVD.

HTN, hypertension; CVD, cardiovascular disease; BP, blood pressure; ACEI/ARB, beta blockers, angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein.

Table 2. Baseline parameters and both the presence of HTN and pre-existing CVD using the multiple Logistic regression.

	OR	95%CI
Age ≤ 40 years	Reference	
Age 41-50 years	2.24	1.38 to 3.63
Age 51-60 years	3.36	2.11 to 5.35
Age 61-70 years	5.68	3.58 to 9.02
Age ≥ 71 years	12.35	7.57 to 20.16
Sex (male as a reference)	0.78	0.60 to 1.00
Systolic BP (per increase 10 mmHg)	1.06	1.01 to 1.11
Current smoking (yes/no)	1.48	1.02 to 2.15
Diabetes mellitus (yes/no)	2.87	2.23 to 3.69
Hyperlipidemia (yes/no)	1.81	1.40 to 2.37
Hemoglobin (per increase 1 g/dL)	1.04	1.00 to 1.09

The following parameters at baseline were in the multiple Logistic regression model: age, sex, body mass index, systolic BP, diastolic BP, current smoking, current alcohol consumption, 24-hour urine volume, diabetes mellitus, hyperlipidemia, hemoglobin, serum albumin, serum uric acid, eGFR, cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and hs-CRP.

HTN, hypertension; CVD, cardiovascular disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; CI, confidence interval.

Table 3. All-cause and CVD mortality incidence.

	All-cause mortality	CVD mortality	Time at risk (years)	All-cause mortality incidence (/1000 patient-years)	95% CI	CVD mortality incidence (/1000 patient-years)	95% CI
Study population	571	286	10252.5	55.7	51.3 to 59.1	27.9	24.6 to 30.9
Control group	120	56	3729.5	32.2	27.0 to 36.9	15.0	11.0 to 18.7
HTN group	293	147	5221.9	56.1	52.0 to 62.8	28.2	23.5 to 32.8
CVD group	15	7	201.5	74.4	46.5 to 112.9	34.7	9.5 to 60.1
HTN plus CVD group	143	76	1091.6	131.0	116.9 to 151.9	69.6	54.9 to 83.7

Incidence was calculated as number of events divided by total valid observational time at risk, scaled to episodes per 1000 years.

Control group: patients without either HTN or pre-existing CVD.

HTN, hypertension; CVD, cardiovascular disease; CI, confidence interval.

Table 4. Adjusted HRs for mortality among different Cox proportional hazards regression models.

	Model 1		Model 2		Model 3		Model 4	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
All-cause mortality								
Control group	Reference							
HTN group	1.74	1.41 to 2.15	1.78	1.43 to 2.20	1.83	1.47 to 2.27	1.83	1.47 to 2.28
CVD group	2.35	1.38 to 4.02	2.18	1.28 to 3.74	2.12	1.24 to 3.63	2.18	1.27 to 3.74
HTN plus CVD group	4.08	3.20 to 5.20	4.11	3.21 to 5.26	3.92	3.02 to 5.09	3.98	3.07 to 5.17
CVD mortality								
Control group	Reference							
HTN group	1.87	1.38 to 2.55	1.93	1.42 to 2.63	1.90	1.39 to 2.59	1.87	1.37 to 2.54
CVD group	2.33	1.06 to 5.11	2.28	1.04 to 5.00	2.20	1.01 to 4.83	2.11	0.96 to 4.63
HTN plus CVD group	4.65	3.29 to 6.57	4.91	3.47 to 6.95	4.68	3.27 to 6.69	4.68	3.27 to 6.69

Model 1, unadjusted; model 2, model 1 plus age, sex, body mass index, systolic BP, diastolic BP, current smoking, current alcohol consumption, 24-hour urine volume, diabetes mellitus, and hyperlipidemia; model 3, model 2 plus medications; model 4, model 3 plus hemoglobin,

serum albumin, serum uric acid, eGFR, cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and hs-CRP.

Control group: participants without either HTN or pre-existing CVD.

HTN, hypertension; CVD, cardiovascular disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; CI, confidence interval.

Table 5. Adjusted HRs for mortality among the Fine and Gray competing risk models.

	Model 1		Model 2		Model 3		Model 4	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
All-cause mortality								
Control group	Reference							
HTN group	1.57	1.27 to 1.95	1.35	1.06 to 1.72	1.41	1.10 to 1.80	1.37	1.07 to 1.75
CVD group	2.34	1.31 to 4.17	2.22	1.24 to 3.97	2.09	1.15 to 3.79	2.03	1.11 to 3.73
HTN plus CVD group	3.52	2.51 to 4.94	2.91	2.13 to 3.97	3.00	2.19 to 4.12	3.00	2.19 to 4.11
CVD mortality								
Control group	Reference							
HTN group	1.73	1.28 to 2.33	1.57	1.11 to 2.23	1.60	1.13 to 2.26	1.54	1.08 to 2.18
CVD group	2.18	1.09 to 4.37	2.07	0.86 to 4.95	2.04	0.84 to 4.98	2.01	0.83 to 4.89
HTN plus CVD group	4.40	2.55 to 7.58	3.19	2.04 to 4.98	3.17	2.02 to 4.98	3.17	2.03 to 4.97

Model 1, unadjusted; model 2, model 1 plus age, sex, body mass index, systolic BP, diastolic BP, current smoking, current alcohol consumption, 24-hour urine volume, diabetes mellitus, and hyperlipidemia; model 3, model 2 plus medications; model 4, model 3 plus hemoglobin, serum albumin, serum uric acid, eGFR, cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and hs-CRP.

Control group: participants without either HTN or pre-existing CVD.

HTN, hypertension; CVD, cardiovascular disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; CI, confidence interval.

Figures

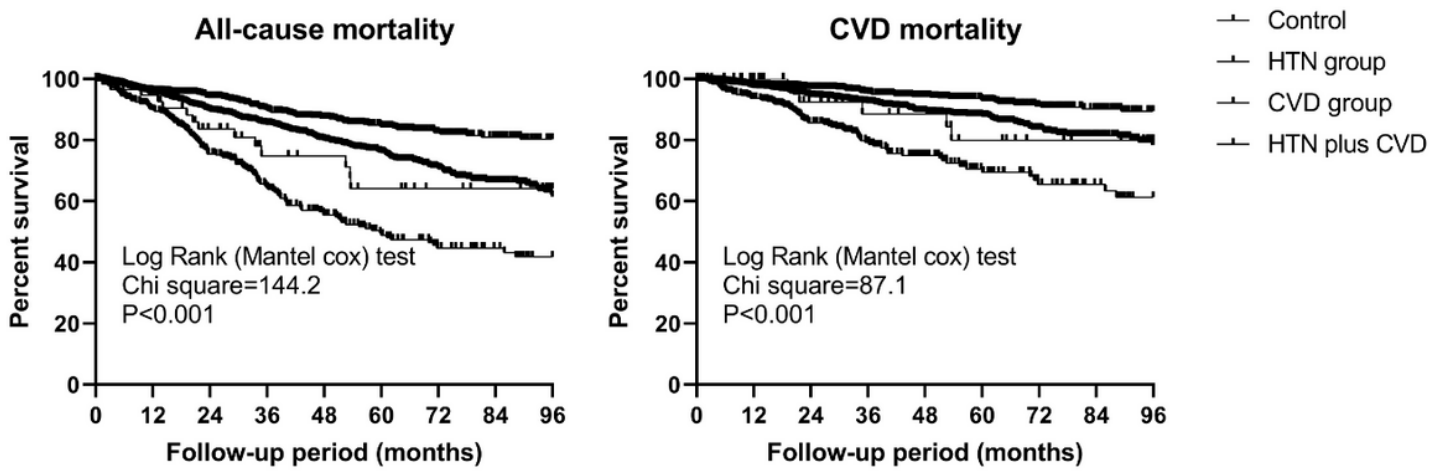

Figure 1

Cumulative survival were lowest in those with both HTN plus pre-existing CVD. Control group: participants without either HTN or pre-existing CVD. HTN, hypertension; CVD, cardiovascular disease.

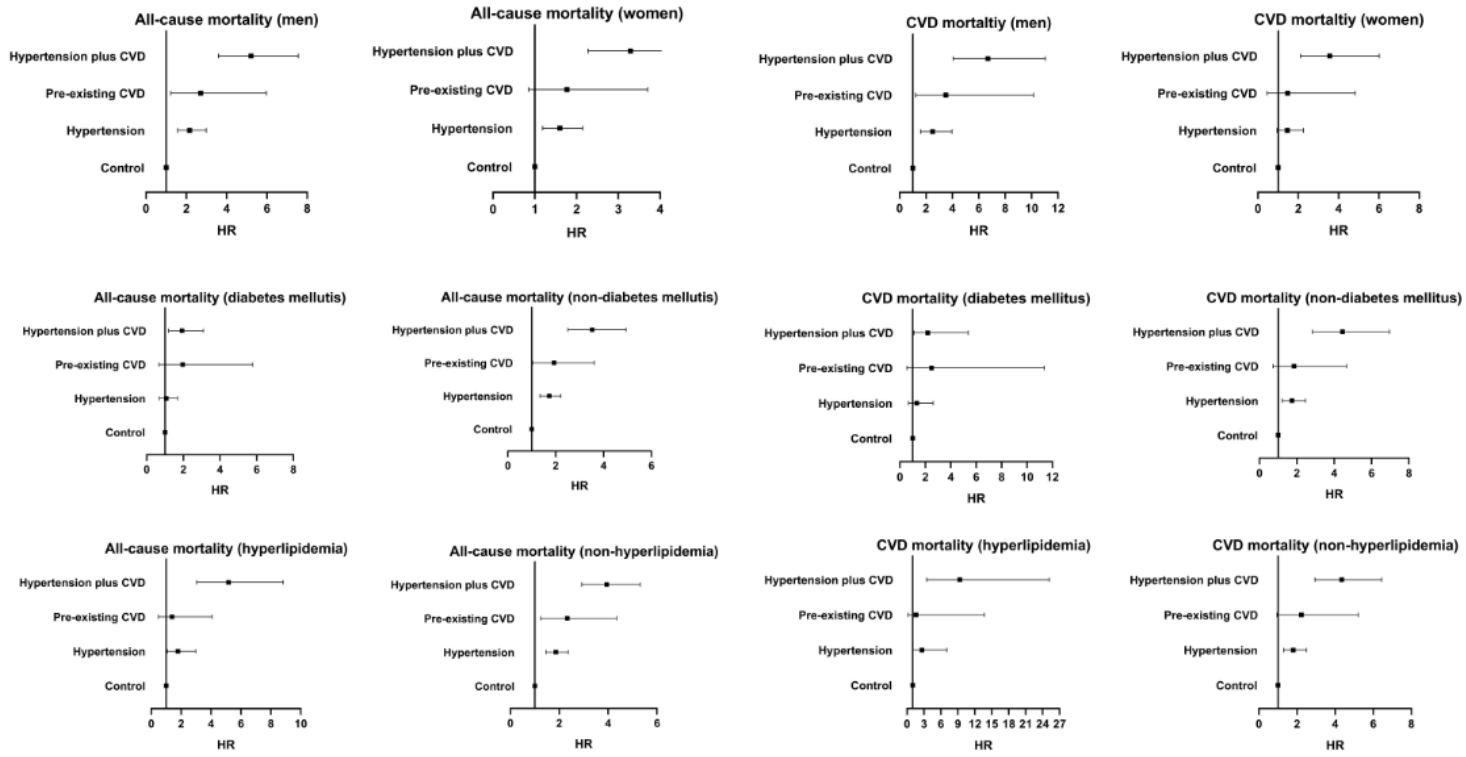

Figure 2

Adjusted HRs for all-cause and CVD mortality among subgroups. Model 1, unadjusted; model 2, model 1 plus age sex, body mass index, systolic BP, diastolic BP, current smoking, current alcohol consumption, 24-hour urine volume, diabetes mellitus, and hyperlipidemia; model 3, model 2 plus medications; model 4, model 3 plus hemoglobin, serum albumin, serum uric acid, eGFR, cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, and hs-CRP. Control group: participants without either HTN or pre-existing CVD. HTN, hypertension; CVD, cardiovascular disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; CI, confidence interval.