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Changes in Pulse Pressure during Hemodialysis Treatment and Survival in Maintenance Dialysis Patients

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Abstract

Background and objectives

Pulse pressure has been shown as a risk factor for mortality in patients on maintenance hemodialysis (MHD). However, the effect of change in pulse pressure during hemodialysis on survival in a large cohort of patients on MHD has not been sufficiently investigated.

Design, setting, participants, & measurements

This study examined the association between time-varying Δ pulse pressure (postdialysis minus predialysis pulse pressure) and mortality in a cohort of 98,577 patients on MHD (July 2001–June 2006) using Cox proportional hazard models with restricted cubic splines.

Results

The average patient age was 62 years old; among the patients, 33% were black and 59% had diabetes. During 134,814 patient-years of at-risk time, 16,054 (16%) patients died, with 6827 (43%) of the deaths caused by cardiovascular causes. In the models including adjustment for either predialysis systolic BP or mean arterial BP, there was a U-shaped association between change in pulse pressure during hemodialysis and all-cause mortality. In the systolic BP plus case mix plus malnutrition-inflammation complex syndrome–adjusted model, large declines in pulse pressure (>–25 mmHg) and increases in pulse pressure >5 mmHg were associated with higher all-cause mortality (reference: ≥–5 to <5 mmHg): hazard ratios (95% confidence intervals [95% CIs]) for change pulse pressures of <–25, ≥–25 to <–15, ≥–15 to <–5, 5 to <15, 15 to <25, and ≥25 mmHg were 1.21 (95% CI, 1.14 to 1.29), 1.03 (95% CI, 0.97 to 1.10), 1.01 (95% CI, 0.96 to 1.06), 1.06 (95% CI, 1.01 to 1.11), 1.17 (95% CI, 1.11 to 1.24), and 1.15 (95% CI, 1.08 to 1.23), respectively. The U-shaped association was observed with cardiovascular death.

Conclusions

Modest reductions in pulse pressure after hemodialysis are associated with the greatest survival, whereas large declines or rises in pulse pressure are related to higher mortality. Trials determining how to modify pulse pressure response to improve survival in the hemodialysis population are indicated.

Keywords: survival, hemodialysis, hemodynamics and vascular regulation

Introduction

Increased pulse pressure (PP), as a surrogate of vascular stiffness, is an independent predictor of cardiovascular events, all-cause mortality, and cardiovascular mortality observed in the general, elderly, and hypertensive populations (1–5). At any mean arterial BP (MAP) level, patients on maintenance hemodialysis (MHD) have higher PP values than age-matched control subjects with normal renal function (6). Both increased arterial stiffness and PP have been associated with higher risks of cardiovascular events, all-cause mortality, and cardiovascular death in patients on MHD (7–12).

Cardiovascular disease is the leading cause of mortality in patients on MHD (13). Vascular changes, including atherosclerosis and arteriosclerosis, contribute to increased cardiovascular mortality in this population (14,15). Atherosclerosis is associated with increased arterial intima-media thickness leading to luminal obstruction with ischemic events. Arteriosclerosis results in arterial stiffening, increased pulse wave velocity (PWV), systolic BP (SBP), and PP, leading to left ventricular hypertrophy (LVH) and reduced coronary perfusion (16–19).

In patients on MHD, hypervolemia may play an important role on changes in pulse pressure (ΔPP) (20). Volume overload has already been associated with LVH and mortality in patients on MHD (21–23). Combined volume correction with angiotensin-converting enzyme inhibition has been shown to improve aortic PWV in patients on MHD (24). Reductions in PWV may improve survival of patients on MHD (25). Decreased PP during hemodialysis has been demonstrated to be associated with lower risks of hospitalization or death (26). Previous observations are limited by regression models that assume a linear relationship between PP change and mortality. Therefore, they may be underpowered for detecting a U-shaped association of high mortality with either increases or decreases in PP (26). Both large declines and any rises in SBP during hemodialysis have been linked to increased mortality (27). The association between PP change during hemodialysis and mortality has not been sufficiently studied in large cohorts. We hypothesized that any increases or declines in PP during hemodialysis were associated with higher all-cause and cardiovascular mortality in addition to predialysis SBP levels in a large nationally representative cohort of patients on MHD.

Materials and Methods

Study Population and Data

We extracted and examined data from all patients receiving hemodialysis treatment between July 2001 and June 2006 in any of the 580 United States outpatient dialysis facilities of DaVita. The baseline quarter for each patient was the earliest calendar quarter in which the patient's hemodialysis duration was >90 days. Of the 124,277 patients aged 18–99 years old who underwent hemodialysis for >90 days without modality switches during the study period, patients with missing BP measures (n=24,545), those with outliers of BP values (<0.25th or >99.75th percentiles; n=481), or those with outliers of PP values (<0.25th or >99.75th percentiles; n=207) were excluded, resulting in 99,044 patients for PP analysis (Supplemental Figure 1). The study was approved by the institutional review committees of the Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center and DaVita Clinical Research. The requirement for a written consent was exempted because of the large sample size, patient anonymity, and nonintrusive nature of the research.

The creation of the DaVita hemodialysis patient cohort has been described previously (28). All repeated clinical and laboratory measurements for each patient were averaged during any calendar quarters (*i.e.,* over a 13-week interval). Clinical and laboratory parameters for each patient were obtained during the cohort period (July 1, 2001–June 30, 2006), and patients were followed for outcomes until June 30, 2006. Dialysis duration was defined as the duration of time between the first day of hemodialysis treatment and the day that the patient entered the cohort. Demographic data were obtained from the DaVita database. History of preexisting comorbid conditions and tobacco smoking were obtained by linking the DaVita database to the data from the Medical Evidence Form 2728 from the US Renal Data System. Available preexisting comorbidities were grouped into nine categories: ischemic heart disease (IHD), congestive heart failure (CHF), other cardiac diseases, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, and nonambulatory state.

Outcome Measures

All-cause mortality was defined by date of death if it occurred during the cohort period (July 1, 2001–June 30, 2006). The recorded causes of death were obtained from the US Renal Data System, and cardiovascular death was defined as death because of myocardial infarction, cardiac arrest, heart failure, cerebrovascular accident, and other cardiac diseases. Patients who received a kidney transplant or were lost to follow-up were censored at the time of the event.

Main Predictors

Pre- and postdialysis BPs with patients in a sitting position were measured during every hemodialysis session using a digital monitor with automatically inflated BP cuffs attached to a hemodialysis machine on the basis of the standard protocol of hemodialysis units. All recorded BP values were captured electronically within the database. All repeated BP values for each patient were averaged over each 13-week calendar quarter and used in analysis to minimize measurement variability. PP was quantified as the difference between the mean SBP and mean diastolic BP (DBP) for each calendar quarter. ΔPP was defined as postdialysis PP minus predialysis PP. Time-varying ΔPP for each patient was used in our analyses. We divided ΔPP levels *a priori* into seven categories (<–25, ≥–25 to <–15, ≥–15 to <–5, ≥–5 to<5, 5 to <15, 15 to <25, and ≥ 25 mmHg). The ΔPP category of ≥–5 to <5 mmHg was designated as the reference group.

Clinical and Laboratory Measures

MAP was calculated using the following equation: MAP=[(2×DBP)+SBP]/3′. Pre- and postdialysis body weights were recorded at each hemodialysis session. The volume of fluid removed during hemodialysis (ultrafiltration percentage [%UF]) was calculated as follows: %UF=[(predialysis weight–postdialysis weight)/predialysis weight]×100, where weights were measured in kilograms. Blood samples were drawn using uniform techniques in all DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida, usually within 24 hours. All laboratory values were measured using automated and standardized methods in the DaVita Laboratory. Most laboratory parameters were measured monthly, including complete blood cell counts and serum levels of urea nitrogen, creatinine, albumin, calcium, phosphorus, bicarbonate, and total iron-binding capacity (TIBC). Serum ferritin levels were measured at least quarterly. Corrected serum calcium levels were calculated as follows: corrected calcium (mg/dl)= {0.8×[4−serum albumin (g/dl)]}+serum calcium (mg/dl). Most blood samples were collected before hemodialysis, except for postdialysis serum urea nitrogen, to calculate urea kinetics.

Statistical Analyses

We evaluated the association of quarterly ΔPP as a main predictor with all-cause and cardiovascular mortality as outcomes using time-varying Cox proportional hazard regression models and restricted cubic splines. To minimize the influence of outliers, patients with outliers (<1st or >99th percentiles) of ΔPP (n=467) were

excluded from the analyses. Therefore, the final study population consisted of 98,577 patients for the analyses (Supplemental Figure 1). The two separate adjusted models, including either predialysis SBP or predialysis MAP, were performed. For each model, three levels of multivariable adjustment were examined (*1*): minimally adjusted models that included the main predictors (ΔPP), entry calendar quarter, and predialysis SBP or MAP; (*2*) case mix–adjusted models that included covariates in the minimally adjusted models plus age, sex, race/ethnicity (non-Hispanic whites, blacks, Hispanics, Asians, and others), dialysis duration categories (3 to <6 months, 6 to <24 months, 2 to <5 years, and ≥5 years), presence of diabetes, nine preexisting comorbidities, history of tobacco smoking, primary insurance (Medicare, Medicaid, private, and others), types of vascular access (arteriovenous fistula, arteriovenous graft, and catheter), dialysis dose as indicated by single-pool Kt/V (spKt/V), and %UF; and (*3*) case mix and malnutrition-inflammation complex syndrome (MICS)-adjusted models that included all of the covariates in the case mix models plus body mass index (BMI) and serum levels of albumin, creatinine, TIBC, ferritin, calcium, phosphorus, bicarbonate, hemoglobin, peripheral white blood cell count, and lymphocyte percentage. Time-varying covariates included predialysis SBP or MAP, %UF, spKt/V, BMI, and serum levels of albumin, creatinine, TIBC, ferritin, calcium, phosphorus, bicarbonate, hemoglobin, white blood cell count, and lymphocyte percentage. Fixed baseline covariates included age, sex, race/ethnicity, dialysis duration categories, comorbidities, primary insurance, and types of vascular access.

Stratified analysis by predialysis SBP (<120, 120 to <140, 140 to <160, and ≥160 mmHg) was performed to evaluate for the effect modification. Sensitivity analyses using the Cox model were also conducted in subgroups of patients on the basis of baseline age, sex, race/ethnicity, presence or absence of diabetes, IHD, CHF, dialysis duration, and baseline BMI categories. An additional analysis adjusted for either predialysis PP or postdialysis PP was performed. Missing values of time-varying covariates were imputed using the values in the previous quarter, whereas missing data on fixed baseline covariates were imputed by the means or medians of the existing values as appropriate. We reported *P* values from two-sided tests with a significance level set to 0.05. All statistical analyses were performed using Stata version 12.1 (Stata, College Station, TX).

Results

Cohort Description

The baseline characteristics of the 98,577 hemodialysis patients stratified by ΔPP during hemodialysis are summarized in Table 1. The mean±SD patient age at baseline was 62±15 years; 45% of the patients were women, 33% were black, and 59% had diabetes. The mean±SD pre- and postdialysis PPs at baseline were 73±17 and 68±17 mmHg, respectively. Compared with patients with ΔPP of ≥–5 to < 5 mmHg, patients with ΔPP <–5 and >5 mmHg had a higher prevalence of diabetes, IHD, and CHF. Patients with greater reductions in PP during hemodialysis were more likely to have higher predialysis SBP and MAP, but lower postdialysis SBP and MAP. The amount of ultrafiltration per session and spKt/V negatively correlated with ΔPP levels. During 134,814 patient-years of at-risk time, 16,054 (16%) patients died, with 6827 (43%) deaths caused by cardiovascular causes. Crude all-cause and cardiovascular mortality rates were 119 per 1000 patient-years (95% confidence interval [95% CI], 117 to 121) and 51 per 1000 patient-years (95% CI, 49 to 52), respectively.

Association between ΔPP and Mortality

In the minimally adjusted models including either predialysis SBP or predialysis MAP, there was a U-shaped association between ΔPP and all-cause mortality (Figures 1 and 2). Large reductions in PP and increased PP during hemodialysis were associated with higher all-cause mortality. The U-shaped relationship between ΔPP and all-cause mortality persisted in the case mix (Supplemental Figure 2) and case mix plus MICS-adjusted models (Figures 1 and 2). The predialysis SBP-adjusted and MAP-adjusted hazard ratios of all-cause mortality associated with ΔPP during hemodialysis are shown in Table 2. In the SBP plus case mix

plus MICS-adjusted model, compared with patients in the reference category of ΔPP ≥–5 to <5 mmHg, death risks were higher in patients with ΔPP<–25 mmHg (HR, 1.21; 95% CI, 1.14 to 1.29), 5 to <15 mmHg (HR, 1.06; 95% CI, 1.01 to 1.11), 15 to <25 mmHg (HR, 1.17; 95% CI, 1.11 to 1.24), and ≥25 mmHg (HR, 1.15; 95% CI, 1.08–1.23), respectively (Table 2). A similar trend was observed with cardiovascular mortality (Supplemental Figure 3, Table 3).

Sensitivity Analyses

In the case mix plus MICS-adjusted analyses stratified according to predialysis SBP, the U-shaped associations between ΔPP and all-cause mortality were present in the categories of predialysis SBP ≥120 mmHg. In the category of predialysis SBP <120 mmHg, only a decrease in PP during hemodialysis was associated with higher mortality (Figure 3). The *P* value for the interaction between SBP strata and ΔPP for all-cause mortality was <0.001. The U-shaped associations between ΔPP and all-cause mortality were also consistent in all subgroups of patients on the basis of demographics (baseline age, sex, race/ethnicity), presence or absence of diabetes, IHD, and CHF, dialysis duration, and baseline BMI categories (Figure 4). The results of the analyses conducted with and without imputation of missing covariates were essentially the same (Supplemental Table 1). The results did not change in analyses, including outliers <1st percentile and >99th percentile of ΔPP (Supplemental Table 2). The case mix and MICS-adjusted model, including predialysis PP as a covariate, showed the U-shaped association (Supplemental Figure 4A), whereas the model adjusted for postdialysis PP found that a decrease in PP during hemodialysis was associated with greater survival (Supplemental Figure 4B).

Discussion

In this large cohort of 98,577 patients on MHD, we observed a U-shaped association between ΔPP during hemodialysis and mortality. Large declines in PP during hemodialysis were related to higher mortality, whereas moderate reductions in PP were associated with the greatest survival. These associations were observed in all demographic and clinical subgroups. Similar patterns of associations were observed with all-cause and cardiovascular mortality. To our knowledge this is the largest epidemiology study to examine the association of ΔPP over time and subsequent mortality in patients on MHD.

Although we have previously shown that large declines and any rises in SBP during hemodialysis have been linked to higher mortality (27), there may be added benefit in examining changes in intradialytic PP. In the general population, PP has been shown to be a predictor of adverse outcomes independent of SBP. For example, in a study of 69,989 subjects >50 years old, a higher absolute PP was associated with increased cardiovascular mortality even among patients with normal SBP (29). Several earlier studies have also shown that PP is a predictor of cardiovascular events and mortality in patients on MHD (6,11), and recent data suggest that PP may in fact be a better predictor of death and cardiovascular events than other BP parameters in the hemodialysis population (30).

Decreasing PP during hemodialysis has been shown to be associated with improved short-term outcomes. In a cohort of 438 hemodialysis patients, every 10 mmHg decline in PP during hemodialysis was associated with a 20% decreased hazard of death or hospitalization at 6 months (26). Greater reductions in PP induced by hemodialysis could be caused by higher fluid or sodium solute removal in these subjects. PP responses to hemodialysis are closely related to blood volume changes (31). Fluid removal lowers SBP more than DBP, leading to reductions in PP during hemodialysis (32,33). We found that a large reduction in PP was associated with higher mortality. In our study, patients with greater decline in PP after hemodialysis correlated with more fluid removal during hemodialysis. Higher ultrafiltration volumes have been associated with the presence and severity of hemodialysis-induced cardiac injury. Myocardial stunning leads to loss of systolic function and increased cardiac events and mortality (34). It is plausible that subsequent hemodialysis-associated cardiac ischemia might explain our findings. Decreased SBP and PP during hemodialysis were associated with improved arterial stiffness induced by a hemodialysis session (35). Reduction in aortic

stiffness as measured by PWV in response to BP lowering has been shown to improve survival of patients on MHD (25). Molecules that may influence arterial function, such as endothelin, nitric oxide, and angiotensin II, are removed during hemodialysis, resulting in improved arterial stiffness. Tycho Vuurmans *et al.* (24) reported that combined volume correction with angiotensin-converting enzyme inhibition reduced aortic PWV. Several studies have demonstrated that a hemodialysis session led to an improvement in endothelial function (36–38).

Nevertheless, inability to decrease PP during hemodialysis may be the result of the presence of intrinsic vascular lesions. Increased arterial stiffness may be caused by structural changes of artery, which is less dependent on BP (39–43). Arterial stiffening may also result from high BP without structural changes and can be reversed with BP lowering. Past observations investigating the influence of hemodialysis on alterations in arterial compliance as reflected by the aortic augmentation index (AI) showed that patients whose AI remained abnormal after hemodialysis had larger hearts than those whose AIs normalized with hemodialysis. Persistently high AIs after hemodialysis might be explained by the presence of vascular structural damage (44). Vascular calcification has been associated with LVH (45,46), adverse cardiovascular outcomes, and mortality in patients on MHD (47,48).

The association between a rise in PP after hemodialysis and a higher risk of mortality was observed in our study. PP increase during hemodialysis could be a marker of vascular disease or could be caused by alteration in autonomic control. Elevated PP during hemodialysis in patients with peripheral vascular disease may be in response to volume depletion induced by hemodialysis caused by reduced autonomic peripheral control, reduced cardiac baroreflex, and lower sympathetic activity on BP and heart rate (49).

Several limitations of our study bear mention. First, this study was observational in nature, and no causality can be established from the results. Second, increased PP could reflect either decreased vascular compliance (17,19) or hypervolemia (20) in patients on MHD. More precise measurements of vascular stiffness (*e.g.,* PWV, aortic compliance) and volume status (*e.g.,* bioimpedance analysis) were not performed in our study because of limited feasibility of these investigations in the large study population. We lacked information on prescribed dialysate calcium, sodium, bicarbonate concentration, predialysis serum sodium concentration, ultrafiltration rate, and profile during hemodialysis; therefore, we could not determine whether these factors contributed to ΔPP during hemodialysis. Third, we had no information regarding the use of antihypertensive medications, which may confound the association between PP change and mortality. Fourth, we lacked data on patient compliance with hemodialysis treatments, and information on comorbidities was not updated during follow-up, which may result in residual confounding.

Despite the limitations, our study included (*1*) a large sample size of the cohort; (*2*) uniform administrative patient care in a large dialysis organization and laboratory measurements performed at a single facility; (*3*) use of 3-month averaged pre- and postdialysis SBP and DBP data from every single dialysis session to calculate ΔPP and averaged laboratory measures during any calendar quarter to minimize measurement variability; and (*4*) use of time-dependent survival models with multivariable adjustments for time-varying covariates as potential confounders.

In summary, our study demonstrated that modest declines in PP during hemodialysis were associated with improved survival, whereas any rises and large decreases in PP had higher mortality risk. ΔPP during hemodialysis could identify those patients most likely to respond favorably to a therapeutic PP reduction. Our study begs the question whether BP responses to hemodialysis are modifiable where targeting modest reductions in PP during hemodialysis can lead to improved patient survival.

Disclosures

None.

Supplementary Material

Supplemental Data:

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Footnotes

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Figures and Tables

Table 1.

Baseline characteristics of 98,577 hemodialysis patients stratified by change in pulse pressure

Variables	All	ΔPP (mmHg)							*P* Value
		<–25	≥–25 to <–15	≥–15 to <–5	≥–5 to <5	5 to <15	15 to <25	≥25	
n (%)	98,577 (100)	9038 (9)	12,958 (13)	24,424 (25)	27,200 (28)	15,406 (16)	6177 (6)	3374 (3)	
Age (y)	62±15	63±14	62±14	62±15	61±16	62±16	63±15	63±15	0.04
Women	45	50	47	44	42	44	46	49	<0.001
Race/ethnicity									
White	42	44	42	41	41	43	46	45	0.001
Black	33	31	32	33	34	33	31	34	0.02
Hispanic	15	15	15	15	15	14	14	14	0.01
Asian	3	3	4	3	3	3	3	2	<0.001
Others	7	7	7	8	7	7	6	5	<0.001

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Variables	All	ΔPP (mmHg)							*P* Value
		<–25	≥–25 to <–15	≥–15 to <–5	≥–5 to <5	5 to <15	15 to <25	≥25	
HD duration									
3 to <6 mo	57	56	54	55	57	60	63	65	<0.001
6 to <24 mo	18	19	19	19	18	17	16	15	<0.001
2 to <5 y	16	17	18	17	16	15	14	13	<0.001
≥5 y	9	8	9	9	9	8	7	7	<0.001
Comorbidities									
DM	59	68	64	58	55	58	60	62	<0.001
IHD	22	22	21	21	21	22	24	24	<0.001
Cancer	4.6	4.1	4.1	4.4	4.6	5	4.9	5.3	<0.001
CHF	28	29	28	27	27	28	31	30	0.002
COPD	6	6	6	6	6	6	7	6	0.01
CVD	7	8	8	7	7	8	8	8	0.43
Hypertension	80	83	82	80	79	80	81	83	0.001
Other cardiac diseases	6	5	5	5	6	6	6	6	<0.001
PVD	11	13	12	11	11	12	13	13	0.20
Nonambulatory state	2.8	2.7	2.6	2.7	2.8	3.3	3	3.4	<0.001
Current smoking	5	5	5	5	5	5	5	5	0.15
Insurance									
Medicare	68	69	69	68	68	69	69	69	0.23
Medicaid	6	5	5	6	6	6	6	6	<0.001
Private	9	4	9	12	12	7	4	1	<0.001
Others	17	22	17	14	14	18	21	24	0.01
Vascular access									
AVF	30	29	31	31	30	28	25	25	<0.001
AVG	31	30	33	33	32	29	27	24	<0.001
Catheter	39	41	36	36	38	43	48	51	<0.001
Pre-HD BP (mmHg)									
Systolic BP	151±24	172±22	162±21	153±22	146±23	143±24	140±24	137±23	<0.001
Diastolic BP	78±15	80±16	80±15	78±14	77±14	77±15	77±16	77±17	<0.001
PP	73±17	92±15	82±15	75±15	69±15	66±16	64±16	60±16	<0.001
Mean arterial BP	102±17	110±17	107±16	103±15	100±16	99±17	98±17	97±18	<0.001
Post-HD BP (mmHg)									

Variables	All	ΔPP (mmHg)							*P* Value
		<–25	≥–25 to <–15	≥–15 to <–5	≥–5 to <5	5 to <15	15 to <25	≥25	
Systolic BP	141±23	129±19	134±20	136±21	141±22	149±24	157±24	164±24	<0.001
Diastolic BP	73±14	72±14	72±13	72±13	73±13	74±15	74±16	73±17	<0.001
Pulse pressure	68±17	57±15	62±15	64±15	68±15	75±16	83±16	91±16	<0.001
Mean arterial BP	95±16	91±14	92±14	93±14	96±15	99±17	102±17	103±18	<0.001
ΔPP (mmHg)	−5±16	−35±7	−20±3	−10±3	−1±3	9±3	19±3	31±5	<0.001
Time on dialysis (min)	214±28	214±28	214±28	215±28	214±28	214±27	214±28	213±28	0.35
Ultrafiltration (kg/session)	2.6±1.2	2.9±1.3	2.8±1.2	2.7±1.2	2.6±1.2	2.5±1.2	2.4±1.3	2.3±1.3	<0.001
Ultrafiltration (%)[a]	3.4±1.5	3.6±1.5	3.6±1.4	3.5±1.4	3.4±1.5	3.2±1.6	3.1±1.6	3.0±1.6	<0.001
BMI (kg/m^2)[b]	26.9±6.1	27.9±6.5	27.5±6.3	27.0±6.1	26.6±6.0	26.2±5.8	26.3±6.1	26.5±6.2	<0.001
Laboratory measures (baseline)									
Kt/V (single pool)	1.55±0.30	1.56±0.30	1.56±0.30	1.55±0.30	1.54±0.31	1.53±0.31	1.54±0.31	1.53±0.31	<0.001
Albumin (g/dl)	3.7±0.5	3.7±0.4	3.7±0.4	3.7±0.4	3.7±0.5	3.6±0.5	3.6±0.5	3.6±0.5	<0.001
Creatinine (mg/dl)	8.0±3.2	7.7±2.9	8.1±3.1	8.3±3.2	8.1±3.3	7.6±3.1	7.1±3.0	7.0±2.8	<0.001
TIBC (mg/dl)	208±45	212±43	210±43	208±44	207±45	206±46	208±48	207±47	<0.001
Ferritin (ng/ml)[c]	390 (190–683)	373 (184–663)	414 (198–702)	410 (200–698)	391 (189–687)	377 (183–674)	349 (173–640)	341 (174–619)	<0.001
Bicarbonate (mg/dl)	22.1±3.2	22.2±3.2	22.0±3.1	21.9±3.1	22.1±3.1	22.4±3.2	22.6±3.1	22.7±3.2	<0.001
Calcium (mg/dl)	9.5±0.7	9.5±0.7	9.6±0.7	9.6±0.7	9.5±0.7	9.5±0.7	9.5±0.7	9.5±0.6	<0.001
Phosphorus (mg/dl)	5.6±1.5	5.7±1.4	5.7±1.4	5.7±1.5	5.6±1.5	5.5±1.5	5.4±1.5	5.4±1.5	<0.001
Hemoglobin (g/dl)	12.1±1.3	12.3±1.3	12.3±1.2	12.2±1.3	12.1±1.3	12.0±1.4	12.0±1.4	12.1±1.4	<0.001
WBC (×10^3/μl)	7.38±2.43	7.51±2.36	7.42±2.29	7.35±2.42	7.31±2.46	7.36±2.41	7.52±2.60	7.64±2.62	0.04
Lymphocyte (%)	20.6±7.8	20.7±7.4	21.1±7.6	21.0±7.8	20.6±8.0	20.1±7.8	19.8±7.6	19.6±7.7	<0.001

Data are presented as percentages, means±SDs, or as otherwise indicated. The *P* value for trend shows the differences in each variable across ΔPP categories. HD, hemodialysis; DM, diabetes mellitus; IHD, ischemic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; PVD, peripheral vascular disease; AVF, arteriovenous fistula; AVG, arteriovenous graft; PP, pulse pressure; ΔPP, postdialysis pulse pressure minus predialysis pulse pressure; BMI, body mass index; TIBC, total iron-binding capacity; WBC, white blood cells.

[a]Calculated as [(predialysis weight−postdialysis weight)/predialysis weight]×100.
[b]Calculated using postdialysis weight and height.
[c]Median (interquartile range) is used.

Figure 1.

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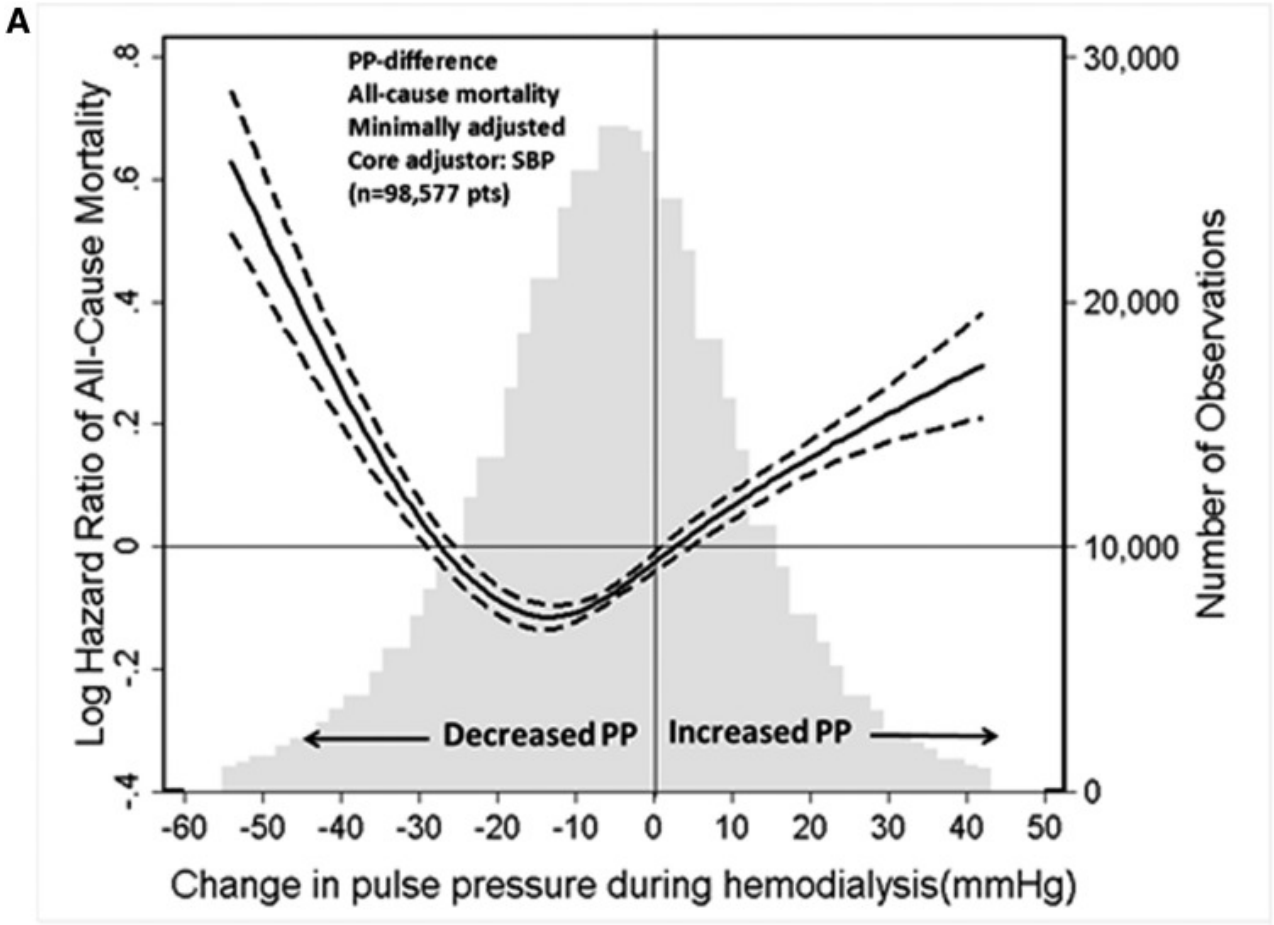

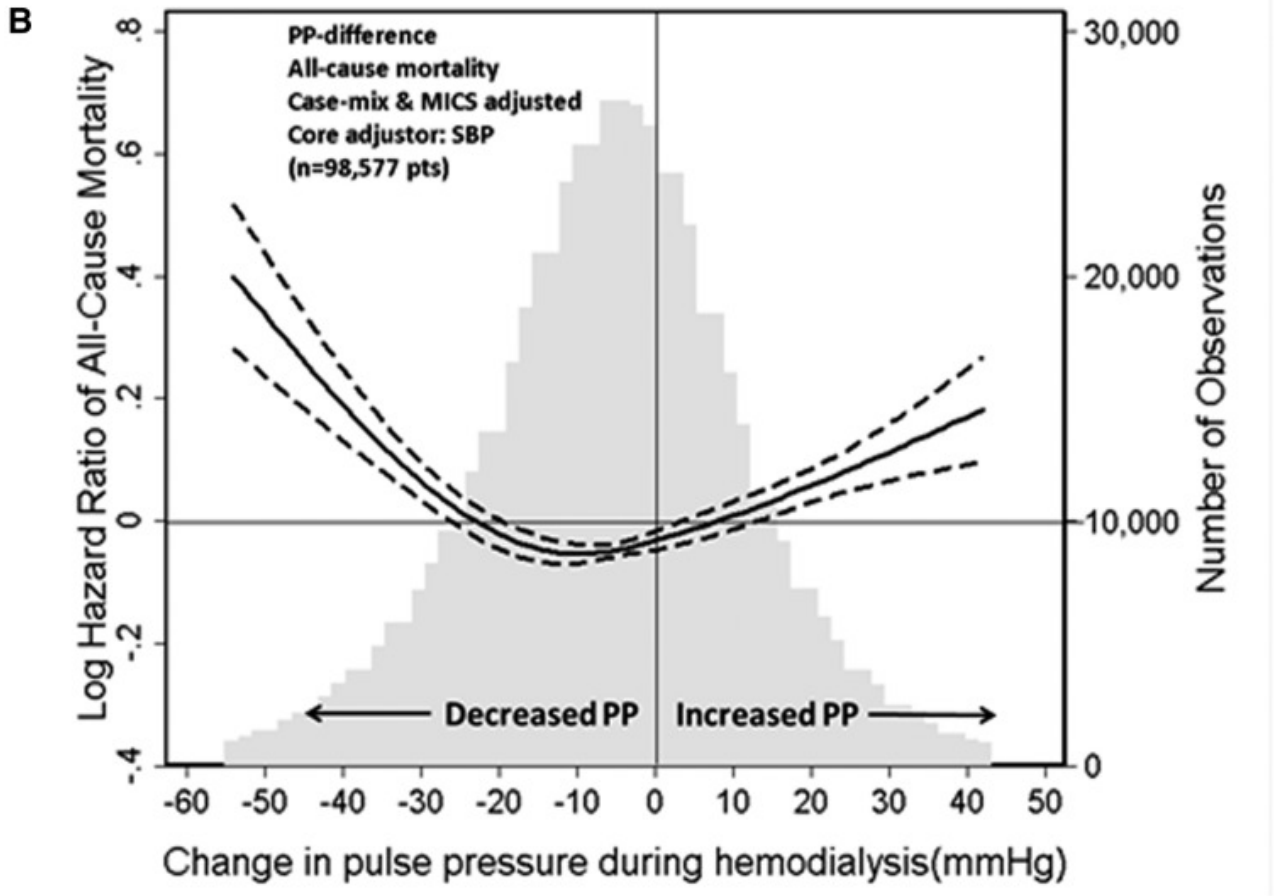

SBP-adjusted hazard ratio for the association between change in pulse pressure during hemodialysis and all-cause mortality. Minimally SBP-adjusted model (A) and SBP plus case-mix plus MICS-adjusted model (B). Dashed lines

represent 95% confidence interval. Change in PP was defined as postdialysis PP minus predialysis PP. Minimally SBP-adjusted model included adjustment for entry calendar quarter and predialysis SBP. SBP plus case mix plus MICS-adjusted model included covariates in the minimally SBP-adjusted model plus age, sex, race/ethnicity, presence of diabetes mellitus, nine preexisting comorbidities, history of tobacco smoking, dialysis duration categories, primary insurance, types of vascular access, dialysis dose as indicated by single pool Kt/V, ultrafiltration percentage, body mass index, serum levels of albumin, creatinine, total iron-binding capacity, ferritin, calcium, phosphorus, bicarbonate, hemoglobin, blood white blood cells, and lymphocyte percentage. MICS, malnutrition-inflammation complex syndrome; PP, pulse pressure; SBP, systolic BP.

Figure 2.

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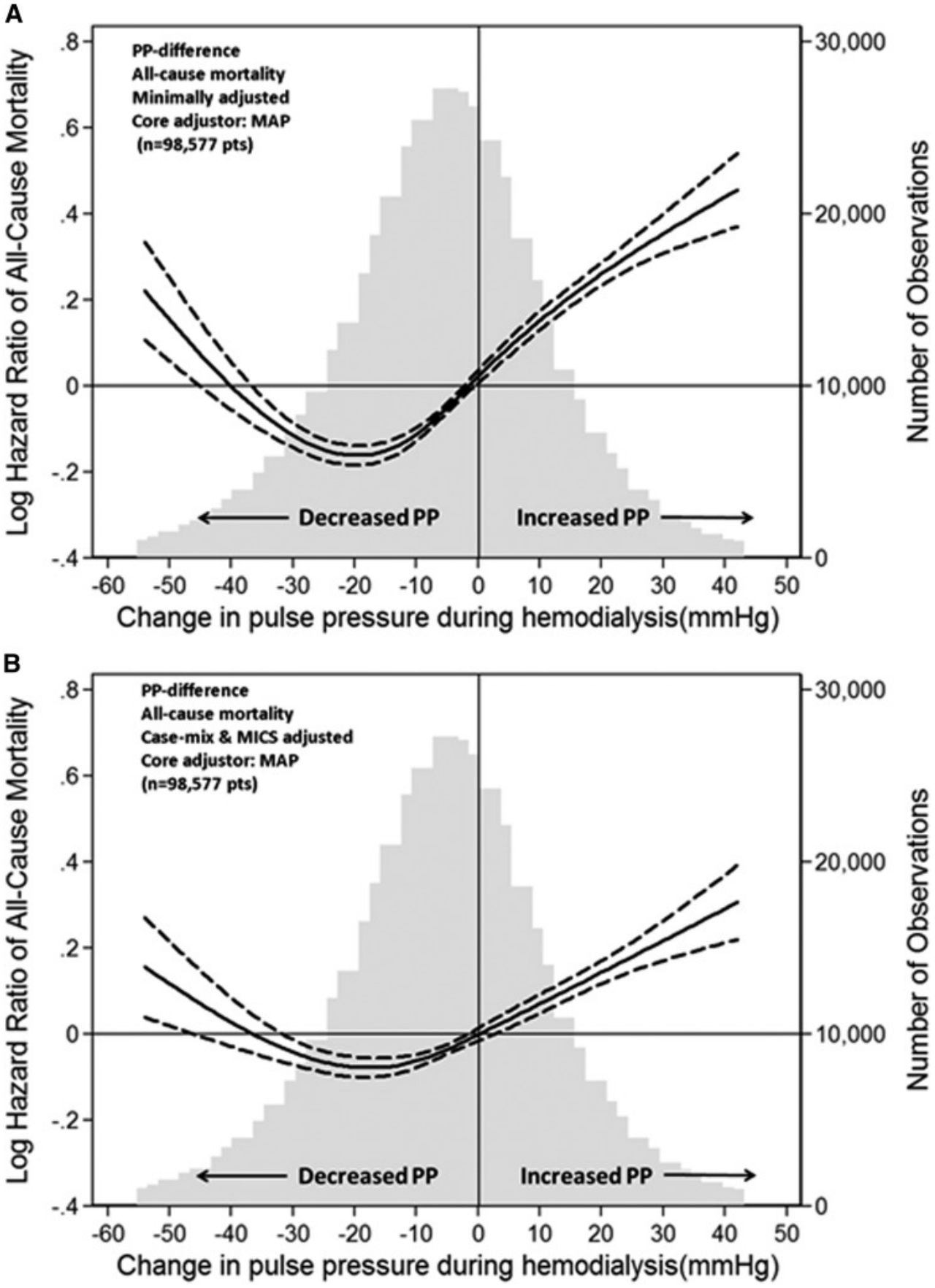


MAP-adjusted hazard ratio for the association between change in pulse pressure during hemodialysis and all-cause mortality. Minimally MAP-adjusted model (A) and MAP plus case-mix plus MICS-adjusted model (B). Dashed lines represent 95% confidence interval. Change in PP was defined as postdialysis PP minus predialysis PP. Minimally MAP-adjusted model included adjustment for entry calendar quarter and predialysis MAP. MAP plus case mix plus MICS-

adjusted model included covariates in the minimally MAP-adjusted model plus age, sex, race/ethnicity, presence of diabetes mellitus, nine preexisting comorbidities, history of tobacco smoking, dialysis duration categories, primary insurance, types of vascular access, dialysis dose as indicated by single pool Kt/V, ultrafiltration percentage, body mass index, serum levels of albumin, creatinine, total iron-binding capacity, ferritin, calcium, phosphorus, bicarbonate, hemoglobin, blood white blood cells, and lymphocyte percentage. MAP, mean arterial BP; MICS, malnutrition-inflammation complex syndrome; PP, pulse pressure.

Table 2.

Hazard ratios (95% confidence intervals) for the association between change in pulse pressure categories (reference: ≥–5 to <5 mmHg) and all-cause mortality using time-varying Cox regression analyses

Δ Pulse Pressure (mmHg)	Minimally SBP Adjusted (*n*=98,577)			SBP and Case Mix Adjusted (*n*=98,577)			SBP and Case Mix and MICS Adjusted (*n*=98,577)		
	HR	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
<–25	1.26	1.18 to 1.34	<0.001	1.12	1.05 to 1.19	<0.001	1.21	1.14 to 1.29	<0.001
≥–25 to <–15	1.00	0.94 to 1.06	0.92	0.95	0.89 to 1.00	0.06	1.03	0.97 to 1.10	0.27
≥–15 to <–5	0.95	0.90 to 0.99	0.02	0.93	0.89 to 0.98	0.01	1.01	0.96 to 1.06	0.74
≥–5 to <5	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
5 to <15	1.13	1.08 to 1.19	<0.001	1.10	1.05 to 1.16	<0.001	1.06	1.01 to 1.11	0.02
15 to <25	1.30	1.23 to 1.37	<0.001	1.24	1.18 to 1.32	<0.001	1.17	1.11 to 1.24	<0.001
≥25	1.27	1.18 to 1.35	<0.001	1.20	1.12 to 1.28	<0.001	1.15	1.08 to 1.23	<0.001
Δ Pulse Pressure (mmHg)	Minimally MAP Adjusted (*n*=98,577)			MAP and Case Mix Adjusted (*n*=98,577)			MAP and Case Mix and MICS Adjusted (*n*=98,577)		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
<-25	0.98	0.92 to 1.04	0.43	0.90	0.85 to 0.96	0.001	1.03	0.97 to 1.10	0.34
≥–25 to <–15	0.88	0.83 to 0.93	<0.001	0.84	0.79 to 0.89	<0.001	0.95	0.89 to 1.00	0.07
≥–15 to <–5	0.90	0.85 to 0.94	<0.001	0.89	0.84 to 0.93	<0.001	0.97	0.92 to 1.02	0.18
≥–5 to <5	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
5 to <15	1.17	1.11 to 1.22	<0.001	1.15	1.09 to 1.20	<0.001	1.09	1.04 to 1.14	<0.001
15 to <25	1.37	1.29 to 1.44	<0.001	1.32	1.25 to 1.40	<0.001	1.23	1.16 to 1.30	<0.001
≥25	1.39	1.30 to 1.49	<0.001	1.33	1.25 to 1.43	<0.001	1.24	1.16 to 1.33	<0.001

Minimally adjusted model included adjustment for entry calendar quarter and predialysis SBP or predialysis MAP. Case mix–adjusted model included adjustment for all covariates in the minimally adjusted model plus age, sex, race/ethnicity, presence of diabetes mellitus, nine preexisting comorbidities, history of tobacco smoking, dialysis duration categories, primary insurance, types of vascular access, dialysis dose as indicated by single pool Kt/V, and ultrafiltration percentage. Case mix and MICS adjusted for covariates in the case mix–adjusted model plus body mass index; serum levels of albumin, creatinine, total iron-binding capacity, ferritin, calcium, phosphorus, bicarbonate, hemoglobin, and white blood cells; and lymphocyte percentage. Δ Pulse pressure, postdialysis pulse pressure minus predialysis pulse pressure; SBP, systolic BP; HR, hazard ratio; MAP, mean arterial BP; 95% CI, 95% confidence interval; MICS, malnutrition-inflammation complex syndrome.

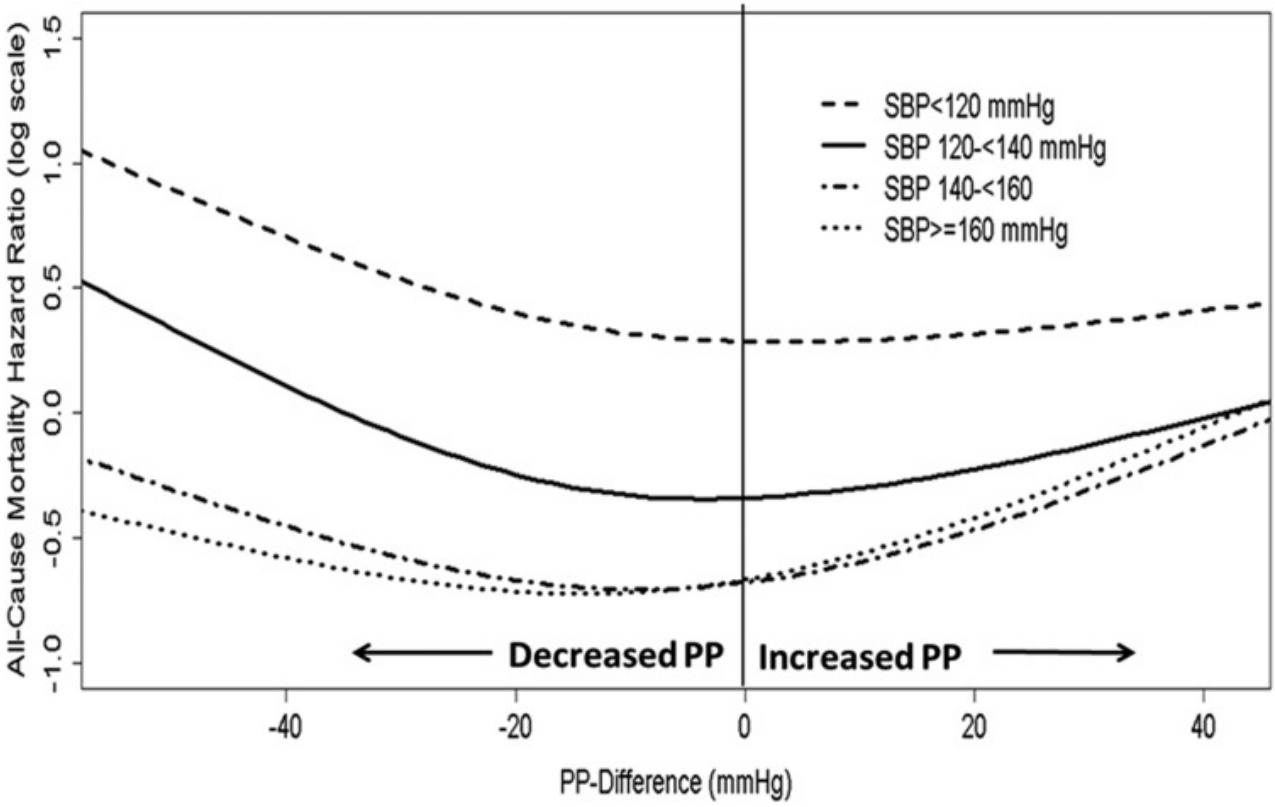
Table 3.

Hazard ratios (95% confidence intervals) for the association of change in pulse pressure categories (reference: ≥–5 to <5 mmHg) with cardiovascular mortality using time-varying Cox regression analyses

Δ Pulse pressure (mmHg)	**Minimally SBP Adjusted (*n*=98,577)**			**SBP and Case Mix Adjusted (*n*=98,577)**			**SBP and Case Mix and MICS Adjusted (*n*=98,577)**		
	HR	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
<–25	1.12	1.02 to 1.23	0.02	0.99	0.90 to 1.09	0.90	1.07	0.97 to 1.18	0.18
≥–25 to <-15	0.86	0.78 to 0.94	<0.001	0.81	0.74 to 0.89	<0.001	0.88	0.80 to 0.96	0.01
≥–15 to <-5	0.85	0.79 to 0.92	<0.001	0.84	0.78 to 0.91	<0.001	0.90	0.84 to 0.97	0.01
≥–5 to <5	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
5 to <15	1.06	0.99 to 1.14	0.10	1.04	0.97 to 1.12	0.28	1.00	0.93 to 1.07	1.00
15 to <25	1.30	1.19 to 1.41	<0.001	1.25	1.15 to 1.36	<0.001	1.18	1.08 to 1.28	<0.001
≥25	1.12	1.01 to 1.24	0.04	1.06	0.95 to 1.18	0.29	1.02	0.92 to 1.14	0.71
Δ Pulse Pressure (mmHg)	Minimally MAP Adjusted (*n*=98,577)			MAP and Case Mix Adjusted (*n*=98,577)			MAP and Case Mix and MICS Adjusted (*n*=98,577)		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
<–25	0.90	0.82 to 0.99	0.03	0.82	0.75 to 0.90	<0.001	0.92	0.84 to 1.01	0.09
≥–25 to <-15	0.77	0.71 to 0.85	<0.001	0.73	0.67 to 0.80	<0.001	0.81	0.74 to 0.89	<0.001
≥–15 to <-5	0.82	0.76 to 0.88	<0.001	0.80	0.75 to 0.87	<0.001	0.87	0.81 to 0.93	<0.001
≥–5 to <5	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
5 to <15	1.09	1.02 to 1.17	0.02	1.07	1.00 to 1.15	0.05	1.02	0.95 to 1.10	0.52
15 to <25	1.36	1.25 to 1.47	<0.001	1.32	1.21 to 1.43	<0.001	1.23	1.13 to 1.34	<0.001
≥25	1.22	1.09 to 1.35	<0.001	1.17	1.05 to 1.30	0.005	1.09	0.98 to 1.22	0.10

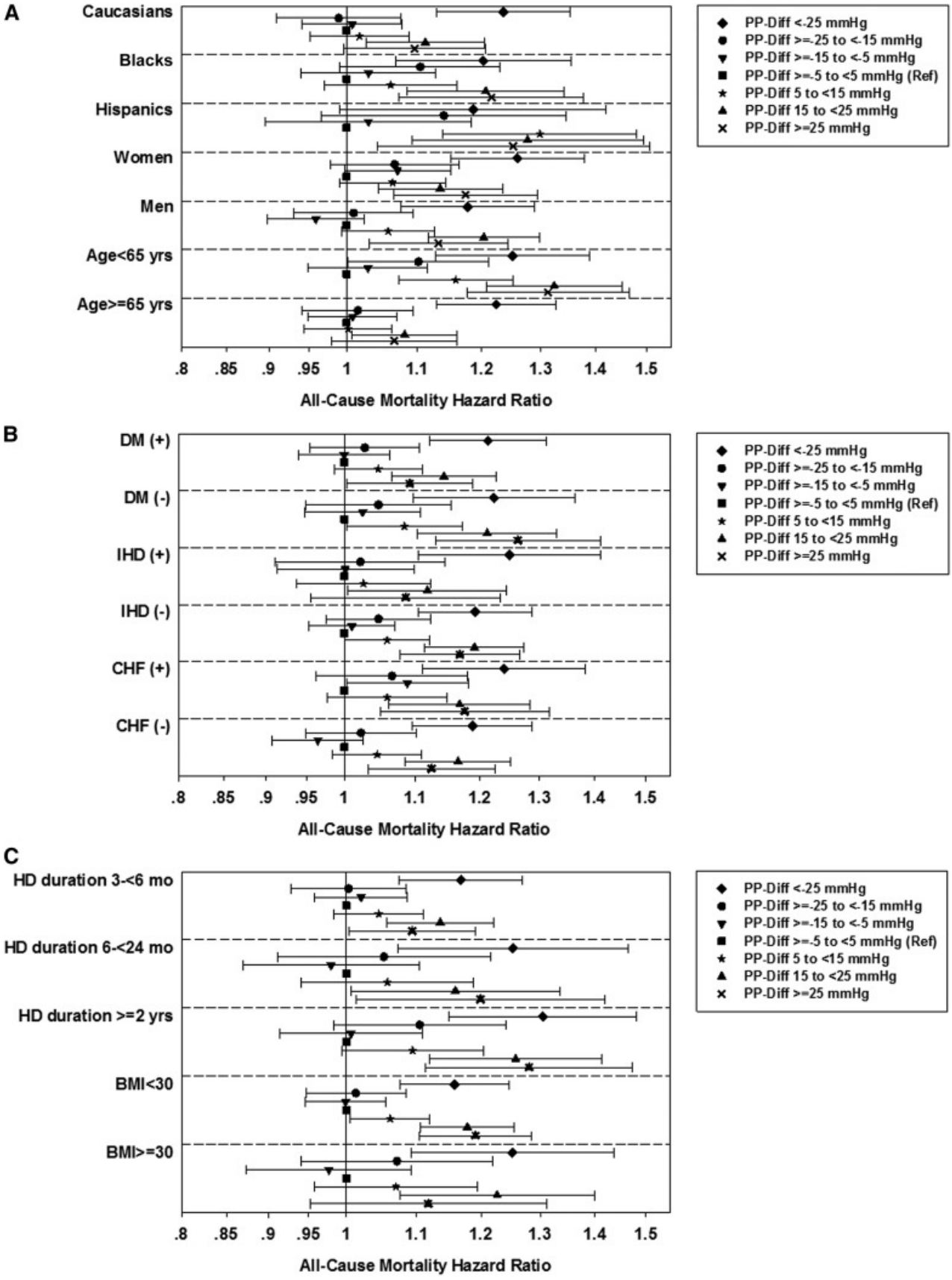
Minimally adjusted model included adjustment for entry calendar quarter and predialysis SBP or predialysis MAP. Case mix–adjusted model included adjustment for all covariates in the minimally adjusted model plus age, sex, race/ethnicity, presence of diabetes mellitus, nine preexisting comorbidities, history of tobacco smoking, dialysis duration categories, primary insurance, types of vascular access, dialysis dose as indicated by single pool Kt/V, and ultrafiltration percentage. Case mix and MICS adjusted for covariates in the case mix–adjusted model plus body mass index, serum levels of albumin, creatinine, total iron-binding capacity, ferritin, calcium, phosphorus, bicarbonate, hemoglobin, and white blood cells, and lymphocyte percentage. Δ Pulse pressure, postdialysis pulse pressure minus predialysis pulse pressure; SBP, systolic BP; HR, hazard ratio; MAP, mean arterial BP; 95% CI, 95% confidence interval; MICS, malnutrition-inflammation complex syndrome.

Figure 3.



Effect modification by predialysis SBP on the association between change in pulse pressure and all-cause mortality for case mix plus MICS–adjusted models. Change in PP was defined as postdialysis PP minus predialysis PP. Case mix plus MICS-adjusted model included adjustment for entry calendar quarter, age, sex, race/ethnicity, presence of diabetes mellitus, nine preexisting comorbidities, history of tobacco smoking, dialysis duration categories, primary insurance, types of vascular access, dialysis dose as indicated by single pool Kt/V, ultrafiltration percentage, body mass index, serum levels of albumin, creatinine, total iron-binding capacity, ferritin, calcium, phosphorus, bicarbonate, hemoglobin, blood white blood cells, and lymphocyte percentage. MICS, malnutrition-inflammation complex syndrome; PP, pulse pressure; SBP, systolic BP.

Figure 4.



Effect of race/ethnicity, sex, age, comorbidities, dialysis duration, and body mass index on the association between change in pulse pressure during hemodialysis and all-cause mortality. All-cause death hazard ratios (95% confidence intervals) comparing change in PP categories (Ref: ethnicity, sex, baseline age (A), presence or absence of DM, IHD, CHF (B), dialysis duration, and baseline body mass index categories (C) for SBP plus case mix plus MICS–adjusted models. The change in PP was defined as postdialysis PP minus predialysis PP. The model included adjustment for entry calendar quarter, predialysis systolic BP, age, sex, race/ethnicity, presence of diabetes mellitus, nine preexisting comorbidities, history

of tobacco smoking, dialysis duration categories, primary insurance, types of vascular access, dialysis dose as indicated by single pool Kt/V, ultrafiltration percentage, body mass index, serum levels of albumin, creatinine, total iron-binding capacity, ferritin, calcium, phosphorus, bicarbonate, hemoglobin, and white blood cells, and lymphocyte percentage. CHF, chronic heart failure; Diff, difference; DM, diabetes mellitus; IHD, ischemic heart disease; MICS, malnutrition-inflammation complex syndrome; PP, pulse pressure; Ref, reference; SBP, systolic blood pressure.

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