

# Optimal cut-off threshold in pulse pressure predicting cardiovascular death among newly diagnosed end-stage renal disease patients

## A prospective cohort study

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### Abstract

Cardiovascular disease (CVD) is the leading cause of death in patients with end-stage renal disease (ESRD) treated by dialysis. Pulse pressure (PP) as an independent prognostic factor of cardiovascular risk might be clinically implicated in predicting the short-term deaths due to cardiovascular diseases in ESRD patients. This study aimed to investigate the dose-response association between PP and risk of cardiovascular mortality in patients initializing peritoneal dialysis (PD). All patients registered with the Henan Peritoneal Dialysis Registry (HPDR) between 2007 and 2014 were incorporated in the current cohort study. PP was assessed by the date of initialisation of PD and cardiovascular mortality in 2 years after the initialisation of PD was defined as the outcome. All accessible clinical measurements were screened as covariables. Further dose-response relationships between PP and risks were explored using spline models. There was a non-linear relationship between PP and the risk of 2-year death for a cardiovascular diseases ( $P < .001$  for linearity test). The PP associated with the lowest risk of cardiovascular mortality was 61 (95% CI 56–64) mmHg. In ESRD patients initializing PD, PP is a good prognostic factor of risk of short-term cardiovascular mortality. The risk is lowest with a PP of 56 to 64 mmHg.

**Abbreviations:** ESRD = end-stage renal disease, HPDR = Henan Peritoneal Dialysis Registry, PD = peritoneal dialysis, PP = pulse pressure.

**Keywords:** cardiovascular diseases, dose-response relationship, mortality, peritoneal dialysis, pulse pressure

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## 1. Introduction

With the increase prevalence of chronic kidney disease (CKD), the number of patients with end-stage renal disease (ESRD) is increasing rapidly and is becoming one of the major life-threatening diseases worldwide.<sup>[1–3]</sup> Cardiovascular disease is the leading cause of death in patients with ESRD treated by dialysis.<sup>[4]</sup> It has been estimated that 40% to 60% of deaths in peritoneal dialysis (PD) patients are due to cardiovascular events.<sup>[2,5,6]</sup>

Observational study has reported a non-linear association between blood pressure measures (systolic and diastolic blood pressure) and cardiovascular mortality among incident PD patients, with high blood pressure (particularly >145/92 mmHg) being associated with a higher risk of cardiovascular mortality.<sup>[7]</sup>

Vascular stiffness has been revealed to increase myocardial afterload and oxygen demand, to lead to left ventricular hypertrophy and to limit coronary filling during diastole.<sup>[8]</sup> The pulsatile component of blood pressure (pulse pressure [PP]) is a prognostic factor of large artery stiffness and a reflection of the atherosclerotic burden, which itself is an independent predictor of cardiovascular risk.<sup>[9,10]</sup> An elevated pulse pressure is associated with a higher cardiovascular mortality.<sup>[11]</sup>

Previous cohort study revealed that PP was associated with 1-year all-cause mortality among patients underwent hemodialysis, with high PP (>60–69 mmHg) be associated with an increased risk of cardiovascular mortality.<sup>[12]</sup> In another cohort, a significant association was found between 30-month all-cause mortality and PP independent of systolic and diastolic blood pressures, with 1 mmHg increase of PP associated with 20%

higher risk of all-cause mortality.<sup>[13]</sup> However few studies have addressed the association between PP and cardiovascular mortality among patients initializing PD in prospective cohorts. In particular the dose-response association between PP and cardiovascular mortality among incident PD patients was not very clear. The present study aimed to examine this relationship and investigates whether a threshold exists for PP in predicting the risk of 2-year cardiovascular mortality among those initializing PD.

## 2. Methods

### 2.1. Data source and study population

For this study, we used data from the Henan Peritoneal Dialysis Registry (HPDR) to develop and validate the risk score. Henan is a province in the Central of China with the population over 100 million. Briefly, the HPDR is operated under the auspices of the Department of Nephrology, the First Affiliated Hospital of Zhengzhou University and provides an independent audit and analysis of renal care in Henan, China. During the study period, information was prospectively collected electronically from all renal units across Henan. Data arriving at the HPDR are subjected to an algorithm which identifies suspicious values, which are then further verified and corrected where necessary by contacting the renal unit. This study was designed as a cohort study, which included all adults aged more than 18 years who commenced PD between 2007 to 2014 and who had at least 2 years' follow-up. Patients who died, underwent transplant or whose kidney function recovered within 90 days after initialisation of dialysis were excluded (n=16) to avoid a reverse causality association between predictors and outcome. This reflects the standard approach to investigating "real" ESRD patients among all those receiving PD care. We randomly allocated 2 thirds of patients to the derivation dataset and the remaining one third to a validation dataset. Ethics approval was granted by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all participants before inclusion.

### 2.2. Pulse pressure definition

Pulse pressure was defined as systolic minus diastolic blood pressure. Both systolic and diastolic blood pressures were measured at the time when patients initializing PD treatment.

### 2.3. Defining outcome, covariables, and missing data

We defined our primary outcome as recorded death with clinically diagnosed cardiovascular disease.<sup>[14,15]</sup> We also obtained data on other covariables (as listed in Table 1), which can be associated with pulse pressure to allow adjustment for confounding. These data were measured at the time when patients started PD treatment. For co-variables used in the final model, our cohort had missing information on body mass index (13.5%), phosphorus (21.0%), albumin (20.0%), total protein (22.6%), total cholesterol (24.3%), low density lipoprotein (24.6%), fasting glucose (16.0%), sodium (8.0%), systolic blood pressure (4.8%), and diastolic blood pressure (4.8%). We used multiple imputations to replace missing values by using a chained equation approach based on all variables. We created 30 imputed datasets for missing

variables that were then combined across all datasets by using Rubin's rule to obtain final model estimates.<sup>[16]</sup>

### 2.4. Statistical methods

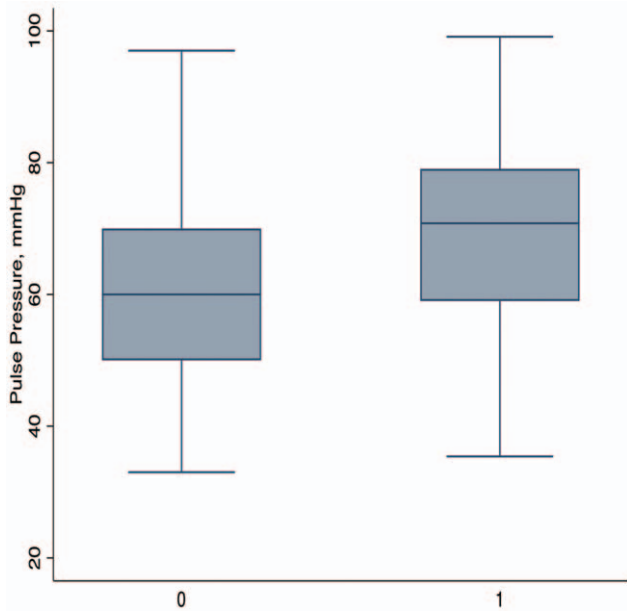
We used Logistic regression model to calculate the incidence rate ratio for cardiovascular mortality according to pulse pressure levels. The dose-response associations between pulse pressure measurements and the risk of cardiovascular mortality were estimated using a linear model, a natural cubic spline model with 3 equally spaced knots determined from the level of pulse pressure measures, and a quadratic spline models. The natural cubic spline model was chosen as the best-fit model for the relationship curve because of its lowest Akaike information Criterion compared with those of the linear model or quadratic spline model. For sensitivity analysis, the natural cubic spline models for the overall dataset were repeated using other potential knots, chosen to lie within the range for minimum to maximum measure of pulse pressure. A linear test was used in the natural cubic spline model to test its linearity of the relationship. The break-point test was carried out to target the potential thresholds (Percentile 5 to Percentile 95 of pulse pressure measures) by incorporating the piecewise term into the cubic spline model. The threshold with a significant break in the regression coefficients and achieving the minimum AIC was chosen as the final threshold. The 95% CI of the threshold was obtained from 1000 bootstrap samples.

All analyses were performed using STATA (STATA SE 15.0 StataCorp, College Station, TX). All *P* values were calculated using 2-tailed tests and a *P* value <.05 was taken to indicate statistical significance.

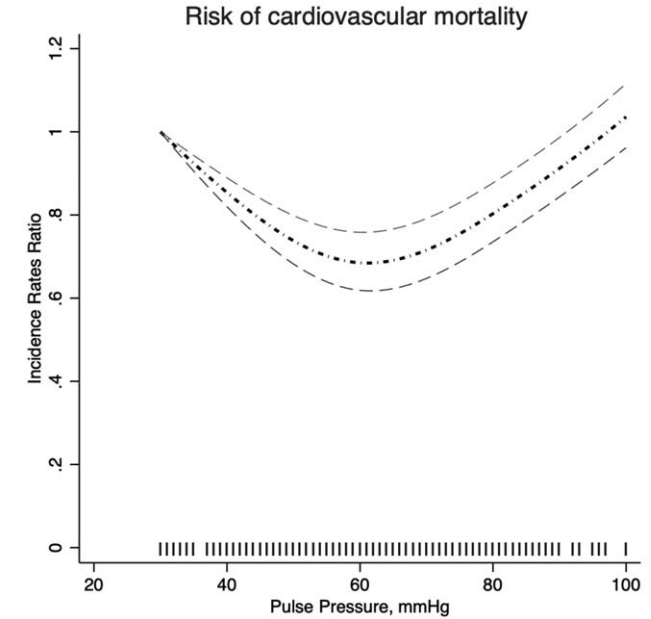
**Table 1**  
Baseline Characteristics of study populations.

	Characteristics
N	3054
Cardiovascular Deaths, n (%)	437 (14.3)
Male Gender, n (%)	1790 (58.6)
Primary Glomerular Disease, n (%)	1446 (47.3)
Age, years	48.9 (38.2 to 59.0)
Haemoglobin, g/L	88.0 (74.5 to 102.0)
Packed cell volume	19.0 (2.5 to 27.5)
Reticulocyte, %	4.8 (13.1 to 60.5)
Phosphorus, mg/dl	1.8 (1.4 to 2.2)
Albumin, g/L	33.5 (29.7 to 37.9)
Total iron binding capacity, $\mu$ mol/L	44.9 (35.0 to 53.0)
FeTIBC, mmol/L	24.9 (20.9 to 41.0)
Creatinine, $\mu$ mol/L	840.8 (633.0 to 1066.0)
estimated Glomerular Filtration rate, mL/min/1.73 m <sup>2</sup>	4.8 (3.6 to 6.8)
Total protein, g/L	57.6 (52.2 to 63.1)
Prealbumin, mg/L	29.3 (196.0 to 363.0)
Total Cholesterol, mmol/L	4.4 (3.6 to 5.2)
Low density lipoprotein, mmol/L	2.6 (1.9 to 3.4)
Fasting glucose, mmol/L	5.0 (4.3 to 6.0)
Sodium, mEq/L	140.0 (136.8 to 142.4)
C-reaction protein, mg/dl	2.5 (1.0 to 5.5)
Body mass index, kg/m <sup>2</sup>	22.7 (20.6 to 24.9)
Systolic blood pressure, mmHg	144.0 (135.0 to 158.8)
Diastolic blood pressure, mmHg	86.5 (80.0 to 95.0)
Cardiovascular diseases, n (%)	1384 (45.3)
Type 2 Diabetes, n (%)	449 (14.7)
Taking antihypertensive treatment, n (%)	1257 (41.2)

Binary variable are displayed as numbers (percentage) and continuous variables are displayed as median (interquartile).



**Figure 1.** Distribution of pulse pressure among patients with and without cardiovascular mortality, 1, indicates having cardiovascular mortality; 0, indicates having no cardiovascular mortality.



**Figure 2.** Dose-response association between pulse pressure and risk of cardiovascular mortality among patients initializing peritoneal dialysis: estimated from original dataset. Characteristics included in Table 1 were adjusted.

### 3. Results

#### 3.1. Characteristics

In our cohort, we analyzed information on 3054 patients with 437 cardiovascular deaths within 2 years of initialisation of PD. Table 1 summarises the basic characteristics of the study population. The 3054 patients with mean age 48.9 years initializing PD treatment were included in this study. The prevalence of pre-existing cardiovascular diseases and type 2 diabetes was 45.3% and 14.7%, respectively. Within 2 years since initialisation of PD, 14.3% deaths due to cardiovascular diseases were observed.

#### 3.2. Distribution of PP

The distribution of PP was presented in Figure 1. Patients with cardiovascular deaths within 2 years of initialisation of PD were more likely to have higher levels of PP comparing with those without cardiovascular deaths, as the median with interquartile range was 70.8 (59.0 to 79.1) and 60.0 (50.1 to 70.2) mmHg, respectively.

#### 3.3. Association between PP and cardiovascular diseases (CVD) mortality and potential threshold

Dose-response relationship curves were derived from the natural cubic spline models within original dataset with adjustment of covariables in Figure 2, which was similar to dose-response relationship curves were derived from the natural cubic spline models within imputed datasets with adjustment of covariables in Supplemental Figure 1, <http://links.lww.com/MD/D90>. There was a non-linear relationship between PP and risk of cardiovascular mortality (linearity test:  $P < .0001$ ). There was strong evidence that a threshold of PP estimated at 61 (95% confidence interval: 56–64) mmHg was associated with the lowest risk of

cardiovascular mortality, as tested by linear threshold models. The increased cardiovascular mortality risks were observed among those with PP above the threshold (Table 2).

### 4. Discussion

We have found that non-linear association between PP and risk of 2-year cardiovascular mortality among patients initializing PD. To our knowledge, this is the first study to examine such risks and we provide strong evidence of a threshold in the relationship between PP and risk of short-term cardiovascular deaths at a PP of 61 mmHg.

PP as an independent prognostic factor of cardiovascular risk has been well established by previous observational and intervention studies, in which PP was associated with increased all-cause mortality from populations underwent dialysis. For example, in a French cohort, it was found PP, a surrogate measure of arterial stiffness, is a better predictor of all-cause mortality risk than either systolic or diastolic blood pressure, at least among hemodialysis patients aged  $>50$  years.<sup>[17]</sup> The independent prognostic value of PP in predicting mortality

**Table 2**  
Adjusted incidence rates ratios for cardiovascular mortality by 1 unit increase in pulse pressure in groups classified by pulse pressure (61 mmHg) among patients initializing peritoneal dialysis.

	Pulse pressure ≤61 mmHg	P value	Pulse pressure >61 mmHg	P value
Adjusted incident rates ratio <sup>‡</sup>	0.93 (0.91 to 0.95)	.047	1.17 (1.12 to 1.19)	<.0001
Adjusted incident rates ratio <sup>*</sup>	0.96 (0.92 to 1.00)	.063	1.26 (1.24 to 1.33)	<.0001

<sup>‡</sup> Indicates age and gender were adjusted.

<sup>\*</sup> Indicates characteristics included in Table-1 were adjusted.

among people having end-stage renal diseases or undergoing dialysis has also been shown previously.<sup>[12,13]</sup>

The risks of elevated blood pressure have been repeatedly demonstrated by clinical observational studies. Many studies have described a gradual increase in the risk of mortality with increasing levels of PP, especially in patients treated by dialysis. In a US retrospective national cohort study, in patients undergoing maintenance hemodialysis, an incremental increase of 10 mmHg in post-dialysis PP was associated with a 12% increase in the hazard for all-cause death within 12 months.<sup>[12]</sup> In another US cohort study, it was found that every 10 mmHg decrease in pulse pressure during dialysis was associated 20% of decrease of 6-month all-cause hospitalization or deaths among patients undergoing maintenance hemodialysis.<sup>[18]</sup> In a French cohort, over median 6.5 years follow-up, 1.85 fold risk of cardiovascular death was observed by every 10 mmHg increase of PP among patients treated by hemodialysis.<sup>[17]</sup>

Although cardiovascular mortality/incidence has been found to have a U-shaped relationship with systolic/diastolic blood pressure in patients with end-stage renal diseases before in epidemiological studies,<sup>[7,19]</sup> its J-shaped relationship with PP has not previously been investigated, especially in terms of the continuous association rather than the categorization of PP. In the US hemodialysis cohort, a J-shape association between PP and 1-year all-cause mortality was identified and PP more than 61 mmHg was found to be associated with significant higher risk of 1-year all-cause mortality.<sup>[12]</sup> Consistent with previous studies, the present study showed a much higher risk of cardiovascular mortality in patients initializing PD whose pulse pressure was both above and below 61 mmHg.

The lowest mortality from cardiovascular diseases (i.e., threshold) has previously been identified at 145/92 mmHg, based on its J-shape relationship with blood pressure in patients initializing PD.<sup>[7]</sup> In particular, 2 American PD cohorts identified a PP threshold at 49 to 67 mmHg among patients with mean age at 50 to 60 years.<sup>[19]</sup> This finding was similar to the results of the present observational study where the lowest risk of cardiovascular mortality was found to be a PP of 61 mmHg for end-stage renal disease patients starting PD treatment.

In patients with end-stage renal diseases, increases in oxidative stress, carbonyl stress, and advanced glycation end-products may combine to exaggerate the alterations in collagen and elastin structure and function, with a resultant loss of vascular elasticity that leads to vascular stiffness. PP is thought to act as a surrogate for this clinical situation.<sup>[20,21]</sup> PP also reflects the vascular stiffness that increases with advancing age and leads to coronary heart disease.<sup>[22–24]</sup> As a result of the earlier vascular aging that occurs with renal failure, an abnormal PP in people initializing PD could explain the risks of cardiovascular mortality observed in the present study.<sup>[22–24]</sup>

Although systolic blood pressure is a strong surrogate in predicting the risk of cardiovascular mortality,<sup>[7]</sup> it might still be worth observing PP in the daily care of people initializing PD in view of its independence as a prognostic factor of coronary mortality. Indeed, the elevated PP observed in people with initialisation of PD and the associated elevation in cardiovascular mortality may imply that PP should be a target for therapeutic intervention in these people. In the study by Lertdumrongluk et al,<sup>[19]</sup> which included people treated by hemodialysis, a reduction in PP was associated with an improvement in outcomes.

Clinically, it is not clear how PP can be reduced: current antihypertensive treatment often focuses on reduction of the extracellular volume or smooth muscle cell tone, thereby reducing systolic and diastolic blood pressure. When both pressures are reduced, PP might not change. Nevertheless, identifying a high or low PP could prompt a review of cardiovascular disease risk factors, or degree of heart failure, with intensification of therapy if appropriate. This could include a discussion with the people about lifestyle factors such as smoking, diet, and physical activity. For example, intervention could be prompted at PPs of  $\leq 50$  and  $\geq 70$  mmHg to take account of biological variation and accuracy issues (and to use rounded numbers to facilitate implementation). The feasibility and impact of such an intervention merits further investigation.

Our results might be influenced by confounding by unmeasured risk factors, for example, those due to under-recording of pre-existing comorbidities and their duration. The duration of reduced renal function would be a particularly important measure prone to under-estimation. Second, we lacked data on lifestyle factors, including smoking, drinking, and physical activity. Third, we did not adjust for PD patients' socioeconomic status that would likely impact on PD patients' treatment/management status and their general health status. Fourth, some clinical prognostic factors that could influence for cardiovascular death outcome, like left ventricular ejection fraction, pulmonary arterial pressure, right ventricular systolic pressure or adequacy of dialysis, and so on, were not available in this study, which suggesting that future external replication studies with more comprehensive clinical measurements are warranted. Finally, the proportion of clinical measurement data that was missing was relatively high requiring multiple imputation, which suggesting that further replication in the external dataset is warranted.

## 5. Conclusion

In summary, there was a non-linear relationship between PP and risk of cardiovascular mortality in patients initializing PD. The PP threshold for the lowest cardiovascular mortality was found to be 61 (95% confidence interval: 56–64) mmHg. PP might be a useful prognostic factor to consider risk in clinical practice.

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**Writing – review & editing:** Dahai Yu, Yamei Cai, Xiaoxue Zhang, Zhanzheng Zhao.

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