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Original Paper

The Association of Weekly pre-Hemodialysis Systolic Blood Pressure and Following Week Mortality

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Key Words
Hemodialysis • Pre-dialysis systolic blood pressure • Mortality

Abstract
Background/Aims: Few studies examine the impact of systolic blood pressure (SBP) on mortality in the incident hemodialysis (HD) period, and throughout the first HD year. This large retrospective observational study analyzes the impact of "current" and cumulative low preSBP <110 mmHg (L), and variations in preSBP on short-term (1 week) mortality over the first HD year. ***Methods:*** Weekly mean preSBP for HD weeks 1 to 51 was categorized into L or high preSBP>=110 mmHg (H) for each patient. A generalized linear model (GLM) was used to compute the probability of death in the following week. The model includes age, gender, race and three preSBP-related parameters: (a) percent of prior weeks with L preSBP; (b) percent of prior weeks with switching between L to H; (c) "current" week's preSBP as a binary variable. Separate models were constructed that include demographics and BP-related parameters (a), (b), and (c) separately. ***Results:*** In a model combining (a), (b), and (c) above, "current" week L preSBP is associated with increased odds ratio for following week mortality throughout the first HD year. The percent of prior week's L and more switching between L and H are less significantly associated with short-term mortality. In models including (a), (b), and (c) separately, "current" L preSBP is associated with higher mortality. ***Conclusion:*** This study confirms an association of L preSBP with increased short-term mortality which is maintained over the first HD year. Percent of L preSBP in prior weeks, switching between L and H, and "current" week L are all associated with short-term mortality risk, but "current" week L preSBP is most significant.

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Introduction

In the general population and in chronic kidney disease (CKD), treatment of high blood pressure is important to prevent cardiovascular and cerebrovascular morbidity and mortality, but this may not be true for hemodialysis (HD) patients. While blood pressure (BP) guidelines in prevalent HD patients focus on BP control to avoid hypertension, recent studies suggest a "reverse epidemiology" for BP in HD patients. Systolic BP (SBP) levels which are considered "normal" in the general population are associated with adverse outcomes for incident HD patients and throughout the first year of HD [1]. A landmark study by Zager described a "U-shaped" curve relationship between HD BP and mortality with pre-dialysis SBP (preSBP) < 110 mmHg associated with increased mortality [2]. Subsequent studies also describe the association of SBP <110 mmHg and increased mortality [3]. In a 2006 study, incident HD patients meeting the recommended SBP target of <140 mmHg had worse one year survival than patients with "elevated" SBP >140 mmHg [1].

In addition to the mortality association with absolute preSBP levels in the incident HD period, BP trends over time are important. It has been observed that recent SBP was more sensitive than remote SBP for one year survival and decreasing SBP is associated with poorer long-term survival [1]. In a study evaluating incident HD patients, greater mortality in the first year of HD was found for patients with temporal BP changes, either SBP decrease or increase compared to stable SBP, even when compared to low absolute BP [4].

PreSBP variability is also reported to increase all-cause mortality in prevalent HD patients. In an analysis using data from the HEMO study, visit to visit preSBP variability was associated with cardiovascular mortality risk and the impact was enhanced by lower baseline preSBP [5]. Flythe et al. evaluated intradialytic SBP variability in prevalent HD patients during a 30 day study period and showed an association of increased SBP variability with both all-cause and CV mortality risk [6].

This large retrospective observational study examines the relationship between preSBP<110 mmHg (L preSBP) and short-term mortality outcomes. We aim to fill an information gap by including patients from the first date of dialysis (FDD) throughout the first year of HD including the critical incident HD period. We analyze the impact of the percent of L preSBP cumulative over time, the switching between L and preSBP>=110 mmHg (H preSBP), and the "current" week L preSBP on the mortality risk in the following week. Study of this ultra-short-term mortality risk may provide insights for clinicians rounding in the dialysis facility. L preSBP as well as preSBP variations which can easily be recognized during clinical rounds could be of importance for the clinician in identifying patients at immediate mortality risk.

Materials and Methods

In this study we analyzed data from 269,397 FMCNA incident HD patients who initiated dialysis between Jan 1, 2004 and Nov 30, 2014, survived more than 7 days on HD, and had at least one preSBP measurement. PreSBP was measured at the start of each HD treatment and recorded in an electronic treatment record. For each week, we computed mean preSBP as the average of all treatments during the week (irrespective of the number of treatments); week 1 is the first week of chronic outpatient HD. For each of the first 51 weeks on HD, we categorized patients into two groups of mean preSBP: patients fell into the "Low" (L) group with average preSBP<110 mmHg or the "High" (H) group with preSBP>=110 mmHg. During the first 51 weeks, patients are likely to have a variety of patterns of H and L preSBP values. For example, some patients may always remain in the H group, while others may always remain in the L group; many patients would experience changes in H and L preSBP values over time. To illustrate this, the following section provides specific example of how these are computed.

Based on this, we computed three separate preSBP related variables for each patient for each of the first 51 weeks:

a) Percentage of weeks with preSBP<110 mmHg up to each week analyzed
b) Percentage of weeks when patients' preSBP changed from H to L or vice versa
c) Binary variable which indicates whether the "current" week's preSBP is below 110 mmHg

For each week, we used a generalized linear model (GLM) to compute the probability of death in the following week. Four different models were constructed. The first three include age, gender, and race as well (a), (b), and (c) separately. Since (a), (b), and (c) are related, an additional model that includes age, gender, race and (a), (b), and (c) was constructed. This means that 204 distinct GLM models were completed: three models 51 times for each of the preSBP variables and one model 51 times that combines all three preSBP variables. After IRB review this research was determined to be exempt from IRB approval.

Example of PreSBP Calculation

As an example, for a patient who has survived 8 weeks we would like to determine their risk of death in week 9. The patient's preSBP pattern is as follows:

- Week 1: L (preSBP<110 mmHg)
- Week 2: H (preSBP>=110 mmHg)
- Week 3: L
- Week 4: L
- Week 5: H
- Week 6: H
- Week 7: L
- Week 8: L

This pattern can be expressed as follows: LHLLHHLL. In the above example, the patient was dialyzed for eight weeks with 5 weeks preSBP being L and the most recent (week 8) preSBP also being L. The patient's preSBP switched from H to L or vice versa 4 times (week 1 to week 2; week 2 to week 3; week 4 to week 5; week 6 to week 7). Three preSBP variables in the model are calculated as follows:

1) percent of prior 8 weeks with L preSBP (<110 mmHg): the number of low weekly preSBP measurements divided by 8, i.e.,

$$\text{Percent of prior 8 weeks with Low preSBP} = \frac{\text{number of L preSBP}}{8} = \frac{5}{8} = 62.5\%$$

2) percent of prior weeks when patients' preSBP switched from L to H or vice versa: the number of switches divided by 7 (the maximum of possible switches), i.e.,

$$\text{Percent of prior 8 weeks with switches} = \frac{\text{number of switches}}{7} = \frac{4}{7} = 57\%$$

3) binary variable if the week 8's preSBP was L: equal to 1 if week 8's preSBP is below 110 mmHg, 0 if week 8's preSBP is equal or above 110 mmHg.

$$\text{indicator of the week 8 preSBP was L} = \begin{cases} 1, & \text{preSBP} < 110 \text{ mmHg} \\ 0, & \text{preSBP} \geq 110 \text{ mmHg} \end{cases} = 1$$

Results

Baseline patient data are shown in Table 1.

Overall mortality rates peak at week 2, rapidly decline in the first 2 months and continue to decrease as the weeks from first outpatient dialysis treatment increase (Fig. 1).

In a model repeated weekly with the historic percent of previous L preSBP, the historic percent of switches between L and H, and most recent or "current" week preSBP<110 mmHg, all co-variates are independently associated with increased mortality in the following week (Fig. 2, 3 and 4). Risk of death is 20 to 50% higher in the following week for every additional

10% more previous weeks with preSBP<110 mmHg (Fig. 2). The risk of death is 10 to 90% higher in the following week for every 10% more previous weeks where preSBP changes from H to L or vice versa (Fig. 3). While a patient's L or H preSBP history impacts ultra-short-term mortality the risk of death in the following week for patients whose most recent preSBP<110 mmHg with odds ratio between 2.6 and 12.4 is most impactful throughout the first year of HD (Fig. 4).

Table 1. Description of the study cohort. *Value or average in the first 30 days of chronic outpatient dialysis with standard deviation in parentheses for continuous variables

Characteristics	Value
Number of patients	269,397
Age	63.26 (15.06)
White %	68%
Black (%)	29%
Hispanic (%)	14%
Male (%)	57%
Catheter access (%) *	66%
Pre-dialysis SBP (mmHg) *	143.63 (21.62)
Pre-dialysis DBP (mmHg) *	74.75 (13.14)
BMI (kg/m^2) *	29.13 (1481.58)
Treatment time (mins) *	217.96 (29.66)
Interdialytic weight gain (kg) *	1.87 (1.06)
Ultrafiltration rate (mL/hr/kg) *	6.1 (12)
Albumin (g/dL) *	3.44 (0.52)
Hgb (g/dL) *	10.18 (1.26)
Arrhythmias (%)	5%
Cerebrovascular disease (%)	3%
CHF (%)	11%
Hypertension (%)	23%
Ischemic heart disease (%)	9%
Diabetic (%)	63%
Average number of comorbidities	6.41 (9.21)

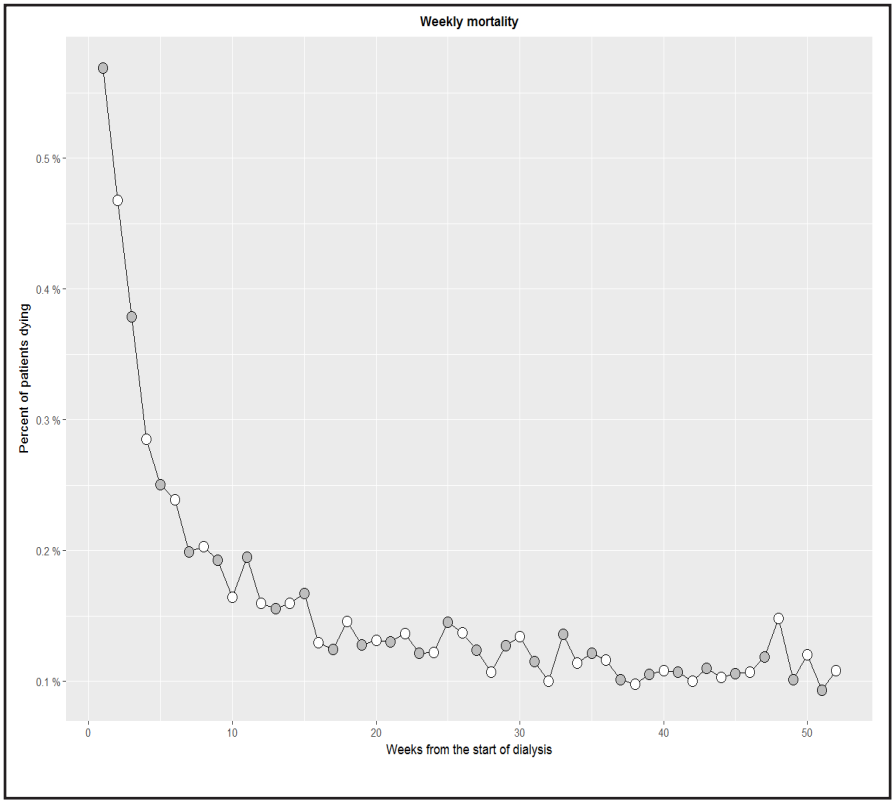

Fig. 1. Proportion of patients dying over 52 weeks (from all causes).

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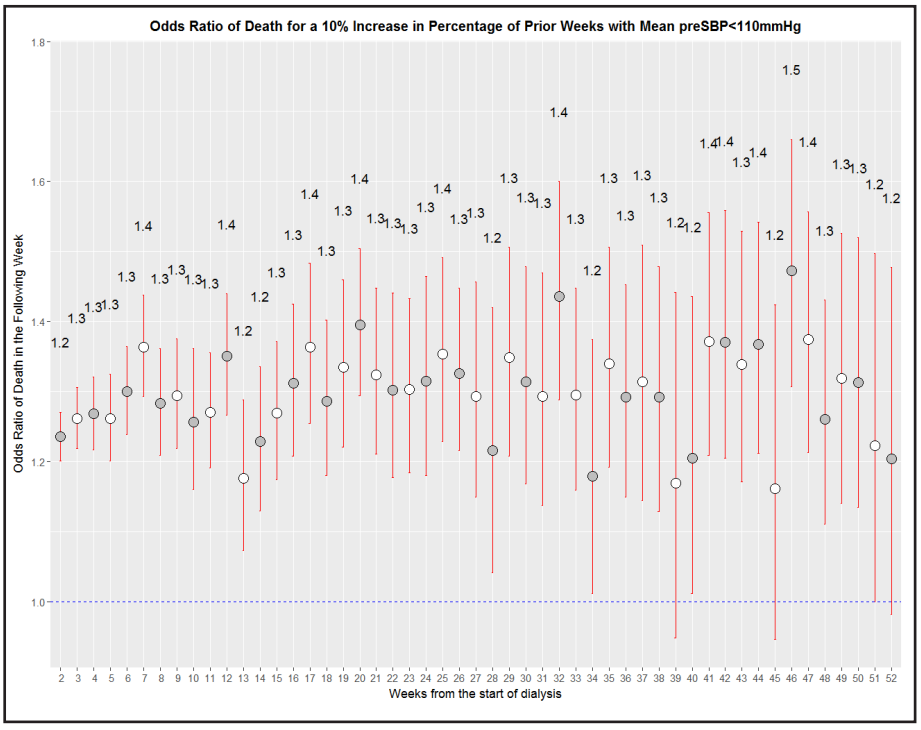

Fig. 2. Effect of historic percent of L preSBP in all prior weeks on following week mortality.

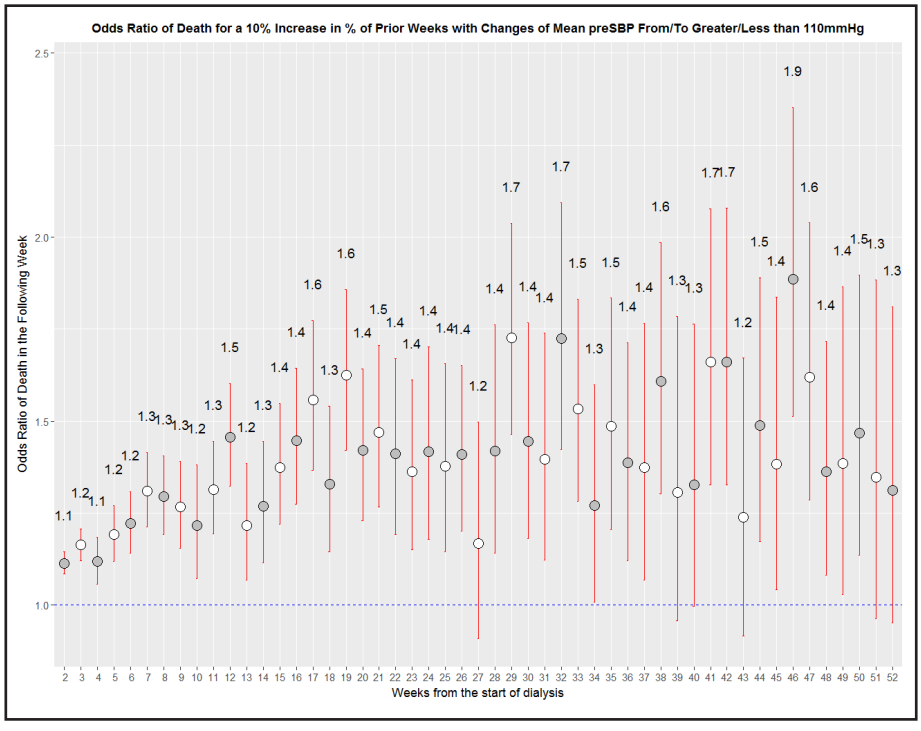

Fig. 3. Effect of historic percent of switching between L and H preSBP in all prior weeks on following week mortality.

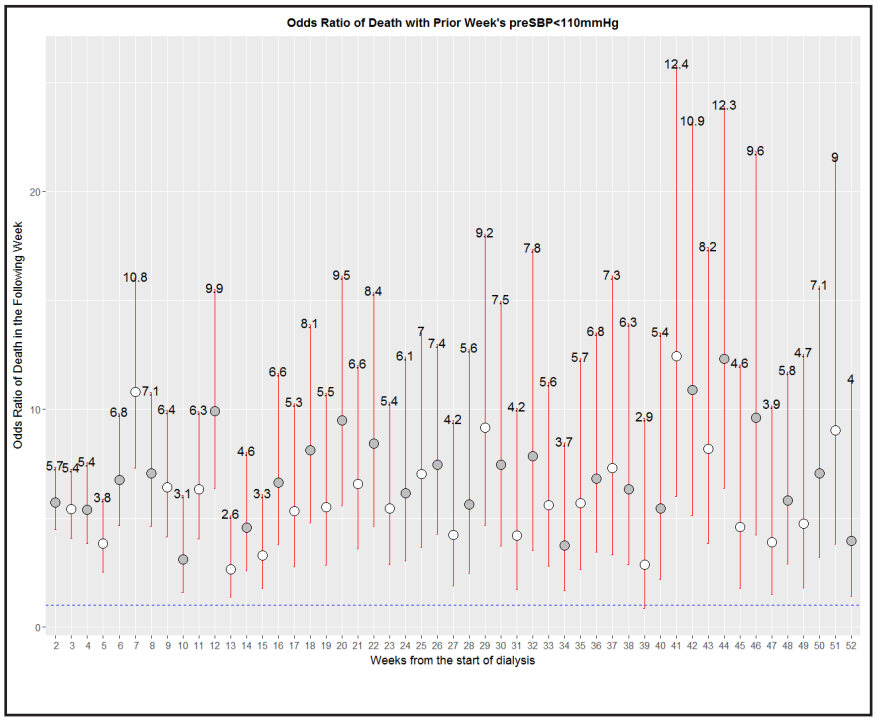

Fig. 4. Effect of "current" week L preSBP on following week mortality.

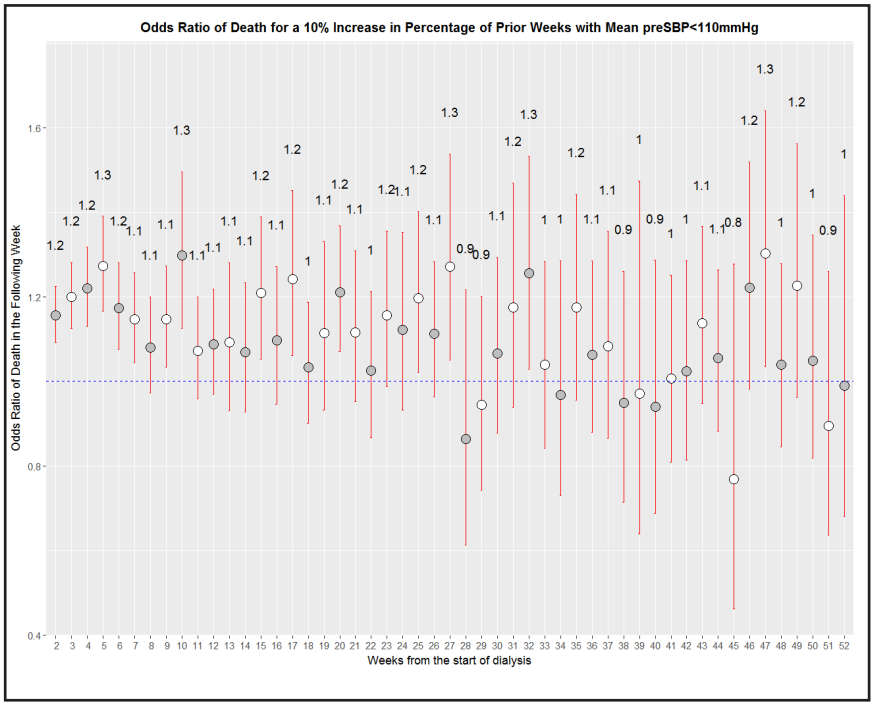

Fig. 5. Independent effect of historic percent of L preSBP in all prior weeks on following week mortality (controlled for percent of weeks with preSBP switching and current L preSBP).

To determine the independent impact of each of the three preSBP variables, a three covariate model was created. Figures 5, 6, and 7 demonstrate the impact of each of the three preSBP variables when controlling for the other two. While the historic percent of previous L preSBP (Fig. 5) and the historic percent of switches between L and H (Fig. 6) appear to generally have a negative impact on survival, most weeks are not statistically significant. "Current" week preSBP<110 mmHg appears to still have a negative impact on short-term mortality throughout the 52 week period (Fig. 7).

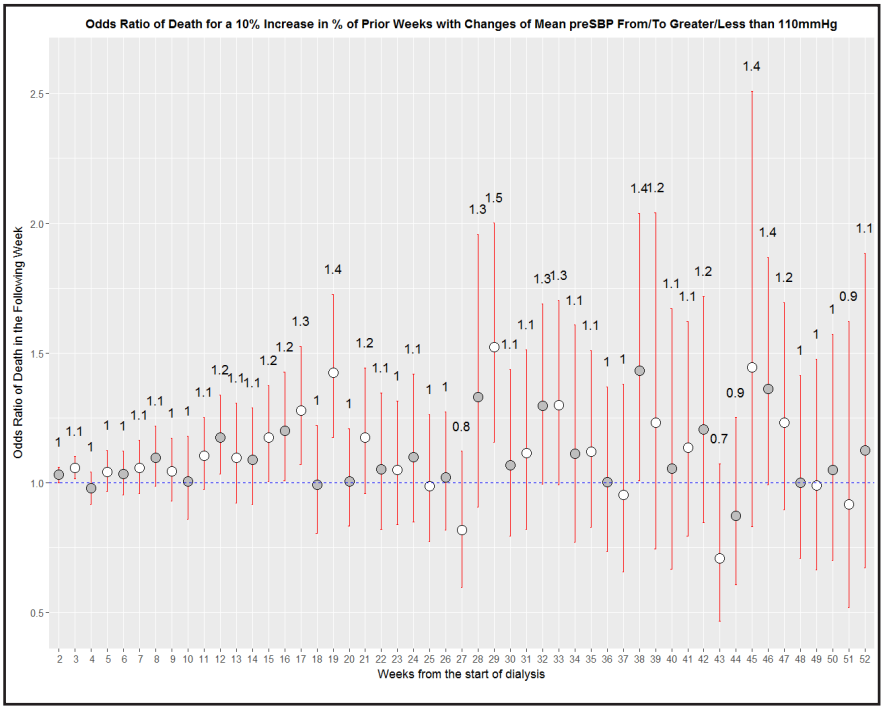

Fig. 6. Independent effect of historic percent of preSBP switching in all prior weeks on following week mortality (controlled for percent of weeks with L preSBP and current L preSBP).

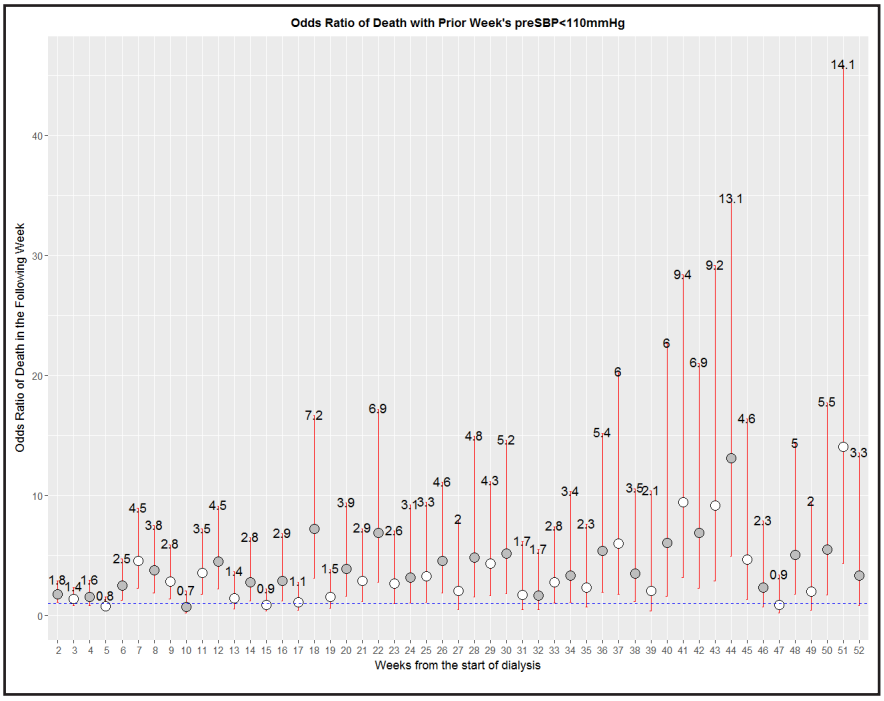

Fig. 7. Independent effect of current week's L preSBP on following week mortality (controlled for percent of weeks with L preSBP and percent of weeks with preSBP switching).

Discussion

This large retrospective observational study of HD patients during the first year of treatment examines the association of L preSBP, defined as preSBP<110 mmHg, and ultra-short-term mortality risk (mortality risk in the following week). In this study weekly

independent models were used to determine the impact of "current" L preSBP on following week mortality. Models including the historic percent of L preSBP and percent of switching from L to H facilitate including the historic pattern of preSBP for patients representing BP trends and variability over time.

We confirmed high relative mortality in the early vintage period in HD which was also observed in other studies [7, 8]. In addition this analysis suggests that "current" week L preSBP is associated with ultra-short-term mortality risk throughout the first year of HD, even though the greatest absolute mortality risk is in the early HD weeks. The non-time overlapping 3 covariate model suggests that historical L preSBP and preSBP variation impact short-term mortality risk, but "current" L preSBP impacts short-term mortality the most. This suggests that a patient who has had historically H preSBP, but then has an average L preSBP in a given week is at risk for increased mortality in the following week.

This study adds to the literature by using a large dataset for weekly mortality risk prediction. PreSBP patterns were assessed weekly from the start of HD, including the first 90-day period, which is often omitted from studies. We focused not only on "current" preSBP levels, but also on historic preSBP and variations in preSBP, as it has been observed that BP trends and variability over time and not simply absolute BP is related to adverse outcomes [4]. Historic preSBP patterns and variations in preSBP after 4 weeks become too complicated for visual display, so we focused on GLM analysis to identify whether historic L preSBP, historic variations in preSBP, or "current" week preSBP was most consistently related to ultra-short-term mortality.

Management of BP in the general population, CKD, and HD patients remains largely focused on interventions and treatment for elevated BP. While this is appropriate in mitigating pre-dialysis intermediate or long-term risk, large epidemiological studies have suggested that low and even low-normal BP (<110-120 mmHg) convey an even higher mortality risk for HD patients [1-3, 9, 10] Li et.al. provided an analysis showing a "robust" association of normal and prehypertension BP with mortality risk in dialysis patients [1]. These authors suggest, contrary to guidelines for the general population, practicing clinicians should consider patient-specific evaluations for dialysis patients with "low" or "low-normal" preSBP [1].

Studies assessing BP trends during the first year on HD have yielded conflicting results. Sipahioglu, et.al. describe an association of both low (baseline preSBP<120 mmHg) and declining preSBP with increased mortality at 6 and 12 months [10]. Raimann et al. also showed the highest mortality in the quartile of patients who experienced the largest decline in BP during the first year on HD [4]. This contrasts with studies from the Tassin group, in which patients in the tertile experiencing the largest decline in preSBP pressure during the first year on HD showed the best outcome [11].

Increased variability in preSBP, expressed as the standard deviation or residuals of the mean in a linear regression, and intradialytic SBP are risk factors for adverse patient outcomes [6, 12, 13]. The reasons for this have not been completely elucidated, but associations with dialysis treatment ultrafiltration, heart failure, diabetes, and central venous catheter use have been described [5, 14]. Other clinical factors associated with BP variability in HD include a reduction in buffering capacity of the arterial wall by increased vascular stiffness in combination with osmotic or fluid changes [6, 15]. We did not study variability or slopes per se, but the results of the present study are in basic agreement with these previous studies. However, we assess the ultra- short-term risk associated with weekly changes in preSBP and to the best of our knowledge this is the first study describing this mortality risk.

Low BP in HD may impair cerebral or cardiac perfusion increasing mortality risk [16]. Underlying comorbidity, such as heart failure, can cause low BP and the subsequent increased mortality risk. In observational studies like ours it cannot be determined if L preSBP causes the increased mortality risk or if it is a marker for underlying co-morbidity that is associated with increased mortality risk. In particular in this study we do not have data to confirm patient volume status at the time of L preSBP, so the impact of volume overload coupled

with L preSBP cannot be assessed independently [17]. Therefore, we agree that low preSBP values or declining preSBP trends should always be interpreted in the clinical context of the patient and should trigger a detailed clinical assessment.

Strengths of this study include the large sample size and the inclusion of patients geographically distributed across the U.S. Data was collected from the first date of outpatient HD, so this analysis includes patients throughout the incident dialysis period.

Limitations of the study include the absence of information on volume status which would help identify patients for whom a low or high BP is a reflection of volume status. We also arbitrarily selected the preSBP level of 110 mmHg as low or "L", however, this is based on the study of Zager et al [2]. We also lack data on medication usage and cardiac structure or function.

Low preSBP values were observed in a relatively small percentage of patients, although due to the size of the database, the number of patients was still relatively large in an absolute sense. We did not correct for different comorbidities or vascular access in this study, as these might be in the causal pathway of the relation between low preSBP and outcome and as such are not confounders. The lack of adjustment does not preclude the usefulness of low SBP values as markers for outcome.

Despite these limitations this study shows an observational association with a commonly available clinical parameter which can alert clinicians to the need for additional evaluation. This paper may also serve as a proof of concept for the persistent short-term risk associated with low preSBP.

Conclusion

This large retrospective observational study reports an association of historic L preSBP, preSBP variability between L and H, and "current" L preSBP with ultra-short-term mortality risk. The "current" L preSBP seems most consistently associated with mortality in the following week throughout the first year of HD. This analysis offers an association of a routinely observed clinical parameter with short-term mortality risk raising awareness of the need for clinical assessment of HD patients with L preSBP.

Disclosure Statement

Peter Kotanko, Dugan W. Maddux, Franklin W. Maddux, and Len A. Usvyat hold stock in Fresenius Medical Care. The remaining authors declared no competing interest.

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