ORIGINAL ARTICLE

Pre-dialysis diastolic blood pressure and intradialytic hypotension in patients undergoing maintenance haemodialysis

Takashi Hara[1] · Yuto Kasahara[1] · Takahiko Nakagawa[1,2]

Abstract

Background Intradialytic hypotension is a clinically relevant complication in haemodialysis patients. Pre-dialysis diastolic blood pressure is routinely measured. However, the association between pre-dialysis diastolic blood pressure and intradialytic hypotension is not well understood.

Methods Patient-level (N = 545) and haemodialysis session-level (N = 3261) data were collected; the exposure variable was pre-dialysis diastolic blood pressure. The primary outcome of interest was the development of intradialytic hypotension, defined as any nadir < 100 mmHg if the pre-dialysis systolic blood pressure was ≥ 160 mmHg, or any nadir < 90 mmHg if the pre-dialysis systolic blood pressure was < 160 mmHg. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using mixed-effects logistic regression for the association between pre-dialysis diastolic blood pressure and intradialytic hypotension, after adjusting for potential confounders.

Results Intradialytic hypotension occurred in 14.4% of the sessions. All sessions were divided into five categories according to pre-dialysis diastolic blood pressure. The adjusted ORs for intradialytic hypotension were 2.72 (95% CI 1.64–4.51), 1.07 (95% CI 0.68–1.66), 1.68 (95% CI 1.08–2.62), and 1.81 (95% CI 1.05–3.14) in sessions with pre-dialysis diastolic blood pressure of < 60 mmHg, ≥ 60 to < 70 mmHg, ≥ 80 to < 90 mmHg, and ≥ 90 mmHg, respectively, compared with the reference pre-dialysis diastolic blood pressure of ≥ 70 to < 80 mmHg. Cubic spline analyses revealed a reverse J-shaped association between pre-dialysis diastolic blood pressure and intradialytic hypotension.

Conclusions Low and high pre-dialysis diastolic blood pressure levels were associated with intradialytic hypotension. This may help identify patients at a high risk of developing intradialytic hypotension.
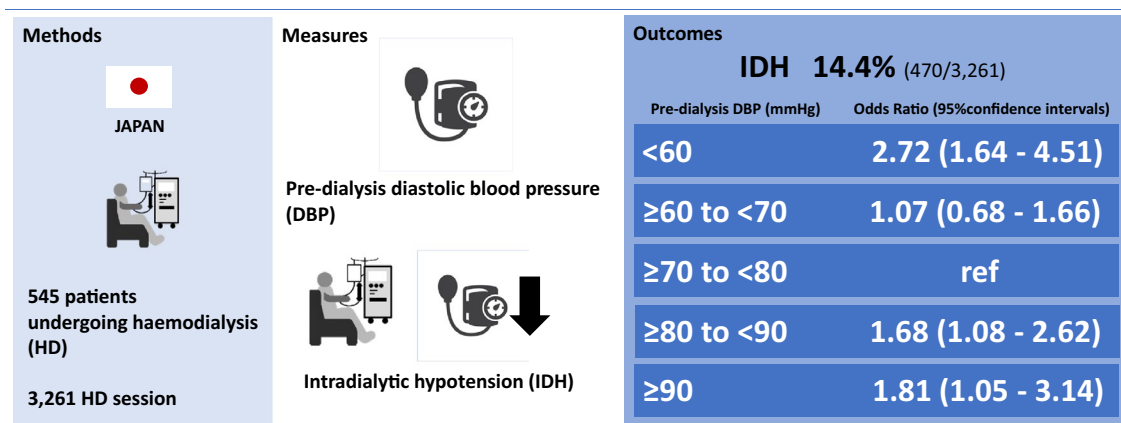

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Graphical abstract

Pre-dialysis diastolic blood pressure and intradialytic hypotension in patients undergoing maintenance haemodialysis

Methods

JAPAN

545 patients undergoing haemodialysis (HD)

3,261 HD session

Measures

Pre-dialysis diastolic blood pressure (DBP)

Intradialytic hypotension (IDH)

Outcomes

IDH 14.4% (470/3,261)

Pre-dialysis DBP (mmHg)	Odds Ratio (95%confidence intervals)
<60	2.72 (1.64 - 4.51)
≥60 to <70	1.07 (0.68 - 1.66)
≥70 to <80	ref
≥80 to <90	1.68 (1.08 - 2.62)
≥90	1.81 (1.05 - 3.14)

Conclusion: Low and high pre-dialysis DBP levels were associated with IDH. This may help identify patients at a high risk of developing IDH.

Takashi Hara, Yuto Kasahara, Takahiko Nakagawa: Pre-dialysis diastolic blood pressure and intradialytic hypotension in patients undergoing maintenance haemodialysis
J Nephrol DOI 10.1007/s40620-022-01292-2

Introduction

Intradialytic hypotension (IDH) is a clinically relevant complication in patients undergoing haemodialysis (HD). Previous studies have noted that IDH is associated with high mortality and incidence of cardiovascular events, vascular failure, loss of residual renal function, intradialytic symptoms, and intradialytic cardiac arrhythmias [1–8]. Nevertheless, there is only weak evidence of a strategy for the prevention and treatment of IDH, which is an area of high unmet need [9–11]. It might be important to identify the factors that predict IDH.

Diastolic blood pressure (DBP) is measured simultaneously with systolic blood pressure (SBP). Previous studies have shown a J-shaped association between DBP and cardiovascular events in the general population and in patients with stable coronary artery disease [12–15]. Low DBP may decrease coronary perfusion to the myocardium, which leads to subclinical myocardial damage [16], whereas high DBP is associated with coronary artery stenosis, which may contribute to cardiovascular events [17]. Therefore, DBP is clinically used as a risk factor and predictor of cardiovascular events.

To our knowledge, the association between pre-dialysis DBP and IDH is not well understood. We hypothesised that high and low pre-dialysis DBP levels are associated with IDH. Given the key role of DBP in the coronary artery, a

history of ischaemic heart disease (IHD) may strongly affect this association. Hence, to clarify the relationship between pre-dialysis DBP and IDH, we conducted a retrospective study using data from a dialysis centre in Japan.

Methods

Study design and population

This was a retrospective cohort study at Rakuwakai Otowa Kinen Hospital, a high-volume dialysis centre in the Yamashina region of Kyoto, Japan. This study included patients undergoing maintenance HD who had data available on pre-dialysis DBP and medical information in December 2017. This study excluded patients with pre-dialysis SBP < 90 mmHg because these patients were not at risk for IDH. The study design was approved by the Rakuwakai Otowa Hospital Ethics Committee (approval number: Rakuoto-Rin-21-022) and conducted according to the Helsinki Declaration of 1975, as revised in 2013.

Exposure

Pre-dialysis DBP was measured in the dorsal position after a few minutes of rest. All HD sessions were divided into five categories according to pre-dialysis DBP

(< 60 mmHg, ≥ 60 mmHg to < 70 mmHg, ≥ 70 mmHg to < 80 mmHg, ≥ 80 mmHg to < 90 mmHg, and ≥ 90 mmHg). A pre-dialysis DBP of ≥ 70 mmHg to < 80 mmHg was used as a reference in our model for categorical variable analysis, as per a previous study [14]. Similarly, for continuous variable analysis, a pre-dialysis DBP of 80 mmHg was used as a reference [14].

Outcomes

The primary outcome of interest was the development of IDH, defined as any nadir < 100 mmHg if the pre-dialysis SBP was ≥ 160 mmHg, or any nadir < 90 mmHg if the pre-dialysis SBP was < 160 mmHg [1]. Pre-dialysis SBP was measured in the dorsal position after a few minutes of rest, and intradialytic blood pressure was measured every 30 min (IDH_{nadir}).

Statistical analysis

Regarding the session-level characteristics categorised by pre-dialysis DBP, continuous data with a normal distribution were summarised as means (standard deviation [SD]), continuous variables with skewed data were presented as medians (interquartile range [IQR]), and dichotomous data were presented as proportions. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for IDH_{nadir} according to the categories of pre-dialysis DBP were calculated using a mixed-effects logistic regression model. A random intercept was included to account for repeated measures within the subjects, imposing a compound symmetric covariance structure. This model was adjusted for age, sex, body mass index (BMI), diabetes as the primary cause of end-stage renal disease (ESRD), haemodialysis vintage, vascular access, dialysate temperature, interdialytic weight gain (IDWG), ultrafiltration rate (UFR), pre-dialysis SBP, treatment modality, use of antihypertensive drugs, use of antihypotensive drugs, IHD, serum albumin level, and C-reactive protein (CRP) level. These variables were based on a priori clinical judgement and existing studies [2, 3, 9–15]. Serum albumin and CRP levels were not available at every dialysis session. Therefore, these values were obtained from the data of the first session.

Furthermore, we analysed the relationship nonlinearly by modelling pre-dialytic DBP as a continuous variable rather than a categorical value using a restricted cubic spline. We used four knots located at the 5th, 35th, 65th, and 95th pre-dialytic DBP, as recommended [18].

The history of IHD as an effect modifier was analysed to assess potential differences in the pattern of association of pre-dialytic DBP categories with IDH_{nadir}. IHD was defined as acute myocardial infarction, unstable angina, and/or revascularisation. ORs were estimated using mixed-effects logistic regression adjusted for the same confounding factors. The reference was non-IHD and pre-dialysis DBP categories of ≥ 70 mmHg to < 80 mmHg. The tests for interactions were assessed using the Wald test.

Two sensitivity analyses were performed to examine the robustness of the association. In sensitivity analysis 1, unadjusted and adjusted incidence rate ratios (IRRs) with 95% CIs were calculated using a Poisson mixed-effects model. A random intercept was included to account for repeated measures within the subjects. In sensitivity analysis 2, unadjusted and adjusted ORs with 95% CIs were calculated using generalised estimating equations with robust variance estimation. Sensitivity analyses of the association between IDH_{nadir} and continuous variables of pre-dialysis DBP were also conducted. In addition, the interaction between pre-dialysis DBP and IHD on IDH_{nadir} was also examined in the two models.

All analyses were performed using Stata Ver. 15.0 software (Stata Corp., College Station, TX, USA). Statistical significance was set at $P < 0.05$.

Results

Session-level characteristics by pre-dialysis DBP categories

A total of 3261 HD sessions from 545 patients were analysed in this study (Supplementary Fig. 1). Table 1 shows the overall session-level characteristics and pre-dialysis DBP categories. The median age was 71.1 years; males, 58.0%; diabetes as the primary cause of ESRD, 42.0%; arteriovenous fistula (AVF), 88.7%; and median haemodialysis vintage, 5.0 years. The patients with low pre-dialysis DBP tended to be older, had a higher proportion of females, had a lower BMI, had a higher history of IHD, and a lower serum albumin level. The patients with high pre-dialysis DBP tended to have a higher proportion of AVF and haemodiafiltration (HDF) as treatment modalities, with higher IDWG, UFR, and pre-dialysis SBP.

Distributions of pre-dialysis DBP

A histogram of the pre-dialysis DBP is shown in Supplementary Fig. 2. This shows a normal distribution (mean, 77.0 mmHg [16.7] mmHg).

Association between pre-dialysis DBP and IDHnadir

Categorical variable analysis

IDH_{nadir} occurred in 14.4% (470/3,261) of all sessions. Table 2 shows the association between the pre-dialysis DBP

Table 1 Session-level characteristics by pre-dialysis DBP categories

	Total (N = 3261)	Pre-dialysis DBP, mmHg				
		< 60 (n = 429)	≥ 60 to < 70 (n = 637)	≥ 70 to < 80 (n = 837)	≥ 80 to < 90 (n = 664)	≥ 90 (n = 694)
Age, years	71.1 (13.3)	79.5 (9.4)	76.2 (10.4)	72.8 (11.1)	68.4 (12.9)	61.6 (14.3)
Male	58.0	39.4	52.1	59.3	60.5	71.0
BMI, kg/m^2	20.6 [18.2–23.0]	19.8 [16.8–21.7]	20.2 [17.6–22.3]	20.3 [18.1–22.5]	20.9 [18.7–23.1]	21.5 [19.6–25.2]
Diabetes as the primary cause of ESRD	42.0	40.3	39.7	40.7	41.6	47.1
Haemodialysis vintage, years	5 [2–10]	5 [2–11]	5 [2–10]	4 [2–9]	4.5 [2–9]	5 [2–10]
Vascular access: AVF	88.7	82.5	89.3	88.2	90.1	91.4
Dialysate temperature, °C	36 [36–36]	36 [36–36]	36 [36–36]	36 [36–36]	36 [36–36]	36 [36–36]
IDWG, kg	2.4 (1.5)	1.8 (1.2)	1.9 (1.1)	2.2 (1.4)	2.5 (1.4)	3.2 (1.8)
Ultrafiltration rate, ml/h	663.9 (283.2)	547.7 (241.2)	578.9 (229.5)	629.7 (243.9)	690.2 (263.0)	830.1 (332.4)
Pre-dialysis SBP, mmHg	149.8 (26.6)	124.3 (22.8)	135.0 (18.6)	146.3 (18.1)	156.8 (19.8)	176.6 (23.4)
Treatment modality: HDF	15.4	7.0	7.9	16.3	19.7	22.2
Use of antihypertensive drugs	59.6	52.2	55.3	60.8	59.6	66.7
Use of antihypotensive drugs	10.7	11.2	11.6	10.8	10.1	10.1
Ischaemic heart disease	24.1	35.0	31.2	22.3	19.4	17.3
Serum albumin, g/dl	3.6 [3.3–3.8]	3.3 [3.0–3.6]	3.4 [3.2–3.7]	3.6 [3.3–3.8]	3.7 [3.4–3.9]	3.8 [3.5–4.0]
CRP, mg/dl	0.2 [0.1–0.7]	0.3 [0.1–1.3]	0.3 [0.1–0.9]	0.2 [0.1–0.7]	0.2 [0.1–0.6]	0.2 [0.1–0.6]

Values for categorical variables are presented as percentages. Values for continuous variables are presented as mean (standard deviation) or median (interquartile range)

DBP diastolic blood pressure, *BMI* body mass index, *ESRD* end-stage renal disease, *AVF* arteriovenous fistula, *IDWG* interdialytic weight gain, *SBP* systolic blood pressure, *HDF* haemodiafiltration, *CRP* C-reactive protein

Table 2 ORs for IDH$_{nadir}$ by pre-dialysis DBP categories

	Pre-dialysis DBP, mmHg				
	< 60	≥ 60 to < 70	≥ 70 to < 80	≥ 80 to < 90	≥ 90
Unadjusted OR	**4.22 (2.63–6.78)**	1.29 (0.84–2.00)	1 (reference)	1.32 (0.86–2.04)	1.07 (0.65–1.75)
Adjusted OR	**2.72 (1.64–4.51)**	1.07 (0.68–1.66)	1 (reference)	**1.68 (1.08–2.62)**	**1.81 (1.05–3.14)**

Bold values indicate statistical significance. The reference was a pre-dialysis DBP category of ≥ 70 mmHg to < 80 mmHg. ORs were estimated using mixed-effects logistic regression for the association between pre-dialysis DBP and IDH$_{nadir}$ adjusted for age, sex, BMI, cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, pre-dialysis SBP, treatment modality, use of antihypertensive drugs, use of antihypotensive drugs, IHD, serum albumin level, and CRP level
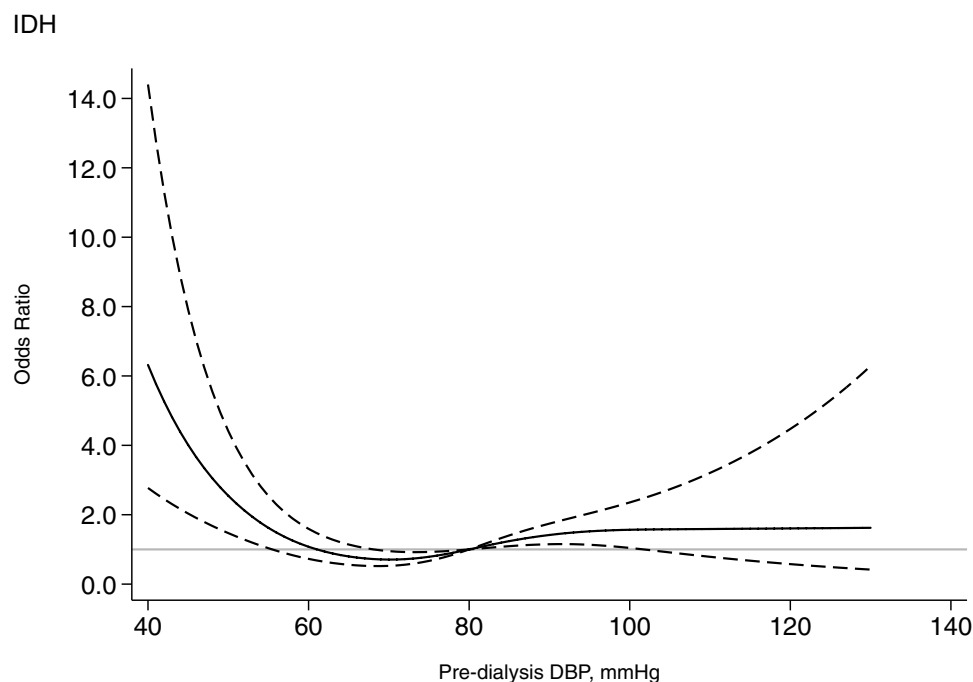
IDH$_{nadir}$ was defined as any nadir < 100 mmHg if the pre-dialysis SBP was ≥ 160 mmHg, or any nadir < 90 mmHg if the pre-dialysis SBP was < 160 mmHg

OR odds ratio, *IDH* intradialytic hypotension, *DBP* diastolic blood pressure, *BMI* body mass index, *ESRD* end-stage renal disease, *IDWG* interdialytic weight gain, *SBP* systolic blood pressure, *IHD* ischaemic heart disease, *CRP* C-reactive protein

categories and IDH$_{nadir}$. The unadjusted ORs for IDH$_{nadir}$ were 4.22 (95% CI 2.63–6.78), 1.29 (95% CI 0.84–2.00), 1.32 (95% CI 0.86–2.04), and 1.07 (95% CI 0.65–1.75) in sessions with a pre-dialysis DBP of < 60 mmHg, ≥ 60 mmHg to < 70 mmHg, ≥ 80 mmHg to < 90 mmHg, and ≥ 90 mmHg, respectively, compared with the reference pre-dialysis DBP of ≥ 70 mmHg to < 80 mmHg. Furthermore, after adjustment for potential confounders, the adjusted ORs for IDH$_{nadir}$ were 2.72 (95% CI 1.64–4.51), 1.07 (95% CI 0.68–1.66), 1.68 (95% CI 1.08–2.62), and 1.81 (95% CI 1.05–3.14) in sessions with a pre-dialysis DBP of < 60 mmHg, ≥ 60 mmHg to < 70 mmHg, ≥ 80 mmHg to < 90 mmHg, and ≥ 90 mmHg, respectively, compared with the reference pre-dialysis DBP of ≥ 70 mmHg to < 80 mmHg.

Continuous variable analysis

Figure 1 shows the association between pre-dialysis DBP as a continuous variable and IDH$_{nadir}$. Restricted cubic spline analysis revealed a reverse J-shaped association between pre-dialysis DBP and IDH$_{nadir}$.

Interaction between pre-dialysis DBP and history of IHD and IDH$_{nadir}$

Table 3 shows that the IHD categories modified the association between pre-dialysis DBP and IDH$_{nadir}$. A history of IHD and pre-dialysis DBP of < 60 mmHg, ≥ 80 mmHg to < 90 mmHg, and ≥ 90 mmHg were more closely associated with IDH$_{nadir}$ than non-IHD and a pre-dialysis DBP of ≥ 70 mmHg to < 80 mmHg (adjusted ORs 3.55 [95% CI 1.58–7.95], 4.11 [95% CI 1.80–9.39], and 6.22 [95% CI 2.44–15.82], respectively). A significant interaction between both IHD and pre-dialysis DBP categories and IDH$_{nadir}$ was observed (P for interaction < 0.001).

Sensitivity analysis

In sensitivity analysis 1, adjusted IRRs for IDH$_{nadir}$ were 1.95 (95% CI 1.36–2.80), 1.14 (95% CI 0.82–1.59), 1.39 (95% CI 0.99–1.95), and 1.48 (95% CI 0.99–2.21) in sessions with a pre-dialysis DBP of < 60 mmHg, ≥ 60 mmHg to < 70 mmHg, ≥ 80 mmHg to < 90 mmHg, and ≥ 90 mmHg, respectively, compared with the reference pre-dialysis DBP

Fig. 1 OR for IDH$_{nadir}$ by pre-dialysis DBP. Note: Restricted cubic spline plots of the ORs for IDH$_{nadir}$ according to pre-dialysis DBP. The solid line represents the OR, and the dotted line represents the 95% confidence interval. The horizontal grey line corresponds to a normal reference OR of 1.0. A pre-dialysis DBP of 80 mmHg was used as the reference in this study. ORs were estimated using mixed-effects logistic regression for the association between pre-dialysis DBP and IDH$_{nadir}$ adjusted for age, sex, BMI, cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultra-filtration rate, pre-dialysis SBP, treatment modality, use of antihypertensive drugs, use of antihypotensive drugs, IHD, serum albumin level, and CRP level. IDH$_{nadir}$ was defined as any nadir < 100 mmHg if the pre-dialysis SBP was ≥ 160 mmHg, or any nadir < 90 mmHg if the pre-dialysis SBP was < 160 mmHg. *OR* odds ratio, *IDH* intra-dialytic hypotension, *DBP* diastolic blood pressure, *BMI* body mass index, *ESRD* end-stage renal disease, *IDWG* interdialytic weight gain, *SBP* systolic blood pressure, *IHD* ischaemic heart disease, *CRP* C-reactive protein

Table 3 ORs for IDH$_{nadir}$ by pre-dialysis DBP categories in the subgroups of Non-IHD or IHD

	Pre-dialysis DBP, mmHg				
	< 60	≥ 60 to < 70	≥ 70 to < 80	≥ 80 to < 90	≥ 90
Non-IHD	**2.95 (1.63–5.32)**	1.06 (0.63–1.81)	1 (reference)	1.35 (0.80–2.26)	1.29 (0.69–2.42)
IHD	**3.55 (1.58–7.95)**	1.62 (0.76–3.43)	1.36 (0.60–3.08)	**4.11 (1.80–9.39)**	**6.22 (2.44–15.82)**

Bold values indicate statistical significance. The reference was non-IHD and pre-dialysis DBP categories of ≥ 70 mmHg to < 80 mmHg. ORs were estimated using mixed-effects logistic regression for the association between pre-dialysis DBP and IDH$_{nadir}$ adjusted for age, sex, BMI, cause of ESRD, vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, pre-dialysis SBP, treatment modality, use of antihypertensive drugs, use of antihypotensive drugs, serum albumin level, and CRP level. (P for interaction < 0.001)

IDH$_{nadir}$ was defined as any nadir < 100 mmHg if the pre-dialysis SBP was ≥ 160 mmHg, or any nadir < 90 mm Hg if the pre-dialysis SBP was < 160 mmHg

OR odds ratio, *IDH* intradialytic hypotension, *DBP* diastolic blood pressure, *IHD* ischaemic heart disease, *BMI* body mass index, *ESRD* end-stage renal disease, *IDWG* interdialytic weight gain, *SBP* systolic blood pressure, *CRP* C-reactive protein

of ≥ 70 mmHg to < 80 mmHg (Supplementary Table 1). Similar results were obtained for the continuous association between pre-dialysis DBP and IDH$_{nadir}$ (Supplementary Fig. 3). A history of IHD and pre-dialysis DBP of < 60 mmHg, ≥ 80 mmHg to < 90 mmHg, and ≥ 90 mmHg were more closely associated with IDH$_{nadir}$ than non-IHD and a pre-dialysis DBP ≥ 70 mmHg to < 80 mmHg (adjusted IRR 2.39 [95% CI 1.42–4.01], 2.44 [95% CI 1.40–4.25], and 2.91 [95% CI 1.57–5.40], respectively). A significant interaction between both IHD and pre-dialysis DBP categories and IDH$_{nadir}$ was observed (P for interaction < 0.001) (Supplementary Table 2).

In sensitivity analysis 2, adjusted ORs for IDH$_{nadir}$ were 2.06 (95% CI 1.45–2.94), 1.03 (95% CI 0.74–1.43), 1.47 (95% CI 1.08–2.00), and 1.59 (95% CI 1.09–2.34) in sessions with a pre-dialysis DBP of < 60 mmHg, ≥ 60 mmHg to < 70 mmHg, ≥ 80 mmHg to < 90 mmHg, and ≥ 90 mmHg, respectively, compared with the reference pre-dialysis DBP of ≥ 70 mmHg to < 80 mmHg (Supplementary Table 3). Similar results were obtained for the continuous association between pre-dialysis DBP and IDH$_{nadir}$ (Supplementary Fig. 4). A history of IHD and pre-dialysis DBP of < 60 mmHg, ≥ 80 mmHg to < 90 mmHg, and ≥ 90 mmHg were more closely associated with IDH$_{nadir}$ than non-IHD and a pre-dialysis DBP of ≥ 70 mmHg to < 80 mmHg (adjusted OR 2.56 [95% CI 1.37–4.77], 2.87 [95% CI 1.58–5.23], and 3.91 [95% CI 2.08–7.36], respectively). A significant interaction between both IHD and pre-dialysis DBP categories and IDH$_{nadir}$ was observed (P for interaction < 0.001) (Supplementary Table 4).

Discussion

In the present study, we observed that both high and low pre-dialysis DBP levels were associated with IDH. Continuous variable analysis revealed a reverse J-shaped association between pre-dialysis DBP and IDH. This association differs across the history of IHD. Additionally, similar results regarding these associations were obtained from the sensitivity analyses.

As with the association of cardiovascular events with both high and low DBP in previous studies [12–15], the present study revealed that both high and low pre-dialysis DBP levels were associated with IDH. However, the difference was that a low pre-dialysis DBP had a much higher risk of IDH than a high pre-dialysis DBP. As a mechanism, it was considered that low DBP decreased coronary perfusion to the myocardium, which may lead to a potential ischaemic state, and cause IDH [16].

In addition, a history of IHD had an effect on the association between pre-dialysis DBP and IDH, which is reasonable considering the mechanism. On the other hand, a combination of a high pre-dialysis DBP and a history of IHD was associated with the highest risk of IDH. This result is similar to previous studies about the association between DBP and cardiovascular events in patients with stable coronary disease [12–15]. A previous study showed that high DBP was associated with arteriosclerosis of the coronary arteries [17]. Arteriosclerosis of the coronary arteries reduces coronary flow reserve (CFR), which is

the ratio of the maximal or hyperaemic flow down coronary arteries to the resting flow [19]. CFR represents the capacity of increasing coronary flow to dilate following an increase in myocardial metabolic demands. Therefore, we presumed that the present state of vulnerability to ischaemia and a history of IHD may synergistically lead to IDH under the load of haemodialysis that reduces myocardial perfusion itself [20].

The clinical implication is that DBP is a routinely measured vital sign that makes it easy to identify high-risk patients with IDH. Although effective treatments for IDH are limited, pre-dialysis DBP and a history of IHD may identify high-risk patients with IDH development, which may allow for close monitoring of target patients.

The major strengths of this study are as follows. This is the first study to reveal the association between pre-dialysis DBP and IDH, and the first study to evaluate the interaction between pre-dialysis DBP and a history of IHD and IDH. Additionally, pre-dialysis DBP is routinely measured, and a combination of pre-dialysis DBP and history of IHD may help identify patients at high risk of developing IDH. Lastly, using various statistical models, the association between pre-dialysis DBP and IDH was consistent, which showed the robustness of the results.

This study has several limitations. First, this was a single-centre study, leading to limited generalisability. Second, there were unknown and unmeasured confounding factors as this was a retrospective cohort study. This study lacked information on cardiac function. Low cardiac function is associated with both low DBP and IDH [21]. Therefore, we might have overestimated the association between low DBP and IDH. However, we minimised the effects by excluding patients with low pre-SBP and adjusting for pre-SBP. Third, this study was observational; therefore, it could not directly show cause-and-effect associations.

In conclusion, our study revealed that low and high pre-dialysis DBP levels were associated with IDH, and the association differed across the history of IHD. This may help identify patients at a high risk of developing IDH.

Declarations

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