Association between haemoglobin concentration and intradialytic hypotension in patients undergoing maintenance haemodialysis: a retrospective cohort study

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ABSTRACT

Objectives Haemoglobin concentration is a potentially modifiable factor that may help lower the risk of intradialytic hypotension (IDH), but its association with IDH is not well understood. This study aimed to clarify the relationship between haemoglobin concentration and IDH.

Design Retrospective cohort study.

Setting We evaluated patients undergoing maintenance haemodialysis in December 2017 at Rakuwakai Otowa Kinen Hospital.

Participants A total of 543 patients were included. We defined exposure according to the following five categories depending on haemoglobin concentrations by 1.0 increments: <9.0, ≥9.0 to <10.0, 10.0 to <11.0, ≥11.0 to <12.0 and ≥12.0 g/dL.

Primary outcome measure The primary outcome of interest was the development of IDH, defined as any nadir <100 mm Hg if the pre-dialysis systolic blood pressure (SBP) was ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP was <160 mm Hg (IDH_{nadir}).

Results Overall, IDH_{nadir} occurred in 14.3% (465/3250) of the sessions. With a haemoglobin concentration of ≥10.0 to <11.0 g/dL set as reference, the adjusted ORs for IDH_{nadir} were 0.82 (95% CI, 0.32 to 2.15), 1.16 (95% CI, 0.56 to 2.39), 1.26 (95% CI, 0.68 to 2.36) and 3.01 (95% CI, 1.50 to 6.07) for haemoglobin concentrations of <9.0, ≥9.0 to <10.0, ≥11.0 to <12.0 and ≥12.0 g/dL, respectively. In the cubic spline analysis, a high haemoglobin concentration was associated with the development of IDH_{nadir}.

Conclusion High haemoglobin concentration is associated with IDH, and thus, the upper limit of haemoglobin concentration should be closely monitored in patients with IDH.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To the best of our knowledge, this study is the first to reveal an association between haemoglobin concentration and intradialytic hypotension.
⇒ Haemoglobin concentration is easily modifiable in clinical practice because it is measured routinely and is a main parameter evaluated by dialysis physicians.
⇒ This was a single-centre study in Japan, and thus, the findings have limited generalisability.
⇒ Lack of information on comorbid conditions other than ischaemic heart disease and diabetes may have led to residual confounding.

INTRODUCTION

Renal anaemia is a major complication in patients undergoing haemodialysis (HD). Previous studies have shown that anaemia is associated with adverse outcomes such as mortality and cardiovascular events.[1–9] Therefore, there have been attempts to improve anaemia using erythropoietin-stimulating agent (ESA) preparations, iron preparations, hypoxia-inducible factor prolyl-hydroxylase inhibitor preparations and red blood cell transfusions.[10] However, previous studies have also reported that the disadvantages of higher haemoglobin targets in ESA treatment outweigh their benefits.[11–16] Therefore, the optimal haemoglobin concentration target in patients undergoing HD remains controversial. Moreover, it may vary depending on the clinical problem in each case.

Intradialytic hypotension (IDH) is a clinically relevant complication in patients undergoing HD. IDH is associated with high mortality and incidence of cardiovascular events.[17–21] However, there is limited evidence to provide a basis for developing the optimal strategy for preventing IDH.[22–24] Further, although the haemoglobin concentration is a potentially modifiable risk factor for IDH, its association with IDH is not well understood. Thus, this study aimed to clarify the relationship between the haemoglobin concentration and IDH.

METHODS

Study design and population

This was a retrospective cohort study of patients undergoing maintenance HD in December 2017 at Rakuwakai Otowa Kinen

Hospital, a high-volume dialysis centre in the Yamashina region of Kyoto, Japan. The eligibility criterion was available data on the haemoglobin concentration and other medical information. This study excluded patients with pre-dialysis systolic blood pressure (SBP) <90 mm Hg because these patients were not at risk for IDH. In addition, we disclosed information about the purpose and implementation of the study to patients and informed them that they had the opportunity to refuse to participate in the study.

Exposure

The exposure of interest was the haemoglobin concentration measured during the week's first session. The haemoglobin concentration was divided into five categories by 1.0 g/dL increments ((1) <9.0 g/dL, (2) ≥9.0 to <10.0 g/dL, (3) ≥10.0 to <11.0 g/dL, (4) ≥11.0 to <12.0 g/dL and (5) ≥12.0 g/dL). For categorical variable analysis, ≥10.0 to <11.0 g/dL was set as a reference based on a previous study.[1] For continuous variable analysis, a concentration of 10.0 g/dL was set as reference.[1] Given that the haemoglobin concentration was not available in all dialysis sessions, the values obtained from the first session were used in the analysis. Given that our facility conducted blood tests every 2 weeks, we considered the data obtained for 2 weeks (about six HD sessions) as one data set.

Outcomes

The primary outcome of interest was the development of IDH, defined as any nadir <100 mm Hg if the pre-dialysis SBP was ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP was <160 mm Hg (IDH_{nadir}).[17] Pre-dialysis SBP was measured mainly in the dorsal position after a few minutes of rest, and intradialytic blood pressure was measured every 30 min.

Statistical analysis

Normally and non-normally distributed continuous data were summarised as the means (SD) and as the medians (IQR); dichotomous data were presented as proportions. Unadjusted and adjusted ORs with 95% CIs for IDH_{nadir} according to the categories of haemoglobin concentration 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), HD vintage, vascular access, dialysate temperature, interdialytic weight gain (IDWG), ultrafiltration rate, treatment modality, ischaemic heart disease (IHD), use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, transferrin saturation (TSAT), ferritin level, serum albumin level, and C reactive protein (CRP) level. These variables were based on a priori clinical judgement and existing studies.[1–9 17–24] Serum albumin and CRP levels were not available at every dialysis session, and thus, the values obtained from the first session were used in the analysis.

Darbepoetin alfa and epoetin beta pegol doses were converted to ESA doses (IU/week) using the following dose conversion ratio: epoetin: darbepoetin alfa:epoetin beta pegol=200:1:1.[25] Furthermore, we used a restricted cubic spline to analyse the relationship between the haemoglobin concentration as a continuous variable and IDH. As recommended, we used four knots located at the 5th, 35th, 65th and 95th haemoglobin concentrations.[26] Two sensitivity analyses were performed to examine the robustness of the association. In sensitivity analysis 1, unadjusted and adjusted ORs with 95% CIs for IDH_{nadir} according to the categories of haemoglobin concentration were calculated using a logistic regression model in the first session (patient-level).

In sensitivity analysis 2, we conducted the same analysis for the association between the assumed haemoglobin concentration and IDH_{nadir}. A previous study showed that each 1 L of ultrafiltration leads to an increase in the haemoglobin concentration of approximately 0.4 g/dL.[27] Therefore, under the assumption that the IDWG dilutes the haemoglobin concentration, the assumed haemoglobin concentration was calculated using the following formula:

Table 1 ORs for IDH_{nadir} by haemoglobin concentration categories

	Haemoglobin concentration, g/dL				
	<9.0	≥9.0 to <10.0	≥10.0 to <11.0	≥11.0 to <12.0	≥12
Unadjusted OR	1.66 (0.67 to 4.13)	1.11 (0.51 to 2.39)	1 (reference)	1.20 (0.63 to 2.31)	**4.31 (2.12 to 8.75)**
Adjusted OR	0.82 (0.32 to 2.15)	1.16 (0.56 to 2.39)	1 (reference)	1.26 (0.68 to 2.36)	**3.01 (1.50 to 6.07)**

Note: Bold values indicate statistical significance A haemoglobin concentration of ≥10.0 to <11.0 g/dL was set as the reference. ORs were estimated using a mixed effects logistic regression for the association between haemoglobin concentration and IDH_{nadir} adjusted for age, sex, BMI, diabetes as the primary cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, treatment modality, IHD, use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, TSAT, ferritin, serum albumin and CRP. IDH_{nadir} is defined as any nadir <100 mm Hg if the pre-dialysis SBP is ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP is <160 mm Hg.
CRP, C reactive protein; ESA, erythropoietin-stimulating agent; ESRD, end-stage renal disease; IDH, intradialytic hypotension; IDWG, interdialytic weight gain; IHD, ischaemic heart disease; TSAT, transferrin saturation.

$$\text{Assumed haemoglobin concentration} = \begin{matrix}\text{baseline haemoglobin concentration} + \\ 0.4\ (\text{baseline IDWG} - \text{eachsessions IDWG}).\end{matrix}$$

All statistical analyses were performed using Stata V.15.0 software (StataCorp). Statistical significance was set at p<0.05.

Patient and public involvement

Neither the patients nor the public were involved in the design, conduct, reporting, or dissemination plans of our research.

RESULTS

Baseline clinicodemographic patient characteristics

A total of 3250 HD sessions of 543 patients were analysed (online supplemental figure 1). Online supplemental table 1 shows the baseline characteristics in the overall cohort and by haemoglobin concentration categories. The median age was 71.0 years, and 58.4% of the patients were male. The primary cause of ESRD was diabetes in 42.2% of the patients, and 89.3% had an arteriovenous fistula (AVF). The median HD vintage was 5.0 years. A higher proportion of the high haemoglobin concentration group had an AVF and used antihypotensive drugs, and that group received a lower ESA dose and had a higher level of serum albumin.

Association between haemoglobin concentration and IDH_{nadir}

Categorical and continuous variable analyses

IDH_{nadir} occurred in 14.3% (465/3250) of all sessions. table 1 shows the association between the haemoglobin concentration categories and IDH_{nadir}.

With a haemoglobin concentration of ≥10.0 to <11.0 g/dL as reference, the unadjusted ORs for IDH_{nadir} were 1.66 (95% CI, 0.67 to 4.13), 1.11 (95% CI, 0.51 to 2.39), 1.20 (95% CI, 0.63 to 2.31) and 4.31 (95% CI, 2.12 to 8.75) for haemoglobin concentrations of <9.0, ≥9.0 to <10.0, ≥11.0 to <12.0 and ≥12.0 g/dL, respectively. After adjusting for potential confounders, the adjusted ORs for IDH_{nadir} were 0.82 (95% CI, 0.32 to 2.15), 1.16 (95% CI, 0.56 to 2.39), 1.26 (95% CI, 0.68 to 2.36) and 3.01 (95% CI, 1.50 to 6.07), respectively.

Figure 1 shows the association between haemoglobin concentration as a continuous variable and IDH_{nadir}. Restricted cubic spline analysis revealed that a high haemoglobin concentration was also associated with the development of IDH_{nadir}.

Sensitivity analysis

In sensitivity analysis 1, with a haemoglobin concentration of ≥10.0 to <11.0 g/dL as reference, the adjusted ORs for IDH_{nadir} were 1.04 (95% CI, 0.35 to 3.10), 1.10 (95% CI, 0.46 to 2.63), 1.11 (95% CI, 0.53 to 2.33) and 2.00 (95% CI, 0.93 to 4.28) for haemoglobin concentrations of <9.0, ≥9.0 to <10.0, ≥11.0 to <12.0 and ≥12.0 g/dL, respectively (table 2).

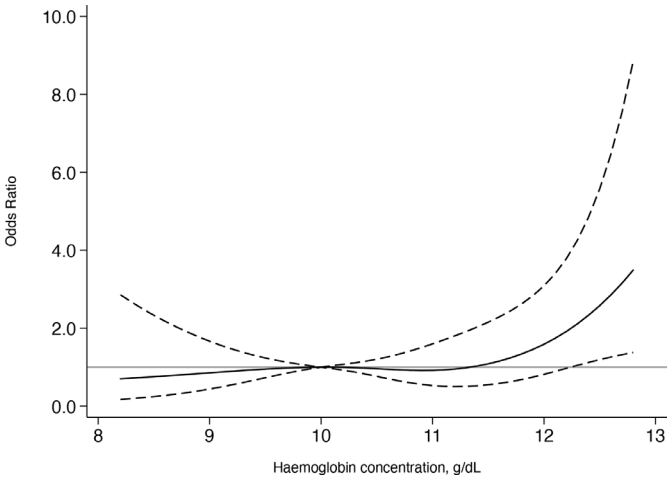

Figure 1 OR for IDH_{nadir} by haemoglobin concentration. Note: Restricted cubic spline plots of the ORs for IDH_{nadir} according to haemoglobin concentration. The horizontal grey line corresponds to a normal reference OR of 1.0. Haemoglobin concentration=10.0 g/dL was used as reference in this study. ORs were estimated using mixed effects logistic regression for the association between haemoglobin concentration and IDH_{nadir} adjusted for age, sex, BMI, diabetes as the primary cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, treatment modality, IHD, use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, TSAT, ferritin, serum albumin and CRP. IDH_{nadir} is defined as any nadir <100 mm Hg if the pre-dialysis SBP is ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP is <160 mm Hg. BMI, body mass index; CRP, C reactive protein; ESA, erythropoietin-stimulating agents; ESRD, end-stage renal disease; IDH, intradialytic hypotension; IDWG, interdialytic weight gain; IHD, ischaemic heart disease; TSAT, transferrin saturation.

Similar results were obtained for the association between the haemoglobin concentration as a continuous variable and IDH_{nadir} (figure 2).

In sensitivity analysis 2, with a haemoglobin concentration of ≥10.0 to <11.0 g/dL as reference, the adjusted ORs for IDH_{nadir} were 1.35 (95% CI, 0.59 to 3.09), 0.95 (95% CI, 0.51 to 1.78), 1.28 (95% CI, 0.79 to 2.06) and 2.52 (95% CI, 1.41 to 4.52) for haemoglobin concentrations of <9.0, ≥9.0 to <10.0, ≥11.0 to <12.0 and ≥12.0, respectively (online supplemental table 2). Similar results were obtained for the association between the haemoglobin concentration as a continuous variable and IDH_{nadir} (online supplemental figure 2).

DISCUSSION

Although the haemoglobin concentration is a potentially modifiable risk factor for IDH, its association with IDH is still unclear. This study found that a high haemoglobin concentration is associated with IDH, both in categorical and in continuous variable analyses. Similar results regarding these associations were obtained in the sensitivity analyses.

Table 2 ORs for IDH_{nadir} by haemoglobin concentration categories in sensitivity analysis 1

	Haemoglobin concentration, g/dL				
	<9.0	≥9.0 to <10.0	≥10.0 to <11.0	≥11.0 to <12.0	≥12
Unadjusted OR	1.81 (0.76 to 4.31)	1.07 (0.48 to 2.42)	1 (Reference)	1.13 (0.57 to 2.25)	**2.72 (1.39 to 5.33)**
Adjusted OR	1.04 (0.35 to 3.10)	1.10 (0.46 to 2.63)	1 (Reference)	1.11 (0.53 to 2.33)	2.00 (0.93 to 4.28)

Note: Bold values indicate statistical significance. A haemoglobin concentration of ≥10.0 to <11.0 g/dL was set as the reference. ORs were estimated using a logistic regression for the association between haemoglobin concentration and IDH_{nadir} adjusted for age, sex, BMI, diabetes as the primary cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, treatment modality, IHD, use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESAs dose, TSAT, ferritin, serum albumin and CRP. IDH_{nadir} is defined as any nadir <100 mm Hg if the pre-dialysis SBP is ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP is <160 mm Hg.
BMI, body mass index; CRP, C reactive protein; ESA, erythropoietin-stimulating agent; ESRD, end-stage renal disease; IDH, intradialytic hypotension; IDWG, interdialytic weight gain; IHD, ischaemic heart disease; TSAT, transferrin saturation.

Consistent with previous findings that a high haemoglobin concentration is associated with cardiovascular events,[1–9] the present study also found that a high haemoglobin concentration is associated with the development of IDH. However, in contrast with previous studies, we found that the risk of IDH was relatively lower in patients with a low haemoglobin concentration.[1–9] This may be related to the amount of extracellular fluid in blood vessels. The haemoglobin concentration was calculated as the amount of haemoglobin relative to the circulating blood volume. It is assumed that the extracellular fluid volume in the blood vessel is relatively low at a high haemoglobin concentration, and the volume can easily decrease due to ultrafiltration, which may lead to the development of IDH.

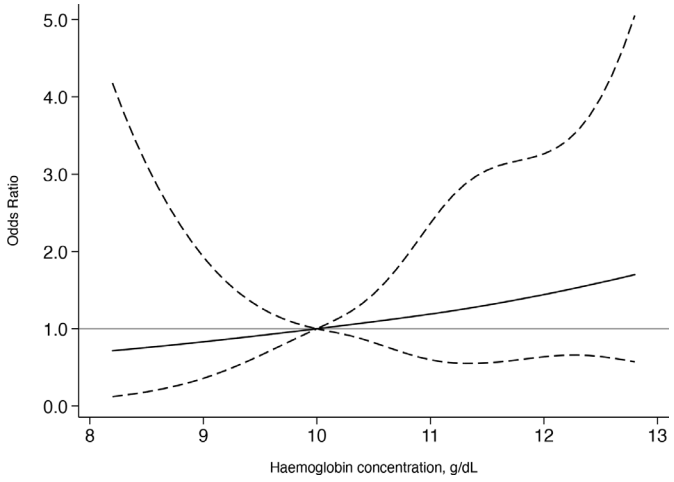

Figure 2 OR for IDH_{nadir} by haemoglobin concentration in sensitivity analysis 1. Note: Restricted cubic spline plots of the ORs for IDH_{nadir} according to haemoglobin concentration. The horizontal grey line corresponds to a normal reference or of 1.0. Haemoglobin concentration=10.0 g/dL was used as a reference in this study. ORs were estimated using a logistic regression model for the association between haemoglobin concentration and IDH_{nadir} adjusted for age, sex, BMI, diabetes as the primary cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, treatment modality, IHD, use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, TSAT, ferritin, serum albumin and CRP. IDH_{nadir} is defined as any nadir <100 mm Hg if the pre-dialysis SBP is ≥160 mm Hg or any nadir <90 mm Hg if the pre-dialysis SBP is <160 mm Hg. BMI, body mass index; CRP, C reactive protein; ESA, erythropoietin-stimulating agents; ESRD, end-stage renal disease; IDH, intradialytic hypotension; IDWG, interdialytic weight gain; IHD, ischaemic heart disease; TSAT, transferrin saturation.

The clinical implication of our findings is that regulating the haemoglobin concentration may help to reduce the occurrence of IDH. Previous studies have shown that a high haemoglobin concentration improves the quality of life,[28–31] while a low haemoglobin concentration is a risk factor for developing cardiovascular events.[1–9] Therefore, no clinical action should be taken to uniformly lower the haemoglobin concentration. However, the treatment and prevention of IDH is an area where there is very little evidence,[22–24] and in consideration of other risks, it may help them if dialysis physicians and their patients are facing trouble with IDH.

The major strengths of this study are as follows. First, to the best of our knowledge, this study is the first to reveal an association between the haemoglobin concentration and IDH. Second, the association between the haemoglobin concentration and IDH was consistent across the various sensitivity analyses, indicating the robustness of the results. Third, the haemoglobin concentration is easily modifiable in clinical practice because it is measured routinely and is a main parameter evaluated by dialysis physicians.

However, this study also has several limitations. First, this was a single-centre study in Japan, and thus, the findings have limited generalisability. Particularly, haemoglobin concentrations in other countries are higher than those in Japan due to differences in the timing of measurements.[32–34] Therefore, the association between a high haemoglobin concentration and the development of IDH may be a more relevant issue in other countries. Second, there were unknown and unmeasured confounding factors. We lacked information on comorbid conditions other than IHD and diabetes. Therefore, our cohort may have included patients with other malignancies and gastrointestinal bleeding. However, the association

between a low haemoglobin concentration and the development of IDH might be overestimated because total circulating blood volume loss is a risk factor for the development of IDH. Third, baseline data were used to define exposure categories in this cohort. The pre-dialysis haemoglobin concentration may vary for each dialysis session.[27] However, the robustness of the results was verified by a sensitivity analysis that considered the pre-dialysis haemoglobin concentration. In future studies, it will be necessary to repeatedly measure the haemoglobin concentration during each HD session. Fourth, we defined IDH as IDH_{nadir} in our study.[17] The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines define IDH as a decrease of either SBP ≥20 mm Hg or mean arterial pressure ≥10 mm Hg and associated symptoms, such as cramping, headache, lightheadedness, vomiting or chest pain during HD.[35] Similarly, the European Best Practice Guidelines (EBPGs) define IDH as a decrease of ≥20 mm Hg in SBP in combination with clinical events and interventions.[36] We were not able to measure the patients' subjective symptoms and obtain detailed information on interventions for blood pressure management due to the retrospective observational nature of the study. However, IDH_{nadir} has been suggested to be related to mortality and cardiovascular events in previous studies and is considered to have a satisfactory criteria-related validity.[17] Thus, we believe that it is a clinically relevant and reasonable definition.

In conclusion, a high haemoglobin concentration is associated with IDH, and thus, its upper limit should be closely monitored in patients with IDH.

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Contributors Research idea and study design: TH, YK, TN; data acquisition: TH, YK, TN; data analysis/interpretation: TH, YK, TN; statistical analysis: TH, YK; supervision or mentorship: TN. Each author contributed to important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. TH is acting as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethical review board of Rakuwakai Otowa Hospital Ethics Committee (approval number: Rakuoto-Rin-21-022). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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Supplementary Table 1. Baseline patient characteristics

	Total (n = 543)	Haemoglobin concentration, g/dl				
		< 9.0 (n = 49)	9.0 to < 10.0 (n = 85)	10.0 to < 11.0 (n = 172)	11.0 to < 12.0 (n = 146)	≥ 12.0 (n = 91)
Age, years	71.0 (13.3)	75.5 (11.9)	69.1 (14.6)	69.5 (13.3)	72.0 (12.6)	71.7 (13.5)
Male	58.4	38.8	62.4	57.6	62.3	60.4
BMI, kg/m^2	20.6 [18.2–23.0]	18.8 [17.5–21.4]	20.8 [19.1–23.2]	20.7 [18.6–23.3]	20.9 [18.6–23.6]	20.3 [17.5–22.4]
Diabetes as primary cause of ESRD	42.2	44.9	45.9	40.1	43.2	39.6
Haemodialysis vintage, years	5 [2–10]	5 [2–11]	5 [3–10]	5 [2–11]	4 [1–7]	5 [2–9]
Vascular access: AVF	89.3	79.6	87.1	90.7	91.1	91.2
Dialysate temperature, ℃	36 [36–36]	36 [36–36]	36 [36–36]	36 [36–36]	36 [36–36]	36 [36–36]
IDWG, kg	2.8 (1.5)	1.8 (1.1)	2.8 (1.9)	3.0 (1.5)	3.0 (1.5)	2.6 (1.3)
Ultrafiltration rate, ml/h	727.6 (280.0)	551.4 (247.1)	735.3 (310.9)	759.4 (281.8)	757.1 (260.1)	707.8 (262.3)
Treatment modality: HDF	15.3	12.2	11.8	20.9	15.8	8.8
History of IHD	24.1	32.7	28.2	23.8	18.5	25.3
Use of antihypertensive drugs	59.7	53.1	60.0	67.4	58.2	50.6
Use of antihypotensive drugs	10.7	6.1	7.1	9.3	10.3	19.8
Use of iron agents	52.7	38.8	54.1	55.8	54.8	49.5
ESA dose, IU/week	5000 [2250–10000]	12000 [6000–20000]	7500 [4000–10000]	4750 [2250–10000]	4000 [2000–8000]	3000 [1000–6000]
TSAT, %	22 [14.6–31.6]	20 [11.6–29.5]	17.2 [12.7–31.5]	21.0 [13.2–28]	24.7 [17.3–32.1]	27.9 [19.8–38.6]
Ferritin, ng/mL	58.3	97.8	59	47.7	51.5	62

	[31–109]	[50.5–243]	[35.9–117]	[27.2–94.1]	[29.8–105]	[44.4–93.4]
Serum albumin, g/dL	3.6 [3.3–3.8]	3.0 [2.4–3.4]	3.5 [3.2–3.8]	3.6 [3.3–3.8]	3.7 [3.4–3.9]	3.7 [3.4–3.9]
CRP, mg/dL	0.23 [0.09–0.73]	0.73 [0.13–3.43]	0.35 [0.12–0.86]	0.27 [0.10–0.61]	0.18 [0.08–0.40]	0.21 [0.07–0.77]

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

Abbreviations: BMI, body mass index; ESRD, end-stage renal disease; AVF, arteriovenous fistula; IDWG, interdialytic weight gain; ESA, erythropoietin-stimulating agents; HDF, haemodiafiltration; IHD, ischaemic heart disease; TSAT, transferrin saturation; CRP, C-reactive protein

Supplementary Table 2. ORs for IDH_{nadir} by the assumed haemoglobin concentration categories in sensitivity analysis 2

	Haemoglobin concentration, g/dl				
	< 9.0	9.0 to < 10.0	10.0 to < 11.0	11.0 to < 12.0	≥ 12
Unadjusted OR	2.10 (0.97–4.57)	0.97 (0.52–1.83)	1 (Reference)	1.29 (0.80–2.07)	**2.78 (1.57–4.93)**
Adjusted OR	1.35 (0.59–3.09)	0.95 (0.51–1.78)	1 (Reference)	1.28 (0.79–2.06)	**2.52 (1.41–4.52)**

Note: Bold values indicate statistical significance A haemoglobin concentration of 10.0 to < 11.0 g/dl was set as the reference. ORs are estimated using a mixed effects logistic regression model for the association between the assumed haemoglobin concentration and IDH_{nadir} adjusted for age, sex, BMI, diabetes as the primary cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, treatment modality, IHD, use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, TSAT, ferritin, serum albumin, and CRP.

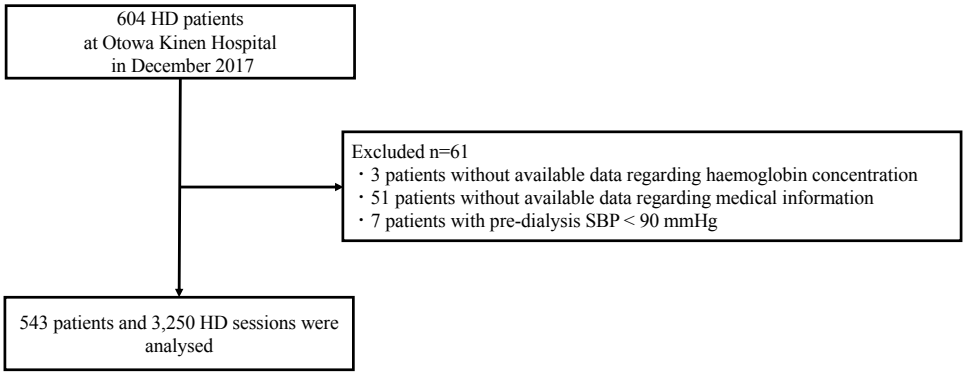
The assumed haemoglobin concentration was calculated using the following formula:

Assumed haemoglobin concentration = baseline haemoglobin concentration + 0.4 (baseline IDWG − each session's IDWG).

IDH_{nadir} is defined as any nadir < 100 mmHg if the pre-dialysis SBP is ≥ 160 mmHg or any nadir < 90 mmHg if the pre-dialysis SBP is < 160 mmHg.

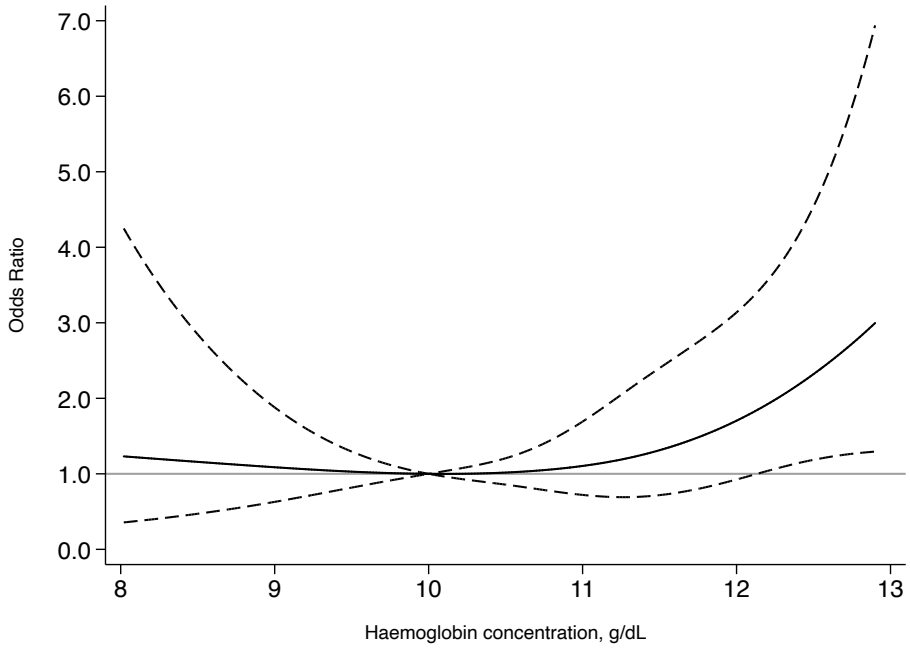
Abbreviations: OR, odds ratio; IDH, intradialytic hypotension; BMI, body mass index; ESRD, end-stage renal disease; IDWG, interdialytic weight gain; ESA, erythropoietin-stimulating agents; IHD, ischaemic heart disease; TSAT, transferrin saturation; CRP, C-reactive protein

Supplementary Figure 1. Flow chart of study participants



Abbreviations: HD, haemodialysis; SBP, systolic blood pressure

Supplementary Figure 2. OR for IDH_{nadir} by the assumed haemoglobin concentration in sensitivity analysis 2.



Note: Restricted cubic spline plots of the ORs for IDH_{nadir} according to the assumed haemoglobin concentration. The horizontal grey line corresponds to a normal reference OR of 1.0. Haemoglobin concentration = 10.0 g/dl was used as reference in this study. ORs were estimated using a mixed effects logistic regression model for the association between the assumed haemoglobin concentration and IDH_{nadir} adjusted for age, sex, BMI, diabetes as the primary cause of ESRD, haemodialysis vintage, vascular access, dialysate temperature, IDWG, ultrafiltration rate, treatment modality, IHD, use of antihypertensive drugs, use of antihypotensive drugs, use of iron agents, ESA dose, TSAT, ferritin, serum albumin, and CRP.

The assumed haemoglobin concentration was calculated using the following formula:

Assumed haemoglobin concentration = baseline haemoglobin concentration + 0.4 (baseline IDWG − each session's IDWG).

IDH_{nadir} is defined as any nadir < 100 mmHg if the pre-dialysis SBP is ≥ 160 mmHg or any nadir < 90 mmHg if the pre-dialysis SBP is < 160 mmHg.

Abbreviations: OR, odds ratio; IDH, intradialytic hypotension; BMI, body mass index; ESRD, end-stage renal disease; IDWG, interdialytic weight gain; ESA, erythropoietin-stimulating agents; IHD, ischaemic heart disease; TSAT, transferrin saturation; CRP, C-reactive protein