

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

Takashi Hara <sup>1</sup>, Yuto Kasahara,<sup>1</sup> Takahiko Nakagawa<sup>1,2</sup>

**To cite:** Hara T, Kasahara Y, Nakagawa T. Association between haemoglobin concentration and intradialytic hypotension in patients undergoing maintenance haemodialysis: a retrospective cohort study. *BMJ Open* 2022;**12**:e064026. doi:10.1136/bmjopen-2022-064026

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-064026>).

Received 23 April 2022  
Accepted 08 August 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Department of Nephrology, Rakuwakai Otowa Hospital, Kyoto, Japan

<sup>2</sup>Department of Biochemistry, Shiga University of Medical Science, Otsu, Japan

## Correspondence to

Dr Takashi Hara;  
[hara.takashi.74x@kyoto-u.jp](mailto:hara.takashi.74x@kyoto-u.jp)

## 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 Kinin 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<sub>nadir</sub>).

**Results** Overall, IDH<sub>nadir</sub> 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<sub>nadir</sub> 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<sub>nadir</sub>.

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

## 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.<sup>1–9</sup> Therefore, there have been attempts to improve anaemia using erythropoietin-stimulating agent (ESA) preparations, iron preparations, hypoxia-inducible factor prolyl-hydroxylase

## 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.

inhibitor preparations and red blood cell transfusions.<sup>10</sup> However, previous studies have also reported that the disadvantages of higher haemoglobin targets in ESA treatment outweigh their benefits.<sup>11–16</sup> 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.<sup>17–21</sup> However, there is limited evidence to provide a basis for developing the optimal strategy for preventing IDH.<sup>22–24</sup> 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 Kinin

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.<sup>1</sup> For continuous variable analysis, a concentration of 10.0 g/dL was set as reference.<sup>1</sup> 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<sub>nadir</sub>).<sup>17</sup> 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<sub>nadir</sub> 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.<sup>1–9 17–24</sup> 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.<sup>25</sup> 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.<sup>26</sup> 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<sub>nadir</sub> 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<sub>nadir</sub>. A previous study showed that each 1 L of ultrafiltration leads to an increase in the haemoglobin concentration of approximately 0.4 g/dL.<sup>27</sup> 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<sub>nadir</sub> 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)	<b>4.31 (2.12 to 8.75)</b>
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)	<b>3.01 (1.50 to 6.07)</b>

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<sub>nadir</sub> 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<sub>nadir</sub> 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.

$$\text{Assumed haemoglobin concentration} = \frac{\text{baseline haemoglobin concentration} + 0.4 (\text{baseline IDWG} - \text{eachsessions IDWG})}{2}$$

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 antihypertensive drugs, and that group received a lower ESA dose and had a higher level of serum albumin.

### Association between haemoglobin concentration and IDH<sub>nadir</sub> Categorical and continuous variable analyses

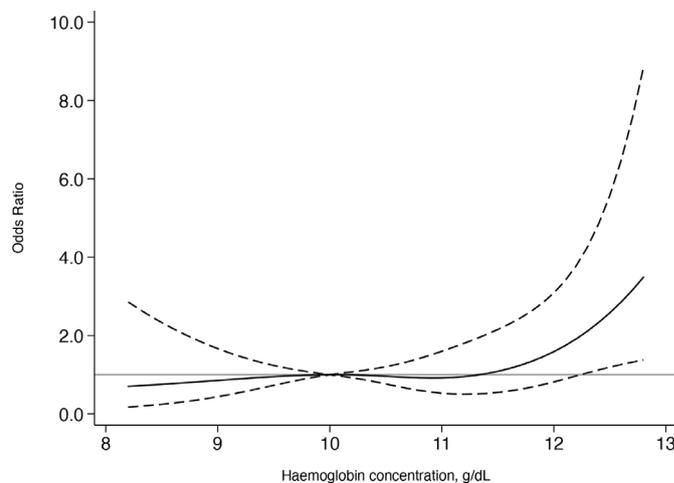
IDH<sub>nadir</sub> occurred in 14.3% (465/3250) of all sessions. table 1 shows the association between the haemoglobin concentration categories and IDH<sub>nadir</sub>.

With a haemoglobin concentration of  $\geq 10.0$  to  $< 11.0$  g/dL as reference, the unadjusted ORs for IDH<sub>nadir</sub> 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  $< 9.0$ ,  $\geq 9.0$  to  $< 10.0$ ,  $\geq 11.0$  to  $< 12.0$  and  $\geq 12.0$  g/dL, respectively. After adjusting for potential confounders, the adjusted ORs for IDH<sub>nadir</sub> 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<sub>nadir</sub>. Restricted cubic spline analysis revealed that a high haemoglobin concentration was also associated with the development of IDH<sub>nadir</sub>.

### Sensitivity analysis

In sensitivity analysis 1, with a haemoglobin concentration of  $\geq 10.0$  to  $< 11.0$  g/dL as reference, the adjusted ORs for IDH<sub>nadir</sub> 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  $< 9.0$ ,  $\geq 9.0$  to  $< 10.0$ ,  $\geq 11.0$  to  $< 12.0$  and  $\geq 12.0$  g/dL, respectively (table 2).



**Figure 1** OR for IDH<sub>nadir</sub> by haemoglobin concentration. Note: Restricted cubic spline plots of the ORs for IDH<sub>nadir</sub> 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<sub>nadir</sub> 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 antihypertensive drugs, use of iron agents, ESA dose, TSAT, ferritin, serum albumin and CRP. IDH<sub>nadir</sub> is defined as any nadir  $< 100$  mm Hg if the pre-dialysis SBP is  $\geq 160$  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<sub>nadir</sub> (figure 2).

In sensitivity analysis 2, with a haemoglobin concentration of  $\geq 10.0$  to  $< 11.0$  g/dL as reference, the adjusted ORs for IDH<sub>nadir</sub> 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  $< 9.0$ ,  $\geq 9.0$  to  $< 10.0$ ,  $\geq 11.0$  to  $< 12.0$  and  $\geq 12.0$ , respectively (online supplemental table 2). Similar results were obtained for the association between the haemoglobin concentration as a continuous variable and IDH<sub>nadir</sub> (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.

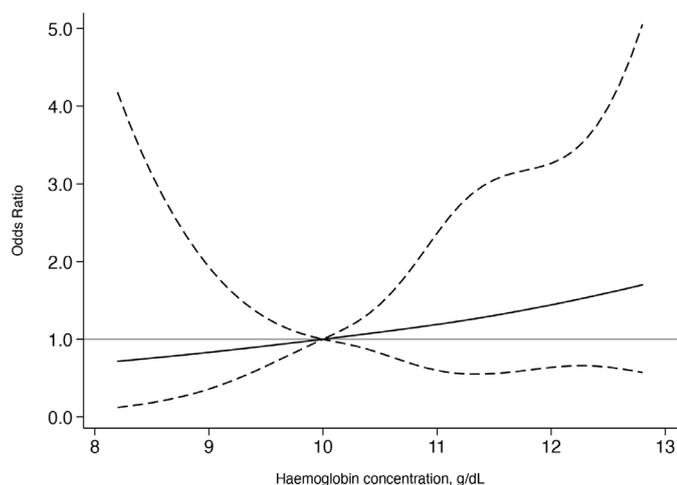
**Table 2** ORs for IDH<sub>nadir</sub> by haemoglobin concentration categories in sensitivity analysis 1

	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)	<b>2.72 (1.39 to 5.33)</b>
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<sub>nadir</sub> 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<sub>nadir</sub> 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,<sup>1-9</sup> 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.<sup>1-9</sup> This may be related to the amount of extracellular fluid in blood



**Figure 2** OR for IDH<sub>nadir</sub> by haemoglobin concentration in sensitivity analysis 1. Note: Restricted cubic spline plots of the ORs for IDH<sub>nadir</sub> 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<sub>nadir</sub> 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<sub>nadir</sub> 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.

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.

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,<sup>28-31</sup> while a low haemoglobin concentration is a risk factor for developing cardiovascular events.<sup>1-9</sup> 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,<sup>22-24</sup> 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.<sup>32-34</sup> 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.<sup>27</sup> 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<sub>nadir</sub> in our study.<sup>17</sup> The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines define IDH as a decrease of either SBP  $\geq 20$  mm Hg or mean arterial pressure  $\geq 10$  mm Hg and associated symptoms, such as cramping, headache, lightheadedness, vomiting or chest pain during HD.<sup>35</sup> Similarly, the European Best Practice Guidelines (EBPGs) define IDH as a decrease of  $\geq 20$  mm Hg in SBP in combination with clinical events and interventions.<sup>36</sup> 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<sub>nadir</sub> has been suggested to be related to mortality and cardiovascular events in previous studies and is considered to have a satisfactory criteria-related validity.<sup>17</sup> 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.

**Acknowledgements** We appreciate the cooperation of the patients and medical staff at Otowa Kinen Hospital.

**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.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**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.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible

for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iD

Takashi Hara <http://orcid.org/0000-0001-8857-0857>

#### REFERENCES

- Madore F, Lowrie EG, Brugnara C, *et al.* Anemia in hemodialysis patients: variables affecting this outcome predictor. *J Am Soc Nephrol* 1997;8:1921–9.
- Li S, Collins AJ. Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients. *Kidney Int* 2004;65:626–33.
- Locatelli F, Pisoni RL, Combe C, *et al.* Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the dialysis outcomes and practice patterns study (DOPPS). *Nephrol Dial Transplant* 2004;19:121–32.
- Pisoni RL, Bragg-Gresham JL, Young EW, *et al.* Anemia management and outcomes from 12 countries in the dialysis outcomes and practice patterns study (DOPPS). *Am J Kidney Dis* 2004;44:94–111.
- Robinson BM, Joffe MM, Berns JS, *et al.* Anemia and mortality in hemodialysis patients: accounting for morbidity and treatment variables updated over time. *Kidney Int* 2005;68:2323–30.
- Regidor DL, Kopple JD, Kovesdy CP, *et al.* Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 2006;17:1181–91.
- Walker AM, Schneider G, Yeaw J, *et al.* Anemia as a predictor of cardiovascular events in patients with elevated serum creatinine. *J Am Soc Nephrol* 2006;17:2293–8.
- Akizawa T, Pisoni RL, Akiba T, *et al.* Japanese haemodialysis anaemia management practices and outcomes (1999–2006): results from the DOPPS. *Nephrol Dial Transplant* 2008;23:3643–53.
- Akizawa T, Saito A, Gejyo F, *et al.* Low hemoglobin levels and hyporesponsiveness to erythropoiesis-stimulating agent associated with poor survival in incident Japanese hemodialysis patients. *Ther Apher Dial* 2014;18:404–13.
- Raichoudhury R, Spinowitz BS. Treatment of anemia in difficult-to-manage patients with chronic kidney disease. *Kidney Int Suppl* 2021;11:26–34.
- Besarab A, Bolton WK, Browne JK, *et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584–90.
- Parfrey PS, Foley RN, Witteich BH, *et al.* Double-Blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 2005;16:2180–9.
- Singh AK, Szczech L, Tang KL, *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085–98.
- Phrommintikul A, Haas SJ, Elsie M, *et al.* Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet* 2007;369:381–8.
- Palmer SC, Navaneethan SD, Craig JC, *et al.* Meta-Analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med* 2010;153:23–33.
- Ye Y, Liu H, Chen Y, *et al.* Hemoglobin targets for the anemia in patients with dialysis-dependent chronic kidney disease: a meta-analysis of randomized, controlled trials. *Ren Fail* 2018;40:671–9.
- Flythe JE, Xue H, Lynch KE, *et al.* Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol* 2015;26:724–34.
- Shoji T, Tsubakihara Y, Fujii M, *et al.* Hemodialysis-Associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int* 2004;66:1212–20.
- Tislér A, Akócsi K, Borbás B, *et al.* The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis. *Nephrol Dial Transplant* 2003;18:2601–5.



- 20 Burton JO, Jefferies HJ, Selby NM, *et al.* Hemodialysis-Induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009;4:914–20.
- 21 Mc Causland FR, Tumlin JA, Roy-Chaudhury P, *et al.* Intradialytic hypotension and cardiac arrhythmias in patients undergoing maintenance hemodialysis: results from the monitoring in dialysis study. *Clin J Am Soc Nephrol* 2020;15:805–12.
- 22 Sars B, van der Sande FM, Kooman JP. Intradialytic hypotension: mechanisms and outcome. *Blood Purif* 2020;49:158–67.
- 23 Reeves PB, Mc Causland FR. Mechanisms, clinical implications, and treatment of Intradialytic hypotension. *Clin J Am Soc Nephrol* 2018;13:1297–303.
- 24 Kanbay M, Ertuglu LA, Afsar B, *et al.* An update review of intradialytic hypotension: concept, risk factors, clinical implications and management. *Clin Kidney J* 2020;13:981–93.
- 25 Yokoyama K, Fukagawa M, Akiba T, *et al.* Ferritin Elevation and Improved Responsiveness to Erythropoiesis-Stimulating Agents in Patients on Ferric Citrate Hydrate. *Kidney Int Rep* 2017;2:359–65.
- 26 Harrell FE. *General aspects of fitting regression models.* In: *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis.* 2nd. New York: Springer New York, 2001: 13–44.
- 27 Bellizzi V, Minutolo R, Terracciano V, *et al.* Influence of the cyclic variation of hydration status on hemoglobin levels in hemodialysis patients. *Am J Kidney Dis* 2002;40:549–55.
- 28 Grunze M, Kohlmann M, Mulligan M, *et al.* Mechanisms of improved physical performance of chronic hemodialysis patients after erythropoietin treatment. *Am J Nephrol* 1990;10 Suppl 2:15–23.
- 29 McMahon LP, McKenna MJ, Sangkabutra T, *et al.* Physical performance and associated electrolyte changes after haemoglobin normalization: a comparative study in haemodialysis patients. *Nephrol Dial Transplant* 1999;14:1182–7.
- 30 Moreno F, Sanz-Guajardo D, López-Gómez JM, *et al.* Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. Spanish cooperative renal patients quality of life Study group of the Spanish Society of nephrology. *J Am Soc Nephrol* 2000;11:335–42.
- 31 Kalantar-Zadeh K, Kopple JD, Block G, *et al.* Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. *J Am Soc Nephrol* 2001;12:2797–806.
- 32 Yamamoto H, Nishi S, Tomo T. Japanese Society for dialysis therapy: guidelines for renal anemia in chronic kidney disease. *Ren Replace Ther* 2015;36:3..
- 33 Kidney disease: improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int* 2012;2:279–335.
- 34 Locatelli F, Bárány P, Covic A, *et al.* Kidney disease: improving global outcomes guidelines on anaemia management in chronic kidney disease: a European renal best practice position statement. *Nephrol Dial Transplant* 2013;28:1346–59.
- 35 K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005;45:S1–153.
- 36 Kooman J, Basci A, Pizzarelli F, *et al.* EBPG guideline on haemodynamic instability. *Nephrol Dial Transplant* 2007;22 Suppl 2:ii22–44.

**Supplementary Table 1.** Baseline patient characteristics

	Total (n = 543)	Haemoglobin concentration, g/dl				
		< 9.0	9.0 to < 10.0	10.0 to < 11.0	11.0 to < 12.0	≥ 12.0
		(n = 49)	(n = 85)	(n = 172)	(n = 146)	(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 <sup>2</sup>	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, °C	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]
	3.6	3.0	3.5	3.6	3.7	3.7
Serum albumin, g/dL	[3.3–3.8]	[2.4–3.4]	[3.2–3.8]	[3.3–3.8]	[3.4–3.9]	[3.4–3.9]
	0.23	0.73	0.35	0.27	0.18	0.21
CRP, mg/dL	[0.09–0.73]	[0.13–3.43]	[0.12–0.86]	[0.10–0.61]	[0.08–0.40]	[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<sub>nadir</sub> 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)	<b>2.78</b> <b>(1.57–4.93)</b>
Adjusted OR	1.35 (0.59–3.09)	0.95 (0.51–1.78)	1 (Reference)	1.28 (0.79–2.06)	<b>2.52</b> <b>(1.41–4.52)</b>

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<sub>nadir</sub> 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.

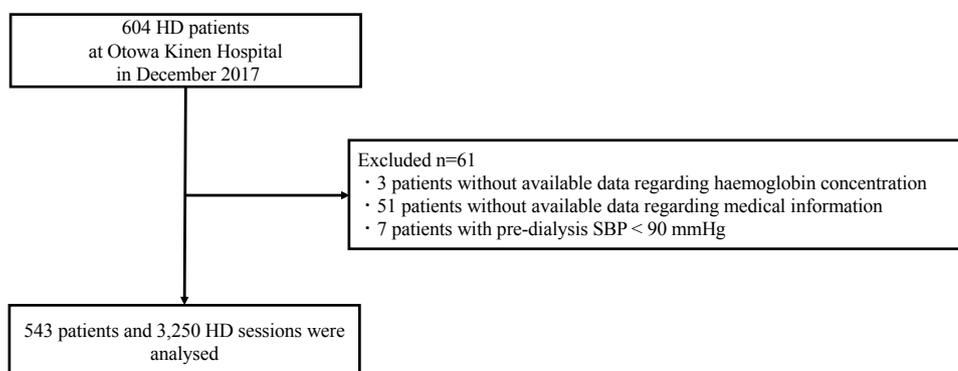
The assumed haemoglobin concentration was calculated using the following formula:

Assumed haemoglobin concentration = baseline haemoglobin concentration + 0.4

(baseline IDWG – each session's IDWG).

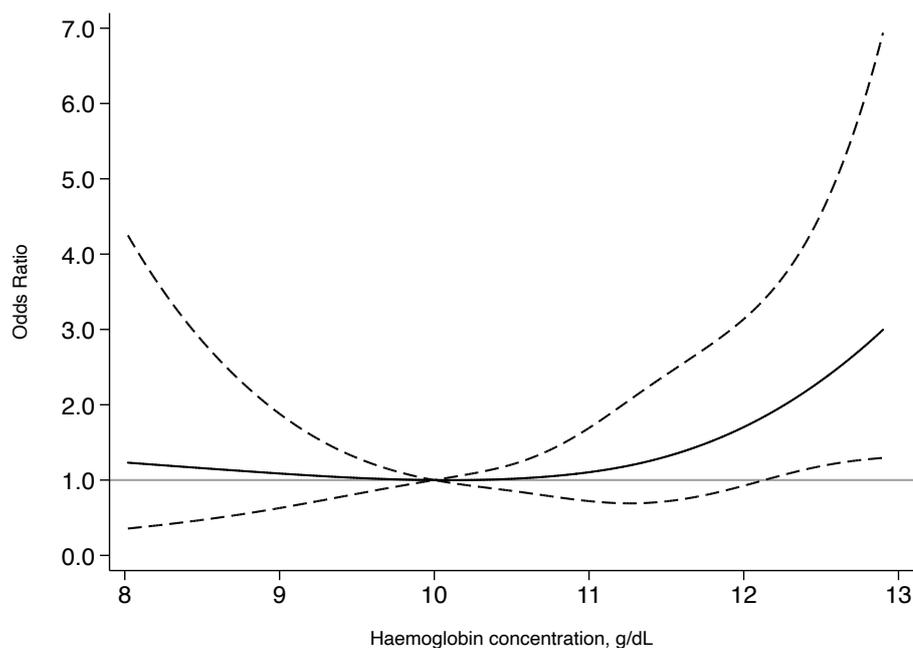
IDH<sub>nadir</sub> is defined as any nadir < 100 mmHg if the pre-dialysis SBP is ≥ 160 mmHg or any nadir < 90 mmHg if the pre-dialysis SBP is < 160 mmHg.

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<sub>nadir</sub> by the assumed haemoglobin concentration in sensitivity analysis 2.



Note: Restricted cubic spline plots of the ORs for IDH<sub>nadir</sub> 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<sub>nadir</sub> 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<sub>nadir</sub> is defined as any nadir < 100 mmHg if the pre-dialysis SBP is  $\geq$  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