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ORIGINAL ARTICLE

Factors affecting pre-end-stage kidney disease haemoglobin control and outcomes following dialysis initiation: a nationwide study

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ABSTRACT

Background. Attaining the narrow haemoglobin (Hb) range recommended by European Renal Best Practice Guidelines renal anaemia guidelines may be difficult, and whether this leads to better outcomes following dialysis initiation is not known.

Methods. This was an observational study from the Swedish Renal Registry 2012–16, including all patients with non-dialysis-dependent chronic kidney disease (CKD) initiating renal anaemia treatment. We evaluated factors associated with off-target Hb attainment (<10 and >12 g/dL). For those who initiated dialysis, we explored associations between the pre-end-stage kidney disease (pre-ESKD) time in which Hb was within or above range, and pre-ESKD Erythropoietin Resistance Index (ERI) with the 1-year risk of death or major adverse cardiovascular events + (MACE+).

Results. About 5000 patients initiated anaemia treatment, contributing to 25 431 consecutive visits over time. Patients with polycystic kidney disease, diabetic nephropathy and nephrosclerosis, with recent bleeding/transfusion, with higher C-reactive protein or abnormal phosphate had higher odds of maintaining Hb below range. Conversely, patients with older age, CKD Stages 3b–4, pyelonephritis, kidney transplant, iron medication, higher ESA doses or abnormal serum calcium and albumin had higher odds of maintaining Hb above range. A total of 1361 patients initiated dialysis, among whom 220 deaths and 453 MACE+ occurred. A greater time spent with a pre-ESKD Hb >12 g/dL was associated with a lower risk of MACE+
(hazard ratio = 0.76; 95% confidence interval 0.61–0.94) after dialysis initiation, and a lower pre-ESKD Erythropoietin Resistance Index (ERI) was associated with improved survival (1.39; 1.02–1.90).

Conclusions. Our study identified populations that require additional efforts to control their Hb. Our outcome analysis supports the value of pre-ESKD anaemia care while illustrating the problems of ESA hyporesponsiveness in clinical practice.

Keywords: death, ESA hyporesponsiveness, haemoglobin control, MACE+, pre-ESKD

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INTRODUCTION

Anaemia is a progressively common complication of chronic kidney disease (CKD) Stages 3–5 [1], primarily attributed to diminished oxygen sensing by the failing kidneys resulting in decreased synthesis of erythropoietin (EPO) and abnormalities affecting iron availability [2]. The current mainstays of renal anaemia treatment are erythropoiesis-stimulating agents (ESAs) and iron supplements [3]. Major clinical trials of ESA use in CKD demonstrated either no benefit or greater harm with normalizing haemoglobin (Hb) compared with lower targets for outcomes including mortality, cardiovascular events and time to dialysis initiation [4–6]. As a result, most guidelines, including the European Renal Best Practice Guidelines (ERBP), recommend a Hb target range of 10–12 g/dL [7]. However, because Hb is highly variable during treatment with ESAs, and multiple factors contribute to ESA hypo-responsiveness [8], attaining such a narrow target range may be challenging. Previous studies have identified predictors of poor Hb in patients with CKD through cross-sectional designs [9–12]. However, predictors may contribute variably over time, justifying the need for regular patient monitoring at the bedside and for longitudinal designs in epidemiological studies.

CKD is a disease continuum, and investigators are gradually adopting a patient perspective in their analytical approaches by evaluating the effect of nephrology care prior to the transition to dialysis on subsequent outcomes. Previous studies have observed that Hb variability [13, 14] or the consistency of pre-end-stage kidney disease (pre-ESKD) anaemia care (i.e. treated versus untreated) [15–17] in the transition period to dialysis predicts subsequent outcomes. Whether attainment of Hb targets or resistance to ESA therapy (which may be a surrogate for inflammation or other comorbidities associated with more severe disease) during pre-ESKD care is associated with outcomes following dialysis initiation is not well studied. We utilized a nationwide cohort of nephrologist-referred patients with CKD receiving anaemia treatment to identify longitudinal predictors of Hb target attainment and to evaluate the association between pre-ESKD Hb target attainment, ESA resistance and outcomes following dialysis initiation.

MATERIALS AND METHODS

Data source

We used data from the Swedish Renal Registry (SRR), a nationwide registry of patients with CKD G3–5 attending routine nephrologist specialist care in Sweden [18, 19]. The SRR collects routine information from stable outpatient nephrologist visits, including attained Hb, use of iron [and type, i.e. intravenous (IV) or oral] and ESA (type and dose). Patients with an incident estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 should be mandatorily enrolled in the registry, but the registry also encourages the inclusion of patients earlier in the course of the disease (<45 mL/min/1.73 m^2) as long as patients are included systematically by the Nephrology clinic. Registrations of subsequent outpatient visits to nephrology care (on average 2–3/year/patient) are thereafter recorded until the start of kidney replacement therapy, death or emigration from the country. Nearly all Nephrology clinics in Sweden (96%) report to the SRR and the estimated national coverage is >75% for nephrologist-referred patients with recognized G4–5 CKD [20]. Via each citizen's unique personal identification number, the SRR was linked to other government-run registries: the Swedish prescribed drug registry provided complete information on all prescribed drugs dispensed at Swedish pharmacies [21]; the Swedish Patient Registry provided information on all outpatient specialist consultations and hospitalizations occurring in Swedish healthcare from 1997 until end of follow-up for information on comorbidities and non-fatal outcomes [22]; and the Swedish Death Registry added information on date and causes of death [23]. Government-run registries are considered to have no or minimal loss to follow-up. The study was approved by the regional ethical review boards and the Swedish National Board of Welfare.

Patient selection

For this study, we included all adult patients recorded between 2012 and 2016 with eGFR <45 mL/min/1.73 m^2 from the initiation of anaemia therapy (ESA, iron or both). We chose this period because it followed the publication of ESA trials and ERBP guidelines. Patients were defined from the index date of first detected anaemia treatment, and data from every subsequent visit after cohort entry was extracted. Individuals who had fewer then two2 visits registered during the non-dialysis phase were excluded, as this was deemed insufficient to evaluate longitudinal determinants of Hb control. We also excluded individuals with a recent or ongoing cancer, defined as a cancer diagnosis within 3 years before index date, and patients whose first patient visit was preceded (within 30 days) by a bleeding episode, or a hospitalization regardless of the cause.

Exposure and outcomes

This study includes two separate cohorts of patients and analyses. In the first cohort, we evaluated all patient visits until death, dialysis or end of follow-up to identify predictors of Hb target attainment. Predictors tested were identified based on biological plausibility, and included demographics, comorbidities (detailed in Supplementary data, Table S1), medications (detailed in Supplementary data, Table S2) and laboratory values. The study outcomes were Hb <10 g/dL and >12 g/dL at each nephrologist visit, and the Hb range 10–12 g/dL was considered the reference category per ERBP guidelines.

The second cohort included patients from the first cohort who had transitioned to dialysis. In this second cohort, we evaluated the association between pre-ESKD Hb attainment, Erythropoietin Resistance Index (ERI) and outcomes during the first year upon initiation of dialysis. The date of dialysis start was the index date. Using all preceding information during pre-ESKD care, we assumed a linear relationship between recorded Hb values (Supplementary data, Figure S1) and calculated the proportion of patient time (in days) until dialysis start in which Hb was maintained within the recommended range of 10–12 g/dL (time in range, TIR) or 12 g/dL (time above range, TAR). Their estimations were as follows:

$$\mathrm{TIR} = \frac{\int_0^T I(10 \le \mathrm{Hb}(t) \le 12)dt}{T}, T : \text{duration of the pre} - \text{ESKD period}$$

$$\mathrm{TAR} = \frac{\int_0^T I(\mathrm{Hb}(t) > 12)dt}{T}, \; T : \text{duration of the pre} - \text{ESKD period}$$

We did not calculate the proportion of time spent <10 g/dL (time below range, TBR), because the proportion of Hb

measurements within this range was negligible. The sum of TAR, TIR and TBR equals 100% of the patient's pre-ESKD recorded time on anaemia treatment.

The Erythropoietin Resistance Index (ERI) was calculated as the weekly weight-adjusted dose of EPO divided by the attained Hb level [24] in all recorded pre-ESKD visits on ESA, and the mean pre-ESKD ERI was computed per patient.

The study outcomes for the second cohort were the occurrence of death (by any cause), and major adverse cardiovascular events + (MACE+). MACE+ was defined as the composite occurrence of non-fatal myocardial infarction, stroke, heart failure or death attributed to cardiovascular disease (CVD), whichever happened first. Outcome definitions are detailed in Supplementary data, Table S3.

Covariates

Demographic data (i.e. age and sex), current medications and clinical data were obtained as entered into the SRR on each visit by the local administrators of each Nephrology unit. Clinical information collected encompasses information on CKD aetiology, body mass index (BMI), routine laboratory biomarkers and CKD-anaemia-specific medications including the use of IV, oral iron and ESA (with doses). Weekly ESA doses for darbepoetin and methoxy polyethylene glycol–epoetin beta were converted to a weekly epoetin equivalent dose derived from the allocated daily doses defined by the World Health Organization Collaborating Centre [25]. Conversion factors of 1:222 and 1:250 were used for the conversion of epoetin:darbepoetin and epoetin:methoxy polyethylene glycol–epoetin beta, respectively. According to the SRR manual, a patient was considered as treated with IV iron for up to 6 months after the last administration of low-frequency, high-dose IV iron. Use of oral iron was identified from pharmacy dispensations as recorded in the Prescribed Drugs Registry up to 3 months before each visit. Comorbid history was defined from relevant diagnoses (International Classification of Diseases 10th revision) or surgical procedure (Nordic Medico-Statistical Committee classification system) before the index date and since 1997, when these classification systems were implemented in Sweden (definitions listed in Supplementary data, Table S1). Use of other relevant medications were defined either as per SRR variables or as per pharmacy dispensations (Anatomical Therapeutic Chemical classification codes) at time of each recorded visit and within 6 months before (definitions listed in Supplementary data, Table S2).

Statistical analyses

Descriptive statistics are presented with continuous variables shown as mean and standard error, if normally distributed, and median and interquartile range (IQR) otherwise.

We used multinomial logistic regression with cluster robust standard errors to estimate the odds ratios (ORs) for Hb target attainment through all repeated patient visits. Predictors were identified on the basis of biological plausibility and updated with values at each visit. In addition, we considered the previous renal anaemia management prescription as a predictor of the current Hb value, as an abnormal Hb value would prompt an adjustment in ESA dose to correct it, and this will impact on the next Hb recorded. Information on some variables was not complete, and the proportion of missingness is reported in Supplementary data, Table S4. We considered these values missing at random, and we used multiple chain equations to generate five imputed datasets with all other covariates as auxiliary covariates in the modelling. The frequency of reporting of outpatient Nephrology visits varies across nephrology units and regions in Sweden. To evaluate the robustness of our results, we repeated our main analysis in patients from the nephrology units that report all outpatient visits into the register.

Next, we used natural cubic splines (with truncated power series as basic functions and knots at 10, 50 and 90% quantiles of distribution) to graphically depict the association between pre-ESKD TIR, TAR and mean ERI and the rate of death or MACE+ during the first year following dialysis initiation. We used Cox regression for the rate of death, Cox regression with competing risk (non-CVD death as competing risk) for the rate of MACE+ associated with categories of TIR, TAR and mean ERI (median value).

All analyses were performed using R version 3.4.3 software (The R Project for Statistical Computing, Vienna, Austria).

RESULTS

Cohort characteristics

After applying inclusion and exclusion criteria, we identified 5000 adult patients with CKD Stages 3b–5 who initiated anaemia treatment in Sweden during 2012–16 (Supplementary data, Figure S2). Characteristics at inclusion are shown in Table 1; patients had a mean age of 69 [standard deviation (SD) 15] years, and 45% were women. Diabetic nephropathy and nephrosclerosis were the main reported causes of CKD, accounting for 25 and 24% of cases, respectively. The majority of patients who initiated anaemia therapy were patients with CKD Stages 4 and 5, and ∼2% were kidney transplant recipients. Hypertension was the most prevalent comorbidity (88% of patients), followed by diabetes (45%) and CVD (43%). As many as 40% of patients initiated iron only, 41% patients initiated ESA only and 19% initiated both ESA and iron.

Predictors of Hb below and above ERBP recommended range

Included patients contributed to 25 431 consecutive visits for the analysis of predictors of off target Hb attainment. The majority of Hb measurements (50%) were kept within ERBP recommended range; 39% of measurements were 12 g/dL, mostly between 12 and 13 g/dL (23%); and only 9% were <10 g/dL. During follow-up, most visits ($n = 14\,768$, 58%) recorded the use of ESA, of which 7931 visits (31%) recorded the use of ESA in combination with iron. Furthermore, 7072 (28%) visits recorded the use of iron treatment only. The remaining visits ($n = 3591$, 14%) corresponded to periods that did not require anaemia treatment.

Multivariable predictors of off-target Hb are shown in Table 2. Briefly, men were more likely than women to have Hb values outside target range (both below and above). Patients with age 65–75 years, CKD Stages 3b and 4, pyelonephritis, transplant recipients, having received iron medication or higher EPO doses, or with higher serum calcium and albumin levels were at higher risk of maintaining Hb values above target range. Conversely, patients with polycystic kidney disease, diabetic nephropathy and nephrosclerosis, those having a recent bleeding or receiving transfusion, those with inflammation [C-reactive protein (CRP) >5 mg/dL], and higher phosphate levels were at increased risk of having Hb values below target range.

Table 1. Baseline characteristics of included patients at the time of their first recorded visit with anaemia treatment

Covariates	Overall
n	5000
Age, mean (SD), years	69 (15)
Women	2229 (45)
BMI, kg/m^2	26.6 (23.5–30.8)
CKD stages, mL/min/1.73 m^2	
G3b 30–44	825 (16)
G4 15–29	2442 (49)
G5 <15	1733 (35)
CKD aetiology	
Diabetic nephropathy	1266 (25)
Nephrosclerosis	1190 (24)
Glomerulonephritis	503 (10)
Pyelonephritis	130 (3)
Polycystic kidney disease	260 (5)
Other	979 (20)
Unknown	672 (13)
Kidney transplanted	78 (2)
Comorbidities, *n* (%)	
Hypertension	4380 (88)
Diabetes mellitus	2253 (45)
CVD	2650 (53)
Medications, *n* (%)	
Initial anaemia treatment	
Only iron (IV or oral)	1998 (40)
Only ESA	2066 (41)
ESA dose (IU/week)	4000 (2200–5874)
Iron and ESA	936 (19)
ESA dose (IU/week)	4000 (2800–6000)
Statin	2900 (58)
Sodium bicarbonate	2336 (47)
Chemistry, median (IQR)	
hsCRP, mg/L	5.0 (2.0–10.0)
Ca^{2+}, mmol/L	2.3 (2.2–2.4)
$PO4^-$, mmol/L	1.3 (1.2–1.6)
PTH, ng/L	16.4 (10.0–27.0)
Albumin, g/L	37 (34–39)

Data are presented as mean (SD), median (IQR) or counts (proportion), as appropriate.
Ca^{2+}, calcium; $PO4^-$, phosphate; PTH, parathyroid hormone.

We observed similar results when we evaluated the subset of patients followed at the nephrology units that report all performed visits into the register (Supplementary data, Table S5).

Pre-ESKD Hb target attainment, ERI and outcomes following dialysis initiation

Of the initial 5000 included patients, 1361 (27%) initiated chronic dialysis during the observation period. Characteristics of these individuals at the time of dialysis initiation are described in Table 3. Mean (SD) age of these patients was 65 (15) years, and 41% were women. The most common comorbidities were hypertension (93%), diabetes mellitus (49%) and heart failure (27%). There were 6587 recorded patient visits recorded to compute pre-ESKD TIR, TAR and mean ERI. The median (IQR) pre-ESKD TIR was 56% (31–79%), median (IQR) TAR 11% (0–43%), with their distributions shown in Supplementary data, Figure S3. The median (IQR) ERI was 0.52 (0.35–0.78) IU/kg/week/g/dL, and lower ERI was associated with higher categories of attained Hb (P for trend <0.001; Figure 1).

Table 2. Multinomial adjusted OR and 95% CIs associated with Hb <10 g/dL and >12 g/dL ERBP recommended target range throughout 25 431 consecutive patients visits

Covariates	OR (95% CI)	
	Hb <10 g/dL	Hb >12 g/dL
Age <65 years	Reference	Reference
Age 65–75 years	0.88 (0.76–1.02)	**1.13 (1.04–1.23)**
Age ≥75 years	**0.85 (0.74–0.98)**	0.98 (0.90–1.06)
Men	**1.23 (1.11–1.37)**	**1.22 (1.15–1.30)**
BMI <18.5 kg/m^2	Reference	Reference
BMI 18.5–25 kg/m^2	0.97 (0.68–1.39)	1.00 (0.81–1.24)
BMI ≥25 kg/m^2	**0.86 (0.77–0.97)**	0.99 (0.93–1.06)
CKD Stage G5	Reference	Reference
CKD Stage G4	**0.80 (0.71–0.91)**	**1.34 (1.24–1.44)**
CKD Stage G3b	**0.59 (0.47–0.75)**	**1.85 (1.66–2.06)**
Glomerulonephritis	Reference	Reference
Pyelonephritis	1.32 (0.89–1.95)	**1.34 (1.10–1.62)**
Diabetic nephropathy	**1.29 (1.03–1.63)**	**0.75 (0.66–0.84)**
Polycystic kidney disease	**1.49 (1.12–1.98)**	**0.77 (0.66–0.90)**
Nephrosclerosis	**1.52 (1.22–1.89)**	**0.82 (0.73–0.92)**
Other aetiology	1.24 (0.996–1.54)	**0.85 (0.76–0.95)**
Unknown aetiology	**1.38 (1.09–1.76)**	**0.88 (0.78–0.996)**
Kidney transplanted	0.78 (0.39–1.59)	**1.83 (1.51–2.22)**
Diabetes mellitus	1.08 (0.93–1.25)	1.02 (0.94–1.10)
Hypertension	0.96 (0.81–1.15)	1.05 (0.96–1.16)
CVD	1.06 (0.95–1.20)	0.97 (0.91–1.04)
Recent transfusion	**1.26 (1.10–1.45)**	0.96 (0.88–1.05)
Recent bleeding	**1.20 (1.05–1.37)**	1.02 (0.95–1.09)
Iron medication use	0.96 (0.87–1.07)	**1.06 (1.002–1.13)**
Non-use of ESA	Reference	Reference
ESA <3600 IU/week	**0.72 (0.63–0.83)**	**0.87 (0.81–0.94)**
ESA 3600–6400 IU/week	0.95 (0.82–1.10)	**1.18 (1.08–1.29)**
ESA ≥6400 IU/week	1.07 (0.91–1.25)	**1.35 (1.21–1.50)**
Statin	**0.86 (0.77–0.96)**	1.04 (0.98–1.11)
Sodium bicarbonate	**0.85 (0.76–0.95)**	0.99 (0.93–1.06)
hsCRP <5 mg/dL	Reference	Reference
hsCRP ≥5 mg/dL	**1.16 (1.04–1.30)**	**0.91 (0.86–0.97)**
Ca^{2+} (mmol/L) low tertile	**1.36 (1.20–1.54)**	**0.82 (0.76–0.88)**
Ca^{2+} (mmol/L) mid tertile	Reference	Reference
Ca^{2+} (mmol/L) high tertile	**0.81 (0.69–0.94)**	**1.21 (1.13–1.30)**
$PO4^-$ (mmol/L) low tertile	0.88 (0.76–1.02)	**1.27 (1.19–1.37)**
$PO4^-$ (mmol/L) mid tertile	Reference	Reference
$PO4^-$ (mmol/L) high tertile	**1.33 (1.17–1.51)**	**0.90 (0.83–0.98)**
PTH (ng/L) low tertile	1.07 (0.93–1.24)	1.00 (0.93–1.08)
PTH (ng/L) mid tertile	Reference	Reference
PTH (ng/L) high tertile	1.11 (0.98–1.26)	0.99 (0.92–1.07)
Albumin (per g/dL higher)	**0.93 (0.92–0.94)**	**1.05 (1.04–1.05)**
Previous Hb (per g/dL higher)	**0.97 (0.97–0.98)**	**1.05 (1.05–1.06)**

Bold text indicates statistically significant higher or lower odds.
Ca^{2+}, calcium; $PO4^-$, phosphate; PTH, parathyroid hormone.

There were 220 deaths recorded during the first year of dialysis. On a continuous scale (Figure 2A and B), we did not observe any association between pre-ESKD TIR and death, but a trend towards lower risk of death was observed as TAR increased. In categorical analyses, patients above median pre-ESKD TIR (56%) [hazard ratio (HR) = 0.96; 95% confidence interval (CI) 0.69–1.33] or TAR (11%) (HR = 0.81; 95% CI 0.59–1.11) were not at a different risk of death compared with patients below these thresholds.

There were 453 MACE+ events recorded during the first year of dialysis. On a continuous scale (Figure 2C and D), we

Table 3. Baseline characteristics of included patients at the time of initiation of chronic dialysis

Covariate	Overall
n	1361
Age, years	65 (15)
Haemodialysis (%)	846 (62)
Peritoneal dialysis (%)	515 (38)
Women (%)	553 (41)
BMI, kg/m^2	26.4 (23.5, 30.3)
Year of dialysis start (%)	
2012–13	425 (31)
2014–15	308 (23)
2016–17	628 (46)
CKD aetiology	
Diabetic nephropathy	433 (32)
Nephrosclerosis	232 (17)
Glomerulonephritis	180 (13)
Pyelonephritis	31 (2)
Polycystic kidney disease	120 (9)
Other	239 (18)
Unknown	126 (9)
Comorbidities, *n* (%)	
Diabetes mellitus	667 (49)
Hypertension	1262 (93)
Myocardial infarction	261 (19)
Heart failure	369 (27)
Cerebrovascular disease	224 (16)
Peripheral vascular disease	227 (17)
Atrial fibrillation	203 (15)
Stroke	147 (11)
Medications, *n* (%)	
ESA	1256 (92)
Iron	919 (68)
ACEIs and ARBs	933 (69)
β-blockers	1041 (76)
Calcium channel blockers	1099 (81)
Statin	805 (59)
Phosphate binders	1134 (83)
Sodium bicarbonate	1042 (77)
Characteristics of their pre-ESKD period	
ERI from all pre-ESKD visits, IU/kg/week/g/dL	0.5 (0.4–0.8)
Slope of eGFR decline, mL/min/1.73 m^2/year	−4.0 (0.2)
Days observed during pre-ESKD	463 (264–788)

Data are presented as mean (SD), median (IQR) or counts (proportion), as appropriate.
ACEIs and ARBs, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

did not observe a clear association between TIR, TAR and the risk of MACE+. On a categorical scale, patients with TIR above the median (56%) were at a 26% higher relative risk of MACE+ that did not reach statistical significance (HR = 1.26; 95% CI 0.99–1.58). Patients with TAR above the median (11%) were at a statistically significantly 24% lower risk of MACE+ (HR = 0.76; 95% CI 0.61–0.94) compared with patients with TAR <11%.

On a continuous scale, higher pre-ESKD mean ERI were associated with an increased risk of death, but no association was found between ERI and MACE+ (Figure 3). On a categorical scale, patients with a pre-ESKD ERI above the mean had a significant higher risk of death (HR = 1.39; 95% CI 1.02–1.90), but no effect on risk of MACE + (HR = 0.87; 95% CI 0.70–1.08) compared with patients below this threshold.

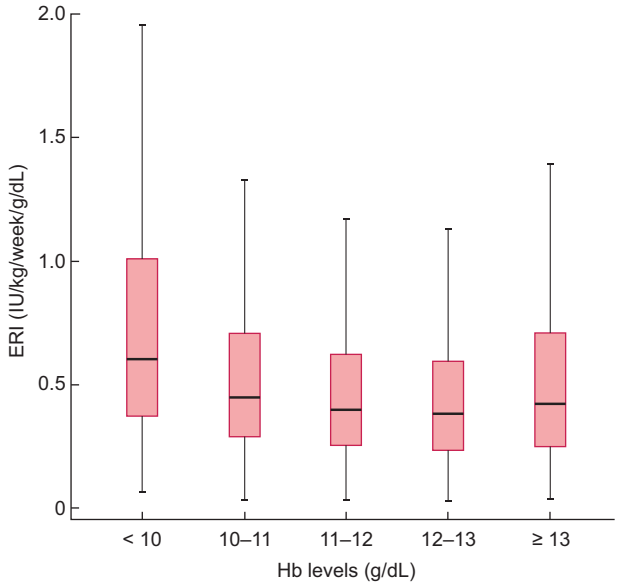

FIGURE 1: ERI distribution across different Hb levels during pre-ESKD recorded visits for patients initiating chronic dialysis.

DISCUSSION

Few studies have evaluated Hb predictors in cross-sectional designs [9–12], and we believe this is the only analysis to date that evaluates Hb target attainment longitudinally through the patient's pre-ESKD journey. As many as 50% of the patient visits in our study reported a Hb within the recommended 10–12 g/dL range, a proportion that agrees with cross-sectional evidence from the dialysis population of the UK [10] or the USA [26]. A high proportion of the remaining patient visits (39%) in our study had Hb measurements above the target range, which also agrees with previous reports of anaemia prevalence in CKD [9–12]. This may reflect the difficulties in adjusting ESA doses in order to achieve narrow Hb targets, and/or it may represent the belief that patients with good response to ESAs—who may easily achieve higher Hb levels—have improved survival. In this sense, our finding that the immediately previous Hb value, iron use and ESA dose are important for predicting Hb both below and above target range is a reflection of such process [27, 28].

Patients with CKD Stage 5 were more likely to maintain Hb in range than patients with CKD Stage 3b or 4, a difference that we speculate may be explained by the more frequent nephrologist consultation and better care at later CKD stages including better Hb monitoring and management. Likewise, patients with a functioning kidney transplant and attending nephrology check-ups were more likely to be above range, which may reflect a more aggressive management of post-transplant anaemia [29, 30]. Men were more likely than women to have Hb outside range, which aligns with and expands a recent report of dialysis patients [31]. This difference may be explained by the lower Hb that healthy women have compared with men [32], together with a poorer response to ESAs [33, 34] and a need for higher ESA doses in women to achieve similar haematocrits as men [33].

This analysis both revealed new predictors of Hb control and confirmed factors previously reported. Our observations that pyelonephritis predicts high Hb values and that polycystic kidney disease, diabetic nephropathy and nephrosclerosis

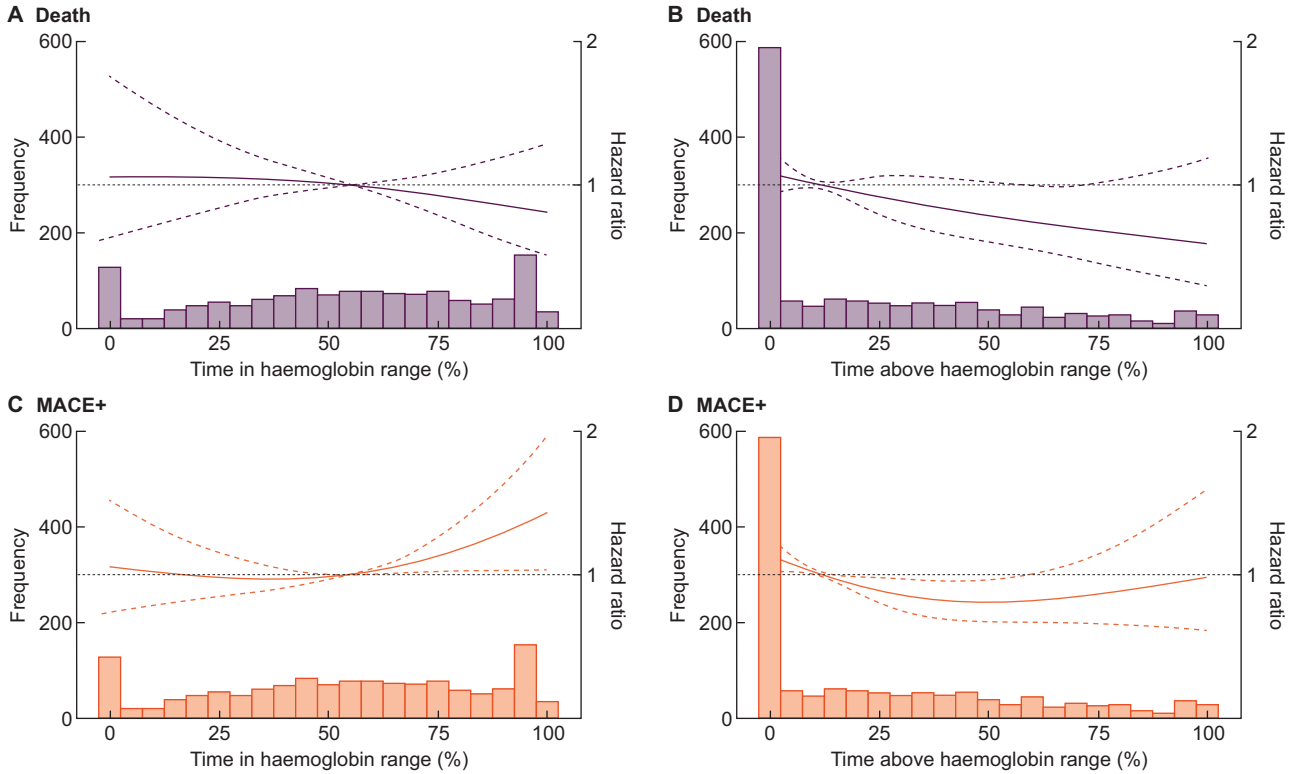

FIGURE 2: Multivariable-adjusted [adjusted for age, sex, BMI, initial dialysis therapy (haemodialysis or peritoneal dialysis), calendar year of dialysis start, diabetes, hypertension, myocardial infarction, stroke, peripheral vascular disease, heart failure, atrial fibrillation, ACEi/ARBs, beta-blockers, calcium blockers, ESA use, iron medication use, statins, phosphate binders, sodium bicarbonate, person-months with renal anaemia during their pre-ESKD phase and slope of eGFR decline during their pre-ESKD phase.] associations between pre-ESKD TIR, TAR and the rate (hazard) of death and MACE+ during the first year after initiation of dialysis. ACEIs and ARBs, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

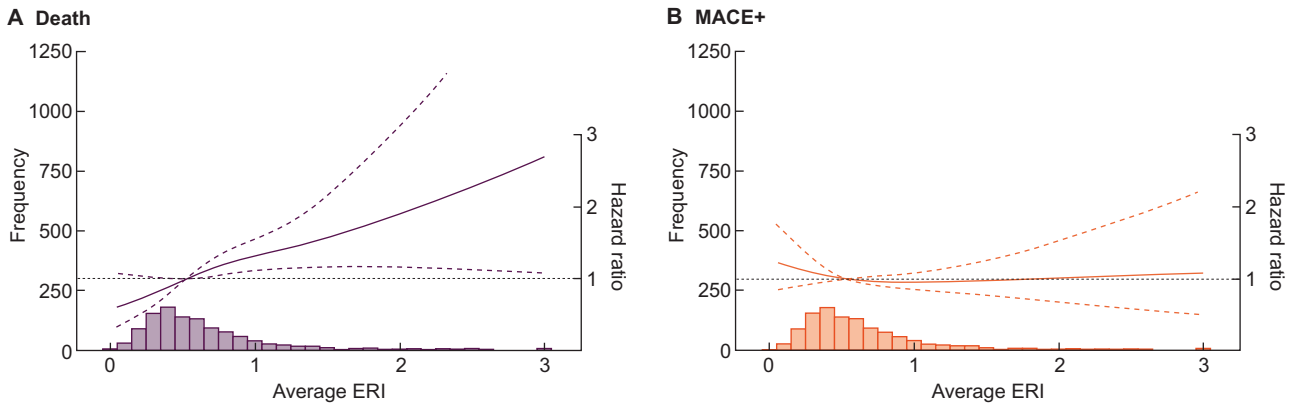

FIGURE 3: Multivariable-adjusted [adjusted for age, sex, BMI, initial dialysis therapy (haemodialysis or peritoneal dialysis), calendar year of dialysis start, diabetes, hypertension, myocardial infarction, stroke, peripheral vascular disease, heart failure, atrial fibrillation, ACEi/ARBs, beta-blockers, calcium blockers, ESA use, iron medication use, statins, phosphate binders, sodium bicarbonate, person-months with renal anaemia during their pre-ESKD phase and slope of eGFR decline during their pre-ESKD phase] associations between pre-ESKD mean ERI and the rate (hazard) of death and MACE+ during the first year after initiation of dialysis. ACEIs and ARBs, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

predict low Hb values are possibly novel. While it is accepted that renal anaemia manifests at a lower eGFR in patients with polycystic kidney disease [35], this is a selection of patients in whom anaemia developed and treatment was initiated. We found no prior studies evaluating anaemia management in patients of this aetiology. Alterations in laboratory biomarkers also predicted Hb target attainment in our study: elevated high-sensitivity CRP (hsCRP) predicted the likelihood to have low Hb values, which aligns with our understanding of inflammation as a key factor for resistance to ESA [36]. In agreement with our results, abnormalities in phosphorus and calcium have been associated with abnormal Hb and altered response to ESA [37, 38]. It is not known whether the associations are mediated through some other component of the CKD–mineral bone disorder syndrome, direct effects of these electrolytes on red blood cells [39, 40] or both. Collectively, our results credibly illustrate the

multiple conditions that may affect Hb control, and identify many of the factors that lead to ESA hypo-responsiveness. As a clinical application, knowledge of patient phenotypes with difficulties in attaining Hb targets may allow the implementation of corrective measures, through more stringent monitoring of Hb, intensified or alternative therapeutic strategies.

Early studies have addressed the value of treating anaemia during the transition to dialysis [16, 17]. Recently, Wetmore *et al.* [41] found that compared with patients with less consistent or no pre-ESKD ESA treatment, patients who received more consistent pre-ESKD ESA treatment had lower risks for death 1 year after the initiation of dialysis. Complementing those studies, we hypothesized that the maintenance of Hb within the recommended target ranges during pre-ESKD care would associate with better outcomes after dialysis initiation. While in our study the time spent with Hb within the recommended ERBP range was not associated with better outcome, we observed that individuals who more frequently maintained Hb above the recommended range (higher TAR) seemed to experience lower MACE risk compared with those with lower TAR. This may sound counterintuitive, given the results from pivotal trials in which targeting higher Hb values with ESA led to increased death/MACE risk [5, 6, 42]. However, our analysis did not evaluate only Hb targets, but achieved Hb levels, which is the result of the strategies used to reach the targets and is influenced by patient's adherence and response to treatment, comorbidities, frailty and lifestyle behaviours. We note that most achieved Hb measurements above range in our study were between 12 and 13 mg/L, and we speculate that a patient more often having Hb within this range is likely someone responding well to ESA treatment. In support of this, our study observed lower ERI with higher attained Hb in this range. It is well established that patients with ESA-resistant renal anaemia have a poorer prognosis than those without [24, 43, 44], and failure to account for individual patients' response to ESA has been proposed [45] to explain the divergence between observational studies comparing the mortality risk of long-acting versus short-acting ESA [46] and meta-analyses of randomized controlled trials [47]. We expand this evidence by showing a higher risk of death for patients with consistently low pre-ESKD ESA responsiveness (high mean pre-ESKD ERI). Our findings on the importance of ESA resistance support a *post hoc* analysis of the CHOIR study demonstrating that ESA dose level, rather than actual Hb level attained, contributes to poor outcome [48], and expands observational analyses in patients on dialysis showing that the time spent with off-target Hb values, rather than Hb variability, explains associations with death [49].

Our study had both strengths and limitations. Key strengths are the complete longitudinal coverage of nephrology-referred patients across a broad CKD spectrum in a nationwide registry with detailed information about diagnosis, laboratory data and treatments. The possibility of linking those records to other healthcare resources allowed us to obtain extensive data on comorbidities, other medications and outcomes. Our main limitation is that we can only evaluate the nephrology visits that are reported to the SRR. Furthermore, while inclusion of patients with CKD 4 in the SRR is mandatory and has virtually complete national coverage, patients with CKD Stage 3b are recorded by the physicians on a voluntary basis and therefore the coverage is likely to be less complete. Thus, it is not known whether non-registered patients or visits differ meaningfully from those who are registered. We recognize that the number of patients initiating dialysis in our study was low, which limits the strength of our conclusions. We acknowledge the lack of information on important haematological covariates including iron dose, ferritin and transferrin saturation, and that causality between the associations reported cannot be inferred from this or any other observational study.

To conclude, this nationwide study of nephrologist-referred patients with non-dialysis-dependent CKD stages treated for renal anaemia identified populations in which efforts to control Hb may require additional or alternative treatment. A greater time spent in a pre-ESKD Hb target range >12 g/dL and a lower pre-ESKD ERI predicted improved survival after dialysis initiation, supporting the value of pre-ESKD anaemia care and illustrating the problems of addressing ESA hyporesponsiveness in clinical practice.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

M.E. reports speaker or advisory board fees from AstraZeneca, Astellas Pharma and Vifor Pharma. G.J. is employed by AstraZeneca. J.J.C. reports funding from Astellas and Vifor Pharma outside the submitted work, and speaker or advisory board fees from Baxter, AstraZeneca and Astellas Pharma. P.B., A.S. and Y.X. have no conflicts of interest to report.

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