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Original Article

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Haemoglobin at time of referral prior to dialysis predicts survival: an association of haemoglobin with long-term outcomes

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Abstract

Haemoglobin (Hgb) levels are known to be associated with numerous adverse outcomes in both chronic kidney disease (CKD) and non-CKD patients.

This analysis evaluates the association of baseline haemoglobin levels on survival in CKD patients, who are followed by nephrologists, irrespective of glomerular filtration rate (GFR), prior to initiation of renal replacement therapy (RRT) and erythropoietin hormone replacement therapy.

Analysis of data from the provincial database (PROMIS, Patient Registration and Outcome Management Information System) in British Columbia, Canada, was undertaken. Records used for the analysis included all CKD patients at first registration: GFR <60 ml/min/1.73 m^2, not yet on dialysis, starting from May 1998 to October 2002, and who had complete data (defined as age and gender, diabetic status, eGFR and Hgb levels).

The primary objective of this study was to determine the association of Hgb and survival controlling for eGFR at first registration value, age, gender and diabetic status. Multivariate Cox proportional hazards analysis with time to death as outcome variable was performed.

The cohort included 3028 patients: the mean age was 65 years, 28% were diabetic, and the mean eGFR in the cohort was 21 ml/min/1.73 m^2. The cohort is representative of the BC CKD and dialysis population regarding ethnicity: 64% Caucasian, 32% Asian. Median follow-up was 27 months, 1 year survival was 0.92, 2 year survival was 0.85. Hgb at initial registration is a statistically independent predictor of survival (RR = 0.875 for every 10 g/l, 95% CI: 0.835–0.917, $P = 0.0001$), after adjusting for age, gender, diabetic status and baseline eGFR. Further analysis, controlling for RRT, demonstrated a similar association between Hgb and survival (RR = 0.853 for every 10 g/l, 95% CI: 0.799–0.910, $P = 0.0001$), after adjusting for above variables. Substantial variation in Hgb values exists at all GFR levels.

These findings underscore the importance of evaluating Hgb at all GFR levels, and the need to study the impact of modification of Hgb at different GFR levels on survival.

Keywords: anaemia; chronic kidney disease; independent effect; observational cohort study; survival

Introduction

The common finding of anaemia in patients with chronic kidney disease (CKD) has generated much interest over the last two decades. The adverse consequences of anaemia in patients with CKD have been well documented [1–4], and treatment strategies for anaemia have been developed as a consequence. The optimal haemoglobin (Hgb) target continues to be debated [5], and the complexity of the relationship between Hgb levels and specific physiological processes are still being investigated. There is accumulating data that the Hgb level is both directly and indirectly related to survival in patients with CKD, but most of these data have been accumulated in patients on dialysis [6]. Little information exists as to the long-term impact of the level of Hgb early in the course of CKD, at stages 2–4. Recent US Medicare data in the predialysis period demonstrated that patients receiving no or less erythropoietin hormone replacement therapy (EHRT) had a higher relative risk of cardiac events and death compared to those patients receiving EHRT more frequently [7]. In addition, there is growing evidence in the cardiovascular literature that anaemia is associated with increased morbidity and mortality in patients with myocardial infarctions and congestive heart failure [8–9].

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Lower Hgb levels are associated with adverse outcomes in patients with CKD, specifically, lower Hgb levels are related to changes in cardiac structure and function in populations prior to dialysis, on dialysis and after kidney transplant [10–11]. Other adverse effects include impaired cognition, reduced quality of life, sleep disturbances and decreased exercise tolerance [2,4,12]. Cardiovascular disease (CVD) is well recognized as associated with reduced survival in patients with CKD, and is the leading cause of death in patients on dialysis. The association of CKD with lower Hgb levels, higher prevalence of CVD and poor survival lends support to the hypothesis that Hgb level and survival may be directly related.

Improving poor survival rates for patients with CKD is an important objective and one that requires an improved understanding of those factors that impact on survival. In reviewing accumulated data, other investigators have focused on a variety of factors thought to contribute to the reduced survival in patients with CKD. In addition to CVD and lower Hgb levels, markers of inflammation (such as C reactive protein), disturbed endothelial function, and of malnutrition, as well as levels of parathyroid hormone, calcium and phosphate abnormalities, homocysteine levels, dyslipidaemias, and asymmetrical dimethylarginine (ADMA), have all been associated with reduced survival or cardiovascular events in patients with CKD [13–15]. This underscores the complexity of the relationship between Hgb level and outcomes in CKD. There does not currently exist a thorough description of impact of Hgb levels at glomerular filtration rates (GFRs) below 60 ml/min/1.73 m^2, in patients known to nephrologists.

The current analysis was undertaken to describe the prevalence of anaemia in CKD and to explore the relationship between Hgb levels and patient survival, in a large cohort of patients with GFR values <60 ml/min/1.73 m^2, referred to nephrologists in British Columbia Canada, followed for a median of 27 months (range 1–67). The primary objective was to demonstrate the association of haemoglobin, prior to dialysis initiation, with survival, after adjusting for demographic variables, level of GFR and other covariates known to impact on outcome of kidney patients. In addition, we explored whether or not a differential relationship between Hgb and outcome exists depending on the level of GFR.

Study design and methods

This study was designed as a survival analysis of a cohort of 3028 patients registered in the provincial CKD database, between May 1998 and October 2002. All patients in the province of British Columbia Canada are registered into the provincial database upon being seen by nephrologists. Entry criteria for the database include calculated GFR <60 ml/min/1.73 m^2 or diagnosis of kidney disease, presumed to be chronic on the basis of biopsy diagnosis, ultrasound or clinical history of deterioration, and having been referred to a nephrologist. Thus, this is a cohort of patients with CKD, who are not on dialysis at the time of referral. All patients signed informed consent allowing access to data for statistical and research purposes.

British Columbia is the third largest province in Canada, with approximately 4 million inhabitants. As of October 2002, over 2000 dialysis patients were registered, and there were approximately 2600 CKD patients, not on dialysis. There is a comprehensive database, which captures all patients seen by nephrologists. This longitudinal database is used for clinical, administrative and research purposes. Once registered, patients are tracked over their entire clinical course, thus complete data including medication lists, dialysis start dates and death are accessible. All patients referred to nephrologists, who qualified according to above definitions (i.e. chronic kidney disease stages 3–5; GFR <60 ml/min/1.73 m^2), were entered into the database.

We included all patients with complete data at initial registration. Complete data for the purposes of this analysis included: demographics, diabetic status, level of kidney function derived from serum creatinine, Hgb level and medication profiles. Patients who moved out of the province were lost to follow-up; all others were included. Data regarding date of death is included in the database and validated using Vital Statistics records.

Explanatory variables and definitions

Demographic variables such as age, gender, diagnosis of kidney disease, are entered into the database as part of essential information. Diabetic status (either insulin requiring or non-insulin requiring) is entered as a comorbid condition, and the level of kidney function at the time of registration is also entered. Laboratory values including Hgb, transferrin saturation, serum chemistries are all either manually entered or automatically uploaded from laboratory systems in the province. Changes in treatment status (from CKD to dialysis or transplant or death) are captured within the database, as it forms the basis of funding of kidney services. Any patient requiring erythropoietin therapy must have Hgb and transferrin saturation values entered into the database before the prescription for the drug can be processed. Other medications are entered into the database as well, and for the purposes of this analysis, we were particularly interested in those that may impact Hgb. These included ACEi, ARB and iron therapy. Erythropoietin therapy was included as an explanatory variable only, if it was initiated immediately after the baseline Hgb.

Statistical analysis

Descriptive statistics are presented as mean with standard deviation or median with interquartile range, depending on the underlying distribution. Continuous and categorical variables were compared across CKD stages using ANOVA or Kruskal–Wallis and chi-square tests, respectively. We used the *t*-test or the Wilcoxon rank sum test, where appropriate, to compare continuous variables by anaemia status. Categorical variables by level of Hgb were compared using the chi-square test. Patient survival was estimated using the Kaplan–Meier method. Survival curves by Hgb levels were compared using the log-rank test. A *P*-value of less than 0.05 for two-sided univariate tests was considered significant.

The Cox proportional hazards model was used to identify important predictors of mortality. All models included age, gender, diabetes, GFR estimated using abbreviated MDRD formula (16) and Hgb. The interaction of Hgb level with other statistically significant covariates was tested by adding an interaction term to the models.

Additional modelling was performed using subgroups of patients who had additional laboratory measures, known to impact on outcome, available. Also, the models controlling for the start of dialysis were run in order to account for potential risk factors that are different in those who do and do not start dialysis during the observation period.

Data are presented in both continuous and categorical format, so as to ensure interpretability for both clinical investigators and for clinicians. Statistical analyses were performed using the SAS software, version 8.2 (SAS Institute, Cary, NC).

Results

The cohort consisted of CKD patients registered from May 1998 to October 2002 in BC, who were not receiving dialysis and included 3028 patients. All patients were followed for a mean of 27 months (P25–P75: 19–38 months); for the purposes of this analysis, patient follow-up ended on 31 December 2003.

Baseline clinical and laboratory variables by level of kidney function

Table 1 demonstrates the characteristics of the population by the level of kidney function (estimated GFR). Note the relatively large number of patients at each stage (3, 4 and 5) upon entry to the database, but the majority of patients are first seen at eGFR levels between 15–29 ml/min. Note that within each stage of CKD, substantial variability exists; nonetheless, most haematological and biochemical parameters worsen at lower stages of CKD.

Of key interest, the mean Hgb by level of eGFR and the number of patients at each level of eGFR, are presented. The mean Hgb is lower at each level of eGFR values ($P < 0.0001$).

The prevalence of diabetes mellitus (DM) at each stage of CKD is different, being significantly higher at lower levels of eGFR (32 *vs* 27%, $P = 0.01$), but overall the prevalence is 28%. Note that diabetics are underrepresented in the earlier stage cohort. Parathyroid harmone (PTH) increases across all stages of eGFR, and the serum calcium levels fall while phosphate rises.

Table 1. Description of patient characteristics as a total group, and by level of GFR at time of presentation to nephrologists, and registration in the provincial database

Variable	*N*	Total	GFR <15 ($n=974$)	GFR 15–29 ($n=1452$)	GFR 30–59 ($n=602$)	*P*-value
Age	3028	64.8 (15.6)	64.3 (15.1)	65.7 (15.4)	63.3 (16.5)	0.004
Age >75 years	3028	891 (29%)	264 (27%)	459 (32%)	168 (28%)	0.038
Gender (% male)	3028	1783 (59%)	497 (51%)	860 (59%)	426 (71%)	0.001
Diabetes	3028	860 (28%)	312 (32%)	387 (27%)	161 (27%)	0.010
Race	1707					0.019
Caucasian		1086 (64%)	395 (63%)	481 (61%)	210 (71%)	
Asian		540 (32%)	195 (31%)	272 (35%)	73 (25%)	
Other		81 (5%)	35 (6%)	35 (4%)	11 (4%)	
Primary kidney disease	2107					0.002
Diabetes		570 (27%)	203 (29%)	256 (26%)	111 (25%)	
PCKD/Nephr/Cong		370 (18%)	145 (21%)	141 (14%)	84 (19%)	
GN/RenVasc		662 (31%)	200 (29%)	325 (33%)	137 (31%)	
Other		505 (24%)	143 (21%)	258 (26%)	104 (24%)	
eGFR (ml/min)	3028	19 (13–28)	11 (9–13)	21 (18–25)	36 (32–43)	<0.001
Haemoglobin (g/l)	3028	108.7 (20.0)	99.1 (16.9)	110.2 (18.5)	120.3 (21.0)	<0.001
Haematocrit (L/L)	2133	0.33 (0.06)	0.31 (0.05)	0.34 (0.05)	0.36 (0.06)	<0.001
Transferrin saturation	2428	0.23 (0.12)	0.23 (0.12)	0.24 (0.12)	0.23 (0.12)	0.051
iPTH (pmol/l)	1127	10.7 (5.4–19.1)	18.7 (11.0–36.8)	11.0 (5.9–19.0)	5.6 (3.7–9.5)	<0.001
Calcium (mmol/l)	2177	2.22 (0.19)	2.17 (0.24)	2.24 (0.16)	2.27 (0.15)	<0.001
Phosphate (mmol/l)	2151	1.40 (0.39)	1.72 (0.47)	1.31 (0.26)	1.17 (0.22)	<0.001
Albumin (g/l)	2081	36.7 (5.2)	35.8 (5.2)	37.0 (5.1)	37.2 (5.5)	<0.001
Systolic BP	869	141.1 (25.3)	143.9 (24.2)	141.1 (26.1)	138.7 (24.6)	0.108
Diastolic BP	870	76.8 (13.1)	76.7 (13.4)	76.6 (13.1)	77.3 (13.0)	0.809
Weight (kg)	2310	76.1 (19.2)	75.5 (19.1)	75.7 (19.2)	78.0 (19.0)	0.059
Started RRT	3028	1331 (44%)	732 (75%)	534 (37%)	65 (11%)	0.001
Months to RRT	3028	34.3 (31.3–37.5)	7.5 (6.9–8.7)	40.5 (38.4–43.5)	–	<0.001
Documented Rx	1460	1460 (48%)	513 (53%)	667 (46%)	280 (47%)	0.003
Iron use	1460	907 (62%)	326 (64%)	423 (63%)	158 (56%)	0.092
ACEi use	1460	643 (44%)	168 (33%)	316 (49%)	159 (57%)	0.001
ARB use	1460	184 (13%)	35 (7%)	93 (14%)	56 (20%)	0.001

Data are presented: Mean (SD), or Median (25th–75th Percentile), or Number (%).
P-values describe differences between levels of GFR/CKD stage for each variable.

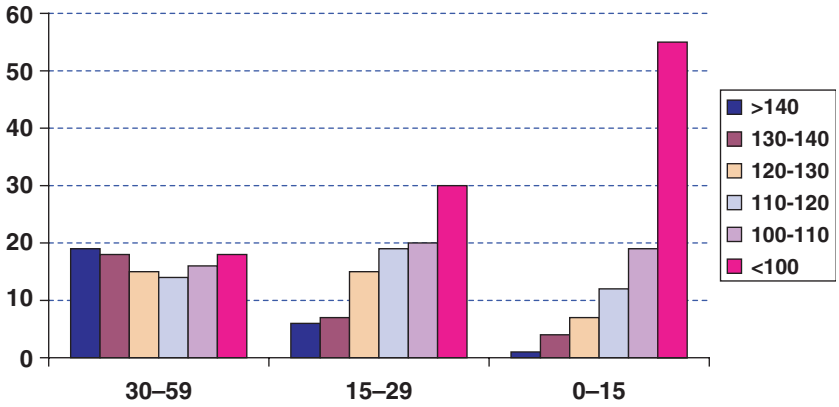

Fig. 1. Describes the prevalence of Hgb values, in deciles above 100 g/l, by each level of GFR. Note the variability at each level of GFR. See text for details.

Furthermore, albumin and body weight demonstrate a significant lowering as CKD stage declines.

The expected differences at the start of renal replacement therapy (RRT) is noted, which is greatest in the group of patients with the lowest eGFR, but occurs as well in a substantial proportion of patients in stage 4, and even some in stage 3. There appears to be variation in the timing of initiation of RRT.

Haemoglobin levels

Figure 1 describes the distribution of Hgb at each level of eGFR. Note that despite significantly different means, there is some degree of overlap between eGFR categories, underscoring the variability of Hgb in patients with CKD at the time of presentation.

Medications that might impact Hgb

The medications that may impact Hgb are displayed in Tables 1 and 2, again by stage of CKD. Note that the use of ACEi and ARB is *less* as eGFR declines, and the use of both iron and hormone replacement therapy increases. However, in patients with the lowest haemoglobin values within each eGFR category, these patients receive ACEi or ARB. Interestingly, over 50% of all patients in each eGFR category were receiving iron therapy (predominantly oral).

Details of anaemia × GFR

Table 2 demonstrates for the total population, as well as at each level of eGFR (<15, 15–30 and 30–59) differences in key variables between those with and without anaemia, defined as Hgb <110. This univariate analysis, presented both for the total group and by level of eGFR, demonstrates the differences in numerous variables, most of which are expected. Calcium and phosphate values, as well as weight and albumin are different between those with Hb <110 and >110; as might be expected at these earlier stages of CKD. At all levels of eGFR, there appear to be small but significant differences in numerous parameters between those with anaemia and those without anaemia.

We demonstrate the substantial use of iron therapy ~74% in the low Hgb group, significantly higher than their non-anaemic cohort.

Commencement of EHRT during follow-up

The number of patients at registration with anaemia, defined here as Hgb <110 g/l, was 1670 (55%). Of those, 90% received EHRT at some point in the course of follow-up, 70% of anaemic patients having EHRT initiated within 3 months of Hgb measurement date. Of 208 CKD stage 3 anaemic patients, 80% started EHRT, and 90% of stage 4 anaemic patients and 93% of stage 5 anaemic patients started EHRT.

Overall, 36% of the CKD population without anaemia (Hgb ≥110 g/l) at the time of registration received EHRT at some point in the course of follow-up. Those with the lowest eGFR were most likely to receive EHRT during subsequent follow-up: 17% of eGFR 30–59 ml/min patients, 38% of eGFR 15–30 ml/min patients and 59% of eGFR <15 ml/min patients. The time to EHRT was substantially shorter in the lower stages of CKD for patients without anaemia at the time of registration: by the end of one-year follow-up, 13%, 25% and 45% of patients CKD stage 3, 4 and 5 respectively, started EHRT.

Survival analysis

Cumulative survival in this cohort was 0.92 (95% CI: 0.91–0.93) at 1 year, and 0.85 (95% CI: 0.83–0.86) at 2 years. Six hundred and seventeen patients (20%) died during the follow-up period (86.5 per 1000 person-years); 47% (293/617) died prior to starting RRT and 53% died after starting RRT. Death rate per 1000 person-years of follow-up prior to RRT start was 59.3. Fifty-eight (10%) of Stage 3 patients died during follow-up, 81% of them before commencing RRT. Of 1452 patients who were Stage 4 at baseline, 288 (20%) died, 56% before reaching RRT. Two hundred and seventy-one (28%) patients who had GFR

Table 2. Anaemia within each CKD stage. This table describes each of the variables as a function of the presence or absence of anaemia, defined as Hgb <110 g/l, in the total cohort, and by level of GFR

Variable	Total ($n=3028$)			GFR < 15 ($n=974$)			GFR 15–29 ($n=1452$)			GFR 30–59 ($n=602$)		
	≥110	<110	*P*-value	≥110	<110	*P*-value	≥110	<110	*P*-value	≥110	<110	*P*-value
N (%)	1358 (45%)	1670 (55%)		245 (25%)	729 (75%)		719 (50%)	733 (50%)		394 (65%)	208 (35%)	
Age	63.5 (15.3)	65.7 (15.7)	<0.001	62.9 (14.4)	64.7 (15.4)	0.098	65.1 (15.0)	66.2 (15.8)	0.177	61.1 (16.2)	67.6 (16.3)	<0.001
Age >75 years	352 (26%)	539 (32%)	0.001	54 (22%)	210 (29%)	0.044	208 (29%)	251 (34%)	0.029	90 (23%)	78 (37%)	0.001
Gender (% male)	929 (68%)	854 (51%)	0.001	165 (68%)	332 (45%)	0.001	469 (65%)	391 (53%)	0.001	295 (75%)	131 (63%)	0.002
Diabetes	330 (24%)	530 (32%)	0.001	54 (22%)	258 (35%)	0.001	179 (25%)	208 (28%)	0.134	97 (25%)	64 (31%)	0.105
Race			0.001			0.001			0.020			0.261
Caucasian	516 (70%)	570 (59%)		121 (75%)	274 (59%)		256 (66%)	225 (56%)		139 (73%)	71 (70%)	
Asian	194 (26%)	346 (36%)		34 (21%)	161 (35%)		117 (30%)	155 (39%)		43 (23%)	30 (29%)	
Other	30 (4%)	51 (5%)		6 (4%)	29 (6%)		15 (4%)	20 (5%)		9 (5%)	2 (2%)	
Primary kidney disease			0.001			0.001			0.001			0.003
Diabetes	225 (22%)	345 (32%)		34 (18%)	34 (34%)		123 (23%)	133 (30%)		68 (24%)	43 (33%)	
PCKD/Nephr/Cong	219 (21%)	151 (14%)		57 (30%)	57 (18%)		95 (18%)	46 (11%)		67 (22%)	17 (13%)	
GN/RenVasc	359 (35%)	303 (28%)		59 (31%)	59 (28%)		195 (36%)	130 (30%)		105 (35%)	32 (24%)	
Other	234 (23%)	271 (25%)		41 (21%)	41 (20%)		129 (24%)	129 (29%)		64 (21%)	40 (30%)	
eGFR (ml/min)	25.1 (11.2)	18.3 (9.6)	<0.001	11.4 (2.5)	10.2 (2.9)	<0.001	22.0 (4.2)	20.9 (4.1)	<0.001	39.3 (7.6)	37.1 (6.8)	<0.001
Haemoglobin (g/l)	126.7 (13.1)	94.0 (10.4)	<0.001	121.7 (10.2)	91.6 (10.8)	<0.001	125.3 (12.0)	95.4 (9.8)	<0.001	132.3 (14.7)	97.5 (8.6)	<0.001
Haematocrit (L/L)	0.38 (0.04)	0.29 (0.03)	<0.001	0.36 (0.03)	0.28 (0.03)	<0.001	0.37 (0.04)	0.29 (0.02)	<0.001	0.39 (0.04)	0.29 (0.02)	<0.001
Transferrin saturation	0.23 (0.17–0.29)	0.21 (0.15–0.27)	<0.001	0.22 (0.16–0.29)	0.20 (0.15–0.28)	0.016	0.23 (0.17–0.29)	0.21 (0.15–0.27)	0.001	0.24 (0.18-0.31)	0.20 (0.15–0.26)	<0.001
iPTH (pmol/l)	9.4 (5.3–16.5)	12.8 (5.8–24.2)	<0.001	16.9 (10.0–34.0)	19.4 (12.2–38.1)	0.160	11.0 (5.9–18.0)	10.9 (5.6–20.0)	0.935	5.8 (3.8–9.5)	4.9 (3.5–8.8)	0.226
Calcium (mmol/l)	2.26 (0.17)	2.18 (0.21)	<0.001	2.24 (0.22)	2.13 (0.25)	<0.001	2.25 (0.15)	2.21 (0.17)	<0.001	2.29 (0.15)	2.20 (0.13)	<0.001
Phosphate (mmol/l)	1.29 (0.31)	1.55 (0.44)	<0.001	1.58 (0.40)	1.79 (0.49)	<0.001	1.27 (0.24)	1.38 (0.29)	<0.001	1.12 (0.20)	1.29 (0.22)	<0.001
Albumin (g/l)	37.9 (4.8)	35.1 (5.4)	<0.001	37.6 (4.8)	34.8 (5.2)	<0.001	38.0 (4.5)	35.4 (5.5)	<0.001	37.9 (5.2)	35.3 (5.6)	<0.001
Systolic BP	139.5 (24.3)	143.8 (26.7)	0.016	143.9 (25.2)	143.8 (23.8)	0.979	139.1 (24.4)	144.9 (28.5)	0.026	138.3 (23.5)	140.2 (28.2)	0.636
Diastolic BP	78.1 (12.6)	74.8 (13.6)	<0.001	79.3 (12.6)	75.1 (13.6)	0.025	77.4 (12.8)	75.1 (13.6)	0.078	78.5 (12.5)	72.7 (13.9)	0.006
Weight (kg)	79.9 (19.1)	73.4 (18.7)	0.002	79.7 (18.4)	74.3 (19.2)	0.002	79.3 (19.1)	72.7 (18.7)	<0.001	81.0 (19.6)	73.3 (17.2)	<0.001
Iron use	337 (49%)	570 (74%)	0.001	67 (49.6%)	259 (69%)	0.001	175 (50%)	248 (78%)	0.001	95 (47%)	63 (81%)	0.001
ACEi use	340 (50%)	303 (39%)	0.001	42 (31%)	126 (33%)	0.637	178 (51%)	138 (43%)	0.042	120 (59%)	39 (50%)	0.154
ARB use	109 (16%)	75 (10%)	0.001	10 (7%)	25 (7%)	0.754	58 (17%)	35 (11%)	0.034	41 (20%)	15 (19%)	0.842

P-values represent differences in each variable within each level of GFR, between those who are and are not anaemic. Data are presented as Mean (SD), or Median (25th–75th Percentile), or Number (%).

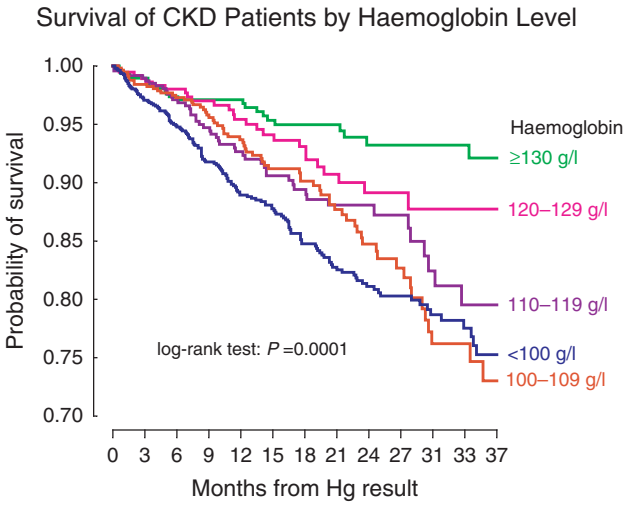

Fig. 2. Kaplan–Meier Survival curve by Hgb level. The probability of death is greatest for those categories with Hgb values <110 g/l. There appears to be a stepwise improvement by decile of Hgb.

Table 3. Adjusted risk ratios for mortality: a multivariate model predicting survival, which is adjusted for age, gender, diabetes, GFR at registration, and Hgb, broken down each decile

Variable	Risk Ratio	95% CI		*P*-value
Age (5 years)	1.318	1.146	1.516	0.0001
Female *vs* male gender	0.824	0.701	0.968	0.0187
Diabetes	1.492	1.261	1.766	0.0001
eGFR (5 ml/min)	0.891	0.851	0.933	0.0001
Hgb ≥140 g/l*	1.00			
Hgb 130–139 g/l	0.992	0.568	1.731	0.9766
Hgb 120–129 g/l	1.126	0.673	1.884	0.6523
Hgb 110–119 g/l	1.500	0.926	2.430	0.0997
Hgb 100–109 g/l	1.770	1.104	2.838	0.0177
Hgb <100 g/l	1.904	1.197	3.027	0.0065

*Haemoglobin: chi-square = 24.73, *P*-value = 0.0002.
Note that levels of Hgb below 110 are highly signficant, and the risk ratios almost double for each decile below 110. Risk ratios are presented with 95% confidence intervals. See text for details.

<15 ml/min at baseline died, of whom 31% did so prior to starting RRT. Causes of death included: cardiovascular (18%), social (i.e. treatment discontinued, 8%), multi-organ system failures (7%), malignancies (5%), infections (2%), uncertain/unknown (48%), and other causes (12%). The high percentage of deaths with uncertain/unknown reflects the outpatient nature of the population. A review of clinical notes reveals that the majority of these are deaths at home, likely representing sudden death and cardiovascular disease; thus we would ascribe conservatively at least 50% of the unknown deaths to cardiovascular disease, leading to CVD as a cause to account for 42%, in keeping with other reports.

Time from registration to death of CKD patients was different relative to the stage of CKD at registration (log-rank test *P*-value = 0.0001). For CKD stage 3, 4 and 5 patients, one-year cumulative survivals were 0.95, 0.93 and 0.89; two-year cumulative survivals were 0.92, 0.84 and 0.80, while 36-month cumulative survivals were 0.88, 0.77 and 0.71, respectively).

Figure 2 demonstrates the Kaplan–Meier survival curves by 10 g/l increments of Hgb (log-rank test *P*-value = 0.0001). Of 1358 patients without anaemia (defined as Hg ≥110), 191 patients (14%) died during the follow-up period (58.3 per 1000 person-years), compared with 426 deaths (26%) among patients with anaemia at the time of registration (110.7 per 1000 person-years; *P* = 0.0001).

Tables 3 and 4 demonstrate the results of multivariate analysis for predictors of survival. The results are presented for the overall group and by stage of CKD at the time of presentation.

After adjusting for age, gender, DM and eGFR level, baseline Hgb levels were significantly associated with increased risk of death. Overall risk ratio per 10 g/l of Hgb is 0.875 (95% CI: 0.835–0.917; *P* = 0.0001). The additional models adjusted for the variables listed above, including albumin, transferrin saturation, calcium, phosphate, PTH and blood pressure levels, identified that only albumin (RR = 0.949 per 1 g/l; 95% CI: 0.930–0.968; *P* = 0.0001), and phosphate (RR = 1.360 per 1 mmol/l; 95% CI: 1.010–1.832; *P* = 0.0429) are statistically significantly associated with survival. However, after adjusting for these two variables, Hgb remains significant (RR = 0.931 per 10 g/l; 95% CI: 0.872–0.993; *P* = 0.0305).

In order to account for potential differential risk after commencement of dialysis, we performed modelling by censoring patients at the start of dialysis. In this cohort 293 deaths occurred during CKD follow-up prior to dialysis. However, the association of Hgb and survival was similar to that when we included all deaths (RR = 0.853 for every 10 g/l, 95% CI: 0.799–0.910, *P* = 0.0001).

Table 3 demonstrates the association between a falling Hgb and survival, such that for each 10 g/l difference in Hgb range, there is a stepwise increase in probability of death. Note that the relative risk of dying for each 10 g/l below 140 ranges from 12 to 90%, but the statistically significant threshold value appears to be less than 110 g/l, where the risk becomes almost 2-fold higher than those patients with Hgb greater than 140, after controlling for age, gender, diabetes and eGFR. Thus, the statistical independence of the association of Hgb on survival is demonstrated.

We had *a priori* hypothesized that the association of Hgb and survival is different at different levels of GFR. Although the interaction term for Hgb × GFR is not statistically significant (*P* = 0.153), we further explored the relationship by creating models for each level of eGFR (Table 4). There is a statistically significant association of small changes in Hgb with survival early in the course of CKD (lower Hgb confers a 20% RR of death, whereas it is only 15% at stage 4 and 10% at stage 5 CKD).

Table 4. Adjusted risk ratios for mortality by level of eGFR. This table describes a multivariate model predicting mortality by each level of GFR, corresponding to stages of CKD. Again, each model is adjusted for age, gender, diabetes, GFR at registration, the initiation of EHRT during the follow-up period, RRT initiated during the follow-up period, and Hgb by increments of 10 g/l

Variable	eGFR: 30–59 ml/min				eGFR: 15–29 ml/min				eGFR: <15 ml/min			
	Risk ratio	95% CI		*P*-value	Risk ratio	95% CI		*P*-value	Risk ratio	95% CI		*P*-value
Age (5 years)	1.582	1.014	2.468	0.0434	1.101	0.899	1.347	0.3524	1.581	1.271	1.966	0.0001
Female *vs* male gender	0.433	0.224	0.837	0.0128	0.825	0.651	1.047	0.1133	0.907	0.713	1.153	0.4259
Diabetes	0.847	0.436	1.644	0.6227	1.685	1.310	2.166	0.0001	1.480	1.155	1.898	0.0020
eGFR (5 ml/min)	1.216	1.027	1.439	0.0230	0.840	0.727	0.971	0.0183	1.062	0.860	1.313	0.5757
Haemoglobin (10 g/l)	0.812	0.714	0.924	0.0015	0.861	0.806	0.920	0.0001	0.914	0.844	0.990	0.0281

Note that at different levels of GFR, there are differential impacts of each of the previously important predictors of survival; specifically Hgb has a lesser impact at lower levels of GFR; the initiation of EHRT being less important at GFR <30 ml/min, and the impact of gender being important at GFR >30 ml/min. Risk ratios are presented with 95% confidence intervals. See text for details.

Discussion

This study describes a survival advantage of higher Hgb in a cohort of patients who survived to be referred to nephrologists, in a universal health care system. The cohort was followed from the time of presentation to nephrology care, and the association demonstrated irrespective of erythropoietin therapy initiation, and after controlling for other factors in CKD patients which are known to impact on survival. It describes the association of different levels of Hgb at earlier stages of CKD with poorer outcomes.

A number of key findings help to broaden our understanding of anaemia at earlier stages of CKD.

Firstly, there is variability in clinical presentation at each stage of CKD in all variables, including Hgb. It is clear that the level of GFR alone does not predict the severity of a number of metabolic and haematologic differences associated with CKD; furthermore, there is a differential use of medications recommended in CKD (ACEi/ARB, etc) at each level of GFR.

The 'initial' Hgb at the time of registration as a CKD patient is associated with survival, irrespective of subsequent therapy, and there appears to be a threshold of 110 g/l, below which the association is most profound.

After adjusting for severity of disease at the time of registration (through eGFR and time to dialysis), the independent association of haemoglobin persists. We demonstrate a greater relative risk of lower Hgb at earlier stages of CKD, when anaemia may be less likely to be noticed or treated. Given the exploratory nature of the analysis, all conclusions remain speculative. This dissociation between Hgb and GFR raises the question as to whether haemoglobin may be a marker for more 'burden of illness'. Lower serum albumin (a marker of both nutritional status and inflammation), higher phosphate and lower calcium (markers for hyperparathyroidism), as well as lower diastolic blood pressure (marker of poor myocardial function or arterial stiffness) are associated with anaemia for all levels of GFR (Table 2). Even when we adjusted for albumin and phosphate levels in the subgroup in which it was available, Hgb still remained associated with survival. Specific inflammatory markers were not measured, and thus cannot comment further on this subject.

We were able to define a threshold value of Hgb of 110 g/l, below which there was a substantial risk of death. This observation adds further credence to already published guidelines regarding 'threshold' levels, and is concordant with other general population cohorts including those with heart failure and oncology patients [8,17]. It is interesting to note that in all interventional trials published to date, [3,18–20], there has been little support for improved intermediate outcomes or survival for Hgb values over 110–120 g/l.

The limitations of this, as all observational studies, is that we cannot conclude that improving Hgb would positively impact outcomes, in the absence of understanding the role of concomitant comorbidities or inflammatory status. Conversely, due to confounding, we cannot absolutely conclude that having a higher Hgb has an effect on mortality.

This observational study does not replace the need for a randomized controlled trial. We have clearly described a large well-characterized cohort of patients cared for by nephrologists, in whom abnormalities of Hgb are common, and highly predictive of survival, at all levels of GFR, even at higher levels of GFR. Haemoglobin is a purported modifiable risk factor for both death and progression of CKD, and has previously been shown to be an important predictor of left ventricular hypertrophy, left ventricular growth and of cardiovascular outcomes in dialysis and transplant populations [1,3,6,8,11]. The consistency of our data with previous cohort studies is important. Previous observations are extended using a large cohort of patients in the current era of epoietin therapy availability, within a closed health care system. The need for early identification and attention to Hgb is underscored by this analysis.

It remains critical that we pursue biologically plausible mechanisms by which Hgb may effect target organs, or improve our understanding of Hgb as a marker of inflammation and erythropoietin

resistance or insufficiency, which themselves directly affect outcomes. Those with the lowest Hg in each cohort (overall, or by GFR) had the greatest evidence of metabolic and nutritional derangements. These may foster anti-eythropoietin cytokines and processes, and thus account for some of the lower Hgb. It may be that therapy should include not only erythropoietin replacement therapy, but in addition, anti-inflammatory, mineral metabolism therapies or nutritional supplementation therapy.

Summary

This cohort study of CKD patients, prior to dialysis, describes a strong association of Hgb with survival, after adjustments for measured known risk factors for death. Long-term interventional studies are required to determine the potential impact of correction of anaemia in earliest phases of CKD, and to determine the optimal target Hgb for this patient population, who are not yet on dialysis.

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