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Higher Haemoglobin Level Variation under Treatment with Erythropoitin is Associated with Mortality in Haemodialysis

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Authors' contributions

This work was carried out in collaboration between all authors. Author JB designed the study, wrote the protocol, performed statistical analyses and wrote the first draft of the manuscript. Author RW managed the literature searches, corrected the draft and provided discussion. Author GG managed the therapeuticcal process. All authors read and approved the final manuscript.

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ABSTRACT

Background: During recent years therapy with erythropoesis stimulating agents (ESA) in chronic kidney disease necessitating dialysis (CKD5D) has been challenged following worse study outcome in patients exceeding upper haemoglobin (Hb) target levels. Considering such difficulties to establish a certain and safe Hb target, a focus more on trends of Hb change and fluctuation might be beneficial to encase alternative parameters and hypotheses into anemia management. We conducted an analysis investigating the association of hemoglobin variation, and achievement of Hb targets with mortality in 245 hemodialysis patients from an outpatient center within 15 years follow-up.
Methods: Variation coefficients of Hb course, Hb levels, proportion of Hb within guideline targets, means of ESA dose and dose response were considered as independent variables. Further variables for population characterization and multivariate survival analysis were age, gender and laboratory surrogates.

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Outcome was computed as
(i) Overall mortality by computing OR for death and
(ii) Mortality difference between two Hb variation groups compared by Kaplan-Meier and multivariate survival analysis.

Results: The OR of death in the higher of two Hb variation groups was 5.01 (95% CI 2.85 to 9.11). Hb variation coefficient above 4% had a strong association with all-cause mortality (LogRank=54.1, p<0.001). Hb variation, Hb levels, Hb within targets and ESA dose response, entered overall and conditional multivariate models for survival (x^2=131.3; p<0.001) with Hb variation holding the strongest place in every model.

Conclusion: This unselected population exhibited a strong, significant association of Hb variation and a weaker association of reaching Hb targets with crude mortality. Clinical pathways as well as future controlled trials should encounter these findings in algorithms for ESA therapy.

Keywords: Anaemia; nephrology; dialysis; chronic renal failure.

1. BACKGROUND

Treatment of renal anaemia with erythropoesis-stimulating agents (ESA) is therapeutical hallmark in patients with chronic kidney disease stage 5 on maintenance renal replacement therapy (CKD5D). However, during recent years this therapy has been challenged from some points of view. Studies paid particular attention to the association of haemoglobin (Hb) target level and outcome. Hb levels exceeding 13 mg/dl have been associated with worse outcome in particular subgroups (stroke, malignancies and severe hypertension [1]). Present guidelines recommend treatment with ESA targeting a Hb level of 11 to 12 mg/dl with a comparable lower evidence grade C [2]. On the other hand, the recommendation not to exceed 13 mg/dl intentionally got the evidence level A arguing for the point, that fluctuation of Hb might have a stronger impact than Hb itself. These considerations are in remarkable contrast to common practice during earlier times, in particular during the period, within the follow-up of this observation was conducted. Considering these difficulties to establish a certain Hb target, a focus more on trends of Hb change and ESA treatment response might be beneficial to encase alternative parameters and hypotheses into the controversial discussion [3]. Hb variability along with ESA therapy is a long-known phenomenon [4] but conflicting research results have been documented concerning the stability of both ESA prescription and its impact on Hb level as well as stability of Hb level course [5-7]. An observational study from the US renal data system in 2010 found both decreased mean and standard deviation Hb compared to earlier periods. Mortality was not investigated [8]. ESA administration itself and increase of Hb after ESA were associated with decreased risk of death, while a diminished Hb response on ESA was a risk predictor for death in other observations [9,10]. A European study found association of mortality only in a subset of patients with higher Hb variability in the lower range of Hb target [11]. Higher Hb variability was associated with higher mortality in non-dialysis CKD [12], but did not predict mortality in a Taiwanese peritoneal dialysis population [13]. Because such observational cross-sectional results are already available, we conducted a long-term retrospective analysis from a large single haemodialysis center and registry in Leipzig (Germany) by investigating Hb level distribution, HB levels, reaching Hb targets and ESA dose fluctuation and the impact of these parameters on patient´s outcome. To consider fluctuations, we employed not only cross-sectional data, but longitudinal series of lab values and investigated the association of maxima, minima, means and variability with survival.

2. MATERIALS AND METHODS

2.1 Patient Population, Data Acquisition and Handling, Patient Consent

We included patients of our single out-patient center which were treated with maintenance dialysis initiating between 1996 and 2011. Patients with less than 6 months observation and less than 10 Hb measurements were excluded (inclusion flow chart Fig. 1). At the end of 2011, observation was stopped. In 2012, treatment and anthropometrical data, patient history, survival and laboratory data were exported to a pseudo-anonymous Microsoft Excel® file and merged to a SPSS® dataset. This final dataset comprised 245 patients and was subjected to further analysis. Non-plausible parameter outliners, i.e. subsequent measurements on same or following

day with more than 50% difference were discarded and variables were computed as given in Table 1.

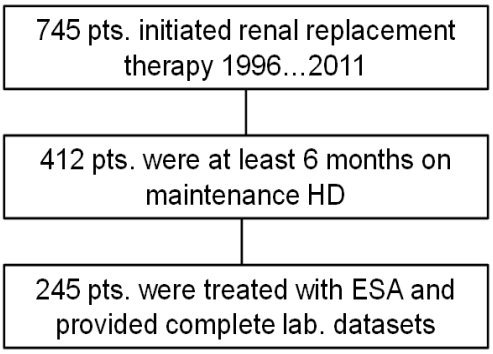


Fig. 1. Flow chart of retrospective patient inclusion

Patients were orally informed about routinely retrieved laboratory results and the intention to conduct scientific analysis using this data. Starting 2001, all patients undersigned written informed consent to agree with participation in a medical outcome quality control system. They were not consented in terms of an interventional trial. All laboratory data were processed by an automated system with link to the clinical data information system. ESA dosage was monitored by manual storage of treatment data in that clinical information system. No funding was obtained for this study. Data are available for sharing with approvals from the appropriate institutions, Ethics committees and Privacy Protection for data transfer.

2.2 Statistical Analysis

Data are presented as means ± standard deviation or proportions. Continuous variables were compared by two-sided Student's t test. Categorical data were assessed by χ^2 statistics.

For survival analyses, the SPSS® version 13.0 program package was used. Univariate analysis (*Kaplan-Meier*) was performed after dichotomizing the population for the appropriate index measure. Survival analyses were performed using death as end-point. Start-time was first dialysis date (survival plots) end-time was end of dialysis date due to death. All events leading to loss of follow-up other than end-points (transplantation, change to another HD unit, change to life-sustaining renal function, end of observation in December 2011) were censored and survival plots were truncated at 15 years. The risk to die was computed during the time period with at least 50% of population at risk, i.e. during the first 5 years. To adjust for influence of covariates on mortality, multivariate *Cox* regression analyses were performed. First, covariates were analysed in a non-conditional overall model in the overall population and in a subgroup with mean Hb < 11g/dl. Second, covariates were subjected to forward conditional step-wise analyses. Covariates remaining in that second equation were considered significant.

Censoring events were change to transplant, change to kidney function and change to another HD center.

Table 1. Description of computed variables of Hb course and ESA therapy

Hb variation coefficient	Standard deviation (SD) of Hb divided by expected Hb times 100
Observation time (y)	Time interval from first to last Hb measurement
Hb (g/dl)	Median Hb value out of all individual measurements
ESA dose / week (IU/week)	Mean ESA dose per week
Hb within target (%)	Proportion of Hb measurements within local treatment target (10-12 g/dL)
Stable phases / year	Proportion of time during one year with Hb within targets and no ESA dose change during 3 months
Unstable phases / year	Proportion of time during one year with either Hb not within targets and/or ESA dose change during 3 months
Mean ESA dose changes per year (n)	Mean number of ESA dose changes within one year
Mean ESA dose increase (%)	Mean increase of ESA dose per dose change
Hb response after ESA increase (g/dl)	Mean response of Hb per ESA dose increase
Mean ESA dose decrease (%)	Mean decrease of ESA dose per dose change

3. RESULTS

The distribution of Hb variation coefficients with regard to ESA weekly dose is given in Fig. 2. Descriptive analysis after dichotomizing for high or low Hb variation coefficients is given in Table 2.

There were significant differences concerning age, observation time, number of measurements and number of unstable phases and extremes of CRP between the 2 groups. No difference was observed concerning values of iron metabolism (transferrin saturation) and Hb level.

A univariate survival analysis (*Kaplan-Meier*) comparing the groups of either high or low Hb variation coefficients showed significantly different survival favouring patients with lower Hb variation (LogRank 54.1, p<0.0001, Fig. 3a) and Hb level > 11 g/dl (LogRank 27.3, p<0.0001). The same but weaker univariate associations were found favouring patients with a high proportion of Hb measurements within target range (LogRank 4.89, p=0.03, Fig. 3b) and patients with ESA doses lower than 8000 IE/week (LogRank 13, p<0.0001). The OR to die during a period with at least 50% of the population at risk (5 years) for patients in the higher of two Hb variations groups was 5.01 (95% CI 2.85 to 9.11). The power to detect the given survival difference at a 0.05 significance level, 2-sided was 99% (accrual interval 6 months, follow-up 36 months, median time to failure 42 months). If a power of 90% would have been aspired a case number of 126 would yield a significant difference.

Parameters were subjected to overall and forward conditional *Cox* regression analysis for overall survival (Tables 3 and 4). Hb variation coefficient, mean Hb, and age entered both analyses with significant results (χ^2=131.3; p<0.001). Hb variation coefficient was the only variable entering the strongest place in every model also in a subgroup with mean Hb < 11g/dL. In other words, Hb variability outperformed mean Hb (which was associated with survival itself) in the overall population and in subgroups with high or low Hb. TSAT as a parameter of iron metabolism did not enter any model to predict mortality.

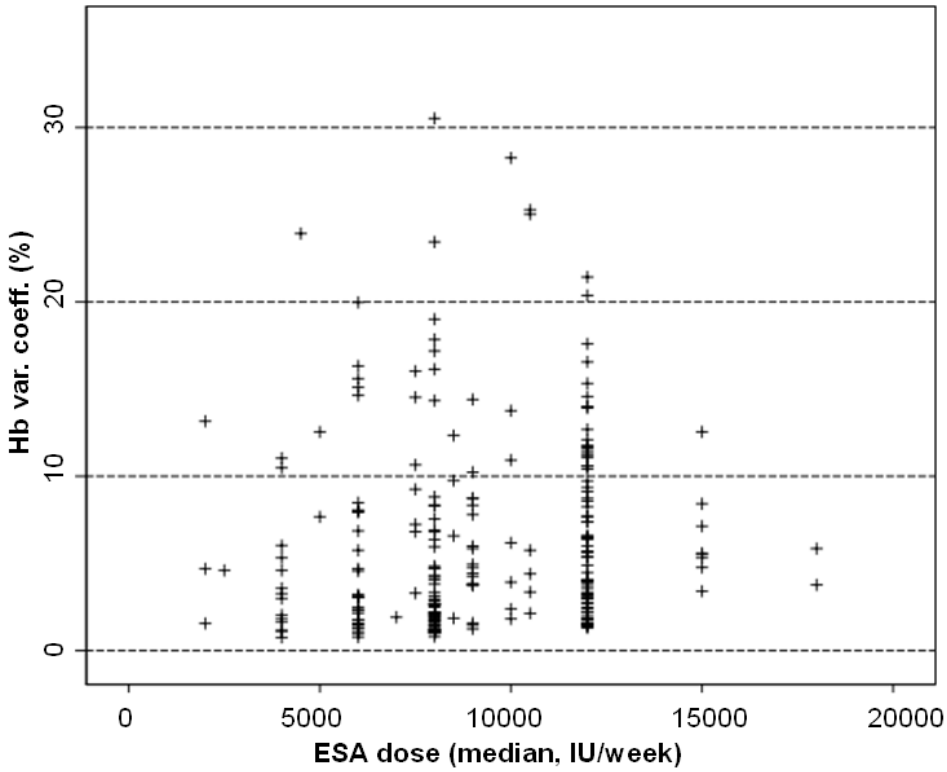


Fig. 2. Hb variation coefficient (%) by mean ESA dose per week

Table 2. Population characteristics in subgroups with high or low Hb variation coefficient

Parameter	Hb variation coefficient		Total	Sign. (p)
	< 4%, n=122 Mean±STD	> 4%, n=123 Mean±STD	n=245 Mean±STD	
Hb variation coefficient (%)	2.23	10.1	6.17	< 0.001
Patients w. blood transfusions (n pts, n units)	3, 27	2, 3	5, 30	>0.001[1]
Male gender (%)	55.7	54.5	55.1	
Age when starting investigation (y)	61.0±15.7	65.0±14.9	63.0±15.4	0.05
Observation time (y)	5.46±2.36	1.41±0.70	3.42±2.67	< 0.001
Median Hb (g/dl)	10.1±0.76	9.89±0.97	9.99±0.873	n.s.
Mean ESA dose / week (IU)	8688±2709	9484±3089	9088±2927	0.033
Number of Hb measurements (n)	77.5±34.4	23.4±17.3	50.3±38.3	< 0.001
Hb within target (%)	57.0±14.1	46.6±18.8	51.8±17.4	0.046
Stable phases / year	0.5±0.31	0.3±0.47	0.4±0.41	<0.001
Unstable phases / year	0.83±0.51	1.46±0.73	1.01±0.69	<0.001
ESA dose changes per year (n)	2.66±1.15	3.20±1.76	2.92±1.50	0.006
Mean ESA dose increase (%)	90.7±36.1	94.0±62.6	92.2±49.8	n.s.
Hb response after ESA increase (g/dl)	0.759±0.684	0.570±0.933	0.665±0.820	n.s
Mean ESA dose decrease (%)	44.9±8.28	44.4±12.9	44.7±10.5	n.s.
Mean CRP (mg/L)	2.33±2.29	2.33±7.33	3.39±5.55	n.s.
Minimum CRP (mg/l)	0.585±1.21	1.08±2.17	.833±1.7698	0.003
Maximum CRP (mg/l)	8.12±8.66	20.6±49.8	14.4±36.3	0.007
Mean transferrin saturation (TSAT, %)	23.3±6.01	23.4±6.34	23.4±6.17	n.s.
Minimum TSAT (%)	11.9±4.52	12.2±4.79	12.0±4.65	n.s.
Maximum TSAT (%)	45.1±21.9	41.6±18.0	43.3±20.0	n.s.

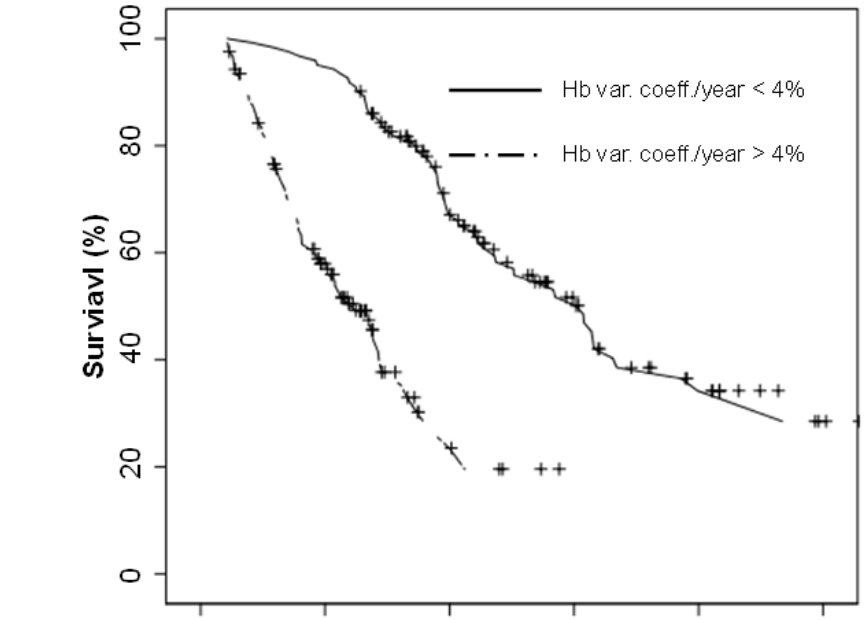
Table 3. Global multivariate survival analysis (*Cox* regression)

Parameter overall	B	Wald	Sig.	Δ HR per unit change (95% CI)	
Hb variation coefficient	21.8	20.8	<0.001	n.a.	n.a.
Hb mean	-0.069	24.6	<0.001	0.255	0.783
Age when starting investigation	0.052	21.19	<0.001	1.030	1.077
Mean ESA dose / week	0.000	1.065	0.30	1.000	1.000
Hb within target	0.004	0.118	0.73	0.981	1.028
Stable phases / year	0.123	0.060	0.81	0.423	3.026
Unstable phases / year	0.76	8.69	0.003	0.003	3.527
ESA dose changes per year	-0.155	1.536	0.215	0.670	1.095
Mean ESA dose increase	0.006	4.371	0.037	1.000	1.011
Hb response after ESA increase	0.004	0.064	0.801	0.973	1.037
Mean TSAT	0.041	0.109	0.703	0.843	1.289

Table 4. Forward conditional multivariate survival analysis (*Cox* regression)

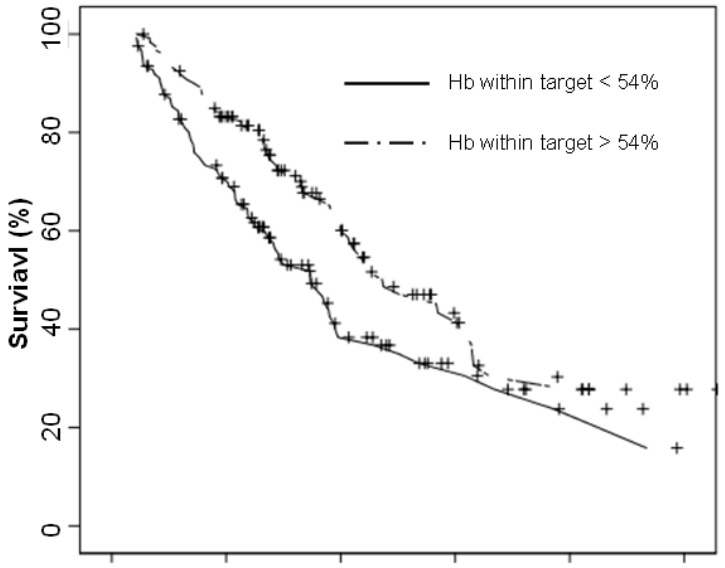
Parameter conditional	B	Wald	Sig.	Δ HR per unit change (95% CI)	
Hb variation coefficient	10.64	63.98	<0.001	n.a.	n.a.
Hb mean	-0.769	42.45	<0.001	0.368	0.584
Age when starting investigation	0.049	36.08	<0.001	1.033	1.067

[1]*Concerning amount of blood transfusions.*



At risk (n)						
Hb var. <4%	122	116	67	34	15	1
>4%	123	58	6	1		

Fig. 3a. Overall patient survival according to Hb var. coeff



At risk (n)						
within target <54%	123	80	26	13	5	1
>54%	122	94	47	21	10	1

Fig. 3b. Overall patient survival according to Hb being in treatment targets

4. DISCUSSION

This analysis of long-term anemia data showed that fluctuation of patient´s Hb course when treated with ESA on hemodialysis was highly associated with survival. This phenomenon was much stronger than the association of ESA dose and dose-response and the proportion of patients reaching Hb treatment targets with survival. Mean Hb value reached significance in multivariate and univariate models, too, but was outperformed by Hb variability in multivariate analyses in the overall population and in subgroups of high and low Hb. Mean Hb value was not different between groups of high or low Hb variability.

Measures of fluctuation of Hb and ESA therapy during long-term treatment are not standardized and not easy to analyze, in particular under conditions of routine and not study conditions. We choose the variation coefficient, a statistical figure that is considered to be robust against fluctuations of the expected variable itself for description of Hb course changes. A similar approach was chosen by Spiegel and coworkers in 2009 [14] describing higher variations in patients treated with ESA than not treated. A recent study from Japan identified the Hb variation coefficient, among other laboratory markers, to be associated with mortality as well [15]. Within our cohort, ESA dose was only slightly different between the Hb variation groups. And interestingly, strong mortality associations were found for unstable Hb/ESA treatment phases and ESA dose change increments as well. Other laboratory parameters except for transferrin saturation had no association with survival.

Obviously, the fact that Hb fluctuation was associated with survival raises the question whether acute bleeding has been the reason of such association and whether the mortality is basically due to bleeding. In such context, one has to consider that subclinical and non-life threatening bleeding is part of a multi-causal complex related to Hb course. In our dataset only one patient was treated with substantial amounts of blood tranfusions due to ESA resistance, but not related to bleeding. We can therefore rule out that bleeding and related deaths do play a biasing role.

Our results do agree with larger registry studies from American dialysis databases [8-9,16] which established associations of higher Hb variation with mortality. A European register study confirmed the association with mortality only for those Hb-fluctuating patients in the lower range of Hb target [11]. Our results do not augment Hb variability only in a low Hb subgroup. Therefore, with regard to current guidelines we would critical consider high ESA doses in those patients with insufficient response and non-stable HB levels. Because being within Hb targets was found to be of much weaker association than crude Hb we would not aim to reach particular values anymore. As in the guidelines already implemented, raising Hb per se, without outliners (evidence grade A) seems to be more important than reaching target corridors (evidence grade C).

Because no randomized prospective trial has been conducted so far, the question of causality cannot be answered from our or other studies. In particular, the question arises whether “high Hb variation” must be considered a sequela of overstimulated ESA therapy or a condition of patients being vulnerable to any disruption of haematopoesis steady-state. It seems plausible that higher Hb variation resembles a status of particular vulnerability but the question whether flattening the Hb course by therapeutic interventions reduces mortality can only by answered by prospective trials. Because such studies are not on the horizon, the foremost result of our present analysis is additional skepticism about taking Hb target values as solely goal of ESA therapy. Stable Hb courses and treatment phases and appropriate ESA dose responses seem to have an at least equivalent impact.

5. CONCLUSION

In summary, our observation showed for the first time in a very long follow-up period that fluctuation of Hb levels (in our data a longitudinal Hb variation coefficient of > 4%) is stronger associated with mortality than reaching Hb guideline levels and mean Hb level itself. This adds observational evidence to the consideration that not Hb level and ESA dose itself, but the Hb response on ESA and the hematological stability of CKD5D patients with ESA therapy should be encountered as therapy targets. The strength of such finding comes from a very long follow-up period (up to 15 years) and from the statistical strength of the effect. The limitation is of course based on the observational, retrospective character of the registry-based analysis.

AVAILABILITY OF SUPPORTING DATA

Raw data will be deposited in the Research Gate® personal profile of JB [http://www.researchgate.net/profile/Joachim_Beige]

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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