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The effect of hemoglobin variability & trends on mortality

Introduction

- Anemia management is a challenging aspect of care for ESRD patients.
- Many factors contribute to variability of hemoglobin (Hb) levels, including reimbursement issues, practice patterns, and medical complications.
- While time below 11 g/dL is known to negatively affect outcomes, less is known about the mortality risk associated with Hb variability.
- This study investigated the effects of Hb variability (cycling), time below target, and Hb trends on mortality.

Methods

- We studied hemodialysis patients who survived the first six months of 2003, had Medicare as primary payer, and had non-missing Epoetin alfa (EPO) and Hb data in each month.
- Hb levels were obtained from the EPO claims, and Hb levels for each month were classified into three ranges:
  - <11 g/dL (low)
  - 11-<12.5 g/dL (mid)
  - ≥12.5 g/dL (high)
- Two methods of further classifying Hb levels were used:
  - 1: Creation of six cycling groups:
    - Consistently low (Hb <11 g/dL for all six months),
    - Consistently mid (Hb 11-< 12.5 g/dL for all six months),
    - Consistently high (Hb ≥ 12.5 g/dL for all six months),
    - Low amplitude low Hb (LAL) where Hb levels switch between both low and mid categories during the six months,
    - Low amplitude high Hb (LAH) where Hb levels switch between both mid and high categories during the six months and,
    - High amplitude (HA) where Hb levels switch between all three categories during the six months.
  - 2: The number and timing of months < 11 g/dL were characterized as:
    - Early (<11 in any of months 1-3)
    - Late (<11 in any of months 4-6)
    - Cycle (<11 early and late).
- Ten comorbid conditions were determined from Medicare Part A and B claims, using ICD9-CM diagnosis codes during the six-month period of Hb classification.
- We used proportional hazards regression to examine: 1) the effect of Hb variability patterns (method 1) on future hospitalization and mortality risk, and 2) the effect of the number and timing of months with Hb < 11 (method 2) on mortality risk
  - The reference group for all analyses was patients with Hb 11-<12.5 for all six months
  - These models were adjusted for age, gender, race, cause of renal failure, and comorbidity
- We used interval Poisson regression to assess the change in the effect of Hb patterns over the course of follow-up time, as opposed to the proportional hazards model, which gives hazard ratios that essentially show the average effect over follow-up time.
  - Hazard ratios for 0-30 days and > 365 days are presented.

Results

- Of the 151,144 pts in the analysis, 9,893 (6.5%) had stable Hb levels of 11-12.5 for each of the 6 months. These patients had the lowest mortality risk (Figures 1 and 2).
- Compared to these patients, the number and timing of Hb values <11 g/dL were most predictive of mortality risk (Figure 4).
- The greater the number of months with a Hb <11, the greater the mortality risk (p<0.001) (Figure 3).
- Patients with Hb < 11 g/dL early had a slightly increased mortality risk when followed by Hb values >11 in months 4-6 (Figure 4).
- The greater the number of months with Hb <11 in the latter half of the entry period, the greater the mortality risk (p<0.001) (Figure 4).

Figure 1
Proportion of patients by Hb cycle group

Table 1
Demographic characteristics by cycling group

Group	Low	Mid	High	LAL	LAH	HA
N:	2,652	9,893	3,053	32,071	43,850	59,625
Age: Mean	56.6	63.3	62.2	61.0	63.1	62.3
SD	16.2	14.6	14.9	15.2	14.9	15.4
%Male	53.1	53.7	57.1	50.8	52.7	48.9
%Female	46.9	46.3	42.9	49.2	47.3	51.1
%White	48.7	56.1	52.0	54.4	53.8	53.0
%Black	46.9	37.5	41.8	39.8	39.8	41.0
%Other	4.3	6.4	6.3	5.9	6.5	6.0
%DM	32.7	42.3	41.5	42.1	42.7	42.8
%HTN	27.9	29.6	28.8	28.0	30.3	29.7
%GN	13.9	12.2	12.9	12.6	11.5	11.4
%Other	25.5	15.9	16.8	16.5	15.5	16.1

Table 2
Mean hemoglobin by cycling group and study month

Group		Low	Mid	High	LAL	LAH	HA
Month							
1	Mean	9.2	11.7	13.6	11.0	12.4	11.6
	SD	1.6	0.4	0.8	1.0	0.9	1.5
2	Mean	9.1	11.7	13.7	11.0	12.5	11.7
	SD	1.6	0.4	0.8	1.0	0.9	1.4
3	Mean	9.1	11.7	13.7	11.0	12.5	11.7
	SD	1.6	0.4	0.8	0.9	0.8	1.4
4	Mean	9.1	11.7	13.7	11.0	12.5	11.8
	SD	1.6	0.4	0.8	1.0	0.8	1.4
5	Mean	9.1	11.7	13.6	11.0	12.4	11.9
	SD	1.6	0.4	0.8	1.0	0.8	1.4
6	Mean	9.2	11.7	13.5	11.0	12.3	11.8
	SD	1.6	0.4	0.8	1.0	0.8	1.5

Figure 2
Proportional Hazards Results for Hospitalization and Mortality

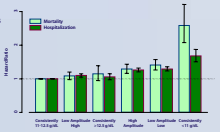


Figure 3
Hazard ratios for mortality based on number low HBs
(Reference group = no low Hb)

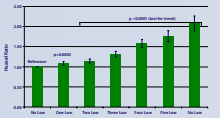


Figure 4
Hazard ratios for mortality based on number and trend of low HBs
(Reference group = consistently mid)

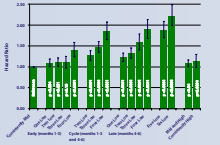
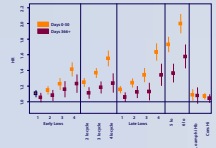


Figure 5
Interval hazard ratios or mortality based on number and trend of low HBs
(Reference group = consistently mid)
Days 0 – 30 and days 366+



- Consistently higher Hb levels were associated with a mildly elevated mortality risk (p=0.08) (Figure 4).
- Results from the interval Poisson regression suggested a decrease in hazard ratios after 1 year, although most groups remained at significantly elevated mortality risk (Figure 4).

Conclusions

- 90% of HD pts experience changing Hb levels over time, and these changes are predictive of mortality risk.
- Patients with Hb levels consistently within the range of 11-12.5 g/dL have the lowest risk of hospitalization and death.
- Although the six cycling groups created, based on amplitude of change, are useful in describing overall variability of Hb levels, the number and timing of Hb values <11 g/dL are most predictive of future mortality risk.
- These data suggest that measures which increase the time a patient's Hb is within the target range of 11-12.5 g/dL may reduce the risk of mortality.

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