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CLINICAL INVESTIGATIONS

Gender differences in the association between discharge hemoglobin and 12-month mortality after acute myocardial infarction

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Background: Anemia at discharge in patients with acute myocardial infarction is associated with poor prognosis; whether this differs in women and men or if there is a threshold value at which these relationships change is unknown.

Hypothesis: Women have a lower discharge hemoglobin (Hb) at which outcomes worsen.

Methods: We identified patients with acute myocardial infarction in the TRIUMPH registry between 2005 and 2008. In multivariable models, we evaluated the relationship between discharge Hb and 12-month mortality and tested whether this relationship varied by gender. We assessed whether the relationship with discharge Hb values was nonlinear using a restricted cubic spline term.

Results: Of 4243 patients with AMI, 32.9% were female. Mean admission Hb was 12.9 ± 1.9 g/dL in women and 14.5 ± 2.0 g/dL in men, with mean discharge Hb 11.4 ± 1.8 g/dL and 12.9 ± 1.9 g/dL, respectively. Lower discharge Hb was independently associated with increased mortality ($P < 0.05$). In multivariable models, discharge Hb decline was similarly associated with increased 12-month mortality in women and men (per 1-g/dL decrease Hb; women HR: 1.24, 95% CI: 1.09-1.42, $P < 0.01$; and men HR: 1.25, 95% CI: 1.13-1.37, $P < 0.01$; P for gender interaction = 0.99). The relationship between discharge Hb and 12-month mortality was linear (P for nonlinear spline term = 0.12).

Conclusions: Lower discharge Hb levels were similarly associated with increased 12-month mortality in women and men. These relationships are linear without a clear threshold, suggesting any decline in discharge Hb is associated with poor outcomes.

KEYWORDS

Acute Myocardial Infarction, Anemia, Gender, Outcomes

1 | INTRODUCTION

Anemia following acute myocardial infarction (AMI) is associated with worse outcomes.[1–6] Women have lower hemoglobin (Hb) levels than men, yet definitions of anemia after AMI are not always gender-specific.[1,7,8] Whether discharge Hb levels following AMI, a potentially modifiable risk factor, are different between women and men and whether these measures are similarly related to poor outcomes by gender is not well known.

Current anemia definitions and transfusion practices commonly rely upon threshold definitions of anemia that have been primarily derived from population Hb norms.[9,10] Studies in cardiac patients that have evaluated the relationship between different population-derived Hb level thresholds for transfusion and outcomes have had variable results.[11] Therefore, it is important to determine whether the relationship between discharge Hb and poor outcomes is, in fact, nonlinear to determine if an outcome-driven threshold for anemia exists.

Accordingly, we compared the relationship between discharge Hb levels during AMI hospitalization and subsequent 1-year outcomes among patients in the 24-center, prospective Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients Health Status (TRIUMPH) registry. Our primary outcome of interest was 12-month mortality following AMI hospitalization. We assessed whether discharge Hb was similarly predictive of poor outcomes in women and men, and whether these relationships were nonlinear or suggestive of a threshold value at which the relationship with poor outcomes abruptly changes.

2 | METHODS

Data were obtained from the prospectively collected TRIUMPH study database, which includes 4340 patients admitted with AMI enrolled between April 11, 2005, and December 31, 2008, at 24 institutions across the United States. The design and methods of the TRIUMPH study have been reported previously.[12] In brief, patients were age > 18 years, with confirmed elevated cardiac biomarkers (troponin or creatinine kinase–MB within 24 hours of admission) and supporting evidence of AMI (electrocardiographic ST-segment changes or prolonged ischemic signs/symptoms).

Trained data collectors performed baseline chart abstraction to document medical history, processes of inpatient care, laboratory results, and treatment. Research staff obtained sociodemographic and clinical data by conducting standardized interviews during hospitalization and at 1, 6, and 12 months after discharge. All participants signed an informed consent approved by participating facilities, and institutional review board approval was obtained at each participating center.

2.1 | Study population

All patients enrolled in TRIUMPH were eligible for inclusion. Patients were excluded if they had incomplete Hb data or they died during hospitalization.

2.2 | Predictor variables

The primary predictor variable for all analyses was discharge Hb, defined as the last Hb value (g/dL) obtained within 48 hours of discharge from the hospital.[2]

Other covariates considered in the multivariable models included patient demographics (age, race, gender) and comorbidities abstracted from patient charts: diabetes mellitus, chronic kidney disease, hypertension, lung disease, acute renal failure, cerebrovascular event, gastrointestinal bleed upon admission (prior to any intervention), congestive heart failure, peripheral vascular disease, history of MI, current smoker, prior coronary artery bypass grafting (CABG) or in-hospital CABG, and in-hospital bleeding events (Thrombolysis In Myocardial Infarction [TIMI] major and minor bleeding events).[13] Additional covariates included medications (antiplatelet agent, β-blocker, angiotensin-converting enzyme inhibitor, glycoprotein IIb/IIIa inhibitor, anticoagulant, statin), Killip class, hospital site, type of infarction (non–ST-segment elevation MI [NSTEMI] or ST-segment elevation MI [STEMI]), and receipt of cardiac catheterization or percutaneous coronary intervention (PCI).

For the in-hospital bleeding events, data abstracters systematically reviewed the charts to record bleeding episodes using the TIMI classification.[13] TIMI major bleeding was defined as intracranial hemorrhage or a Hb decline from admission to discharge ≥5 g/dL in the setting of overt bleeding. TIMI minor bleeding was assigned if the drop in Hb was 3 to 5 g/dL in the setting of observed bleeding. Any bleeding episode with a decline in Hb <3 g/dL was classified as TIMI minimal bleeding.

2.3 | Study outcome

Our primary outcome of interest was 12-month mortality following the index AMI hospitalization. Mortality was confirmed using the Social Security Administration Death Master File.

2.4 | Statistical analysis

Patient characteristics, Hb measures, and bleeding events during hospitalization were compared between women and men using χ^2 tests for categorical variables and Student *t* tests for continuous variables.

In our primary analysis, we used multivariable proportional hazard models to assess the association of discharge Hb with time to death from any cause within 12 months. The hierarchical models were adjusted for patient demographics, clinical characteristics, and clinical site. To test whether associations varied according to patient gender, an interaction term between gender and discharge Hb was included in the models. Next, to determine whether the relationships found in the primary analysis between discharge Hb level and outcomes were nonlinear, restricted cubic spline terms were added to the fully adjusted models.

To see if associations between discharge Hb and outcomes differ in those who were transfused, in a sensitivity analysis, we ran our fully adjusted models among patients who received a blood transfusion.

All analyses were performed using SAS statistical package version 9.4 (SAS Institute, Inc., Cary, NC) and evaluated at a *P* significance level of 0.05.

3 | RESULTS

Among 4340 patients in the TRIUMPH registry, 97 (2.2%) were excluded; 73 (1.6%) for missing Hb values and 24 (0.6%) for death during hospitalization. That left 4243 patients in the final study population.

Baseline patient characteristics are shown in Table 1. Of the 4243 patients in the study population, 1396 (32.9%) were female. The mean age of patients was 59.0 ± 12.3 years, and the majority of patients (67.2%) were white. The majority of patients presented with NSTEMI (57.0%), with 92.1% undergoing cardiac angiography,

TABLE 1 Baseline characteristics overall and by gender

	Overall, N = 4243	Women, n = 1396	Men, n = 2847	*P* Value
Age, y, mean ± SD	59.0 ± 12.3	61.5 ± 13.1	57.8 ± 11.7	<0.01
Race				<0.01
Caucasian	2842 (67.1)	817 (58.7)	2025 (71.4)	
African American	1101 (26.0)	492 (35.3)	609 (21.5)	
Other	287 (6.8)	84 (6.0)	203 (7.2)	
DM	1307 (30.8)	541 (38.8)	766 (26.9)	<0.01
CHF	367 (8.6)	135 (9.7)	232 (8.1)	0.10
Dyslipidemia	2076 (48.9)	698 (50.0)	1378 (48.4)	0.33
HTN	2831 (66.7)	1047 (75.0)	1784 (62.7)	<0.01
PVD	196 (4.6)	80 (5.7)	116 (4.1)	0.02
Prior MI	890 (21.0)	293 (21.0)	597 (21.0)	0.99
Prior PCI	183 (4.3)	59 (4.2)	124 (4.4)	0.85
Prior CABG	481 (11.3)	137 (9.8)	344 (12.1)	0.03
Smoking	2531 (59.7)	721 (51.6)	1810 (63.6)	<0.01
CKD	316 (7.4)	109 (7.8)	207 (7.3)	0.53
Prior cerebrovascular event	211 (5.0)	84 (6.0)	127 (4.5)	0.03
Anemia at arrival	32 (0.8)	16 (1.1)	16 (0.6)	0.04
MI type				<0.01
STEMI	1825 (43.0)	507 (36.3)	1318 (46.3)	
NSTEMI	2418 (57.0)	889 (63.7)	1529 (53.7)	
Killip class				<0.01
I	3730 (88.9)	1186 (86.1)	2544 (90.3)	
II	380 (9.1)	157 (11.4)	223 (7.9)	
III	60 (1.4)	22 (1.6)	38 (1.3)	
IV	25 (0.6)	12 (0.9)	13 (0.5)	
Acute medications on arrival				
ASA	4075 (96.0)	1325 (94.9)	2750 (96.6)	0.01
β-Blocker	3477 (81.9)	1136 (81.4)	2341 (82.2)	0.40
Fibrinolytic	241 (5.7)	54 (3.9)	187 (6.6)	<0.01
Antiplatelet	2878 (67.8)	880 (63.0)	1998 (70.2)	<0.01
Anticoagulant	3830 (90.3)	1233 (88.3)	2597 (91.2)	<0.01
Antithrombin	186 (4.4)	66 (4.7)	120 (4.2)	0.44
GP IIb/IIIa inhibitor	2618 (61.7)	786 (56.3)	1832 (64.3)	<0.01
In-hospital treatment				
PCI	2767 (65.2)	817 (58.5)	1950 (68.5)	<0.01
Coronary angiography	3909 (92.1)	1256 (90.0)	2653 (93.2)	<0.01
CABG	395 (9.3)	112 (8.0)	283 (9.9)	0.04
Adverse events				
Cardiogenic shock	119 (2.8)	38 (2.7)	81 (2.8)	0.82
Cerebrovascular event	23 (0.5)	9 (0.6)	14 (0.5)	0.52
MI	21 (0.5)	5 (0.4)	16 (0.6)	0.37
Thrombocytopenia	51 (1.2)	20 (1.4)	31 (1.1)	0.33
GI bleed	16 (0.4)	3 (0.2)	13 (0.5)	0.23

Abbreviations: ASA, acetylsalicylic acid (aspirin); CABG, coronary artery bypass grafting; CHF, congestive heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; GI, gastrointestinal; GP, glycoprotein; HTN, hypertension; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.
Data are expressed as n (%) unless otherwise noted.

65.2% PCI, and 9.3% having in-hospital CABG. Women were less likely than men to present with STEMI (36.3% vs 46.3%; $P < 0.01$), receive cardiac catheterization (90.0% vs 93.2%; $P < 0.01$), or undergo PCI (58.5% vs 68.5%; $P < 0.01$) during the hospitalization.

Hb measurements and bleeding events during hospitalization are shown in Table 2. The mean admission Hb was 14.0 ± 2.1 g/dL, and the mean discharge Hb was 12.4 ± 2.0 g/dL. Women had lower admission (12.9 ± 1.9 g/dL vs 14.5 ± 2.0 g/dL; $P < 0.01$) and

TABLE 2 Hemoglobin characteristics and bleeding events overall and by gender

		Gender		
	Overall, N = 4243	Women, n = 1396	Men, n = 2847	*P* Value
Admission Hb, g/dL	14.0 ± 2.1	12.9 ± 1.9	14.5 ± 2.0	<0.01
Discharge Hb, g/dL	12.4 ± 2.0	11.4 ± 1.8	12.9 ± 1.9	<0.01
Blood transfusion	473 (11.1)	201 (14.4)	272 (9.6)	<0.01
Bleeding event	420 (9.9)	129 (9.2)	291 (10.2)	0.32
In-hospital bleeding				0.55
None	3823 (90.1)	1267 (90.0)	2556 (89.0)	
Minimal	175 (4.1)	54 (3.9)	121 (4.3)	
TIMI minor	149 (3.5)	49 (3.5)	100 (3.5)	
TIMI major	94 (2.2)	25 (1.8)	69 (2.4)	

Abbreviations: Hb, hemoglobin; SD, standard deviation; TIMI, Thrombolysis In Myocardial Infarction.
Categorical values expressed as n (%); Hb values expressed as mean ± SD.

discharge Hb levels (11.4 ± 1.8 g/dL vs 12.9 ± 1.9 g/dL; $P < 0.01$) compared with men. Bleeding events (TIMI major, minor, or minimal) occurred in 9.9% of patients, and 11.1% of all patients received a blood transfusion during their initial AMI hospitalization. Women had similar rates of bleeding events compared with men (9.2% vs 10.2%, respectively; $P = 0.32$), but women were more likely than men to receive a blood transfusion during their initial AMI hospitalization (14.4% vs 9.6%, respectively; $P < 0.01$; Table 2). Patients with a discharge Hb ≥11 g/dL were more likely than patients with lower discharge Hb to be discharged on dual antiplatelet therapy ($P < 0.01$).

Among the 4243 patients, 6.2% died within 12 months (Figure 1). In unadjusted models, discharge Hb was significantly associated with 12-month mortality (hazard ratio [HR] per 1-g/dL decrease in discharge Hb: 1.41, 95% confidence interval [CI]: 1.32-1.51, $P < 0.01$). In multivariable models adjusting for patient demographic and clinical characteristics, discharge Hb remained significantly associated with 12-month mortality (HR per 1-g/dL decrease in discharge Hb: 1.24, 95% CI: 1.15-1.35, $P < 0.01$). This relationship was similar in women and men (HR = 1.24, 95% CI: 1.09-1.42, $P < 0.01$; and HR = 1.25, 95% CI: 1.13-1.37, $P < 0.01$, respectively; P for gender by discharge Hb interaction = 0.99; Figure 2).

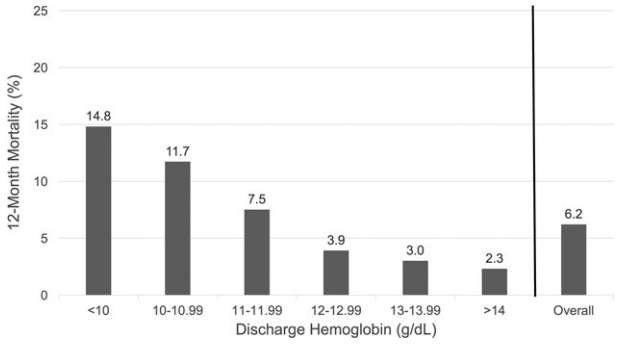

FIGURE 1 Unadjusted 12-month mortality by discharge Hb. In final adjusted models, including restricted cubic spline terms P value for nonlinearity = 0.12. Seventy-four (27.8%) had a Hb ≤10 g/dL, and 55.4% of these patients died of a cardiovascular cause. Cardiovascular death was the most common cause of death in patients with a discharge Hb ≤10 g/dL. Abbreviations: Hb, hemoglobin

In analyses testing the nature of the relationship between discharge Hb level and 12-month mortality, the association was linear ($P = 0.12$ for the nonlinear spline term in the fully adjusted model), suggesting no clear inflection point or threshold value of discharge Hb where outcomes worsen.

In sensitivity analysis evaluating the subset of patients who received a transfusion, unadjusted models showed a significant association between discharge Hb and 12-month mortality (HR per 1-g/dL decrease in discharge Hb: 1.30, 95% CI: 1.04-1.62, $P = 0.02$). In multivariable models adjusting for patient demographic and clinical characteristics, discharge Hb was similarly significantly associated with mortality in women and men (HR per 1-pg/dL decrease in discharge Hb: 1.70, 95% CI: 1.09-2.66, $P = 0.02$; HR: 1.32, 95% CI: 0.94-1.86, $P = 0.11$, respectively; P for gender by discharge Hb interaction = 0.34; Figure 2).

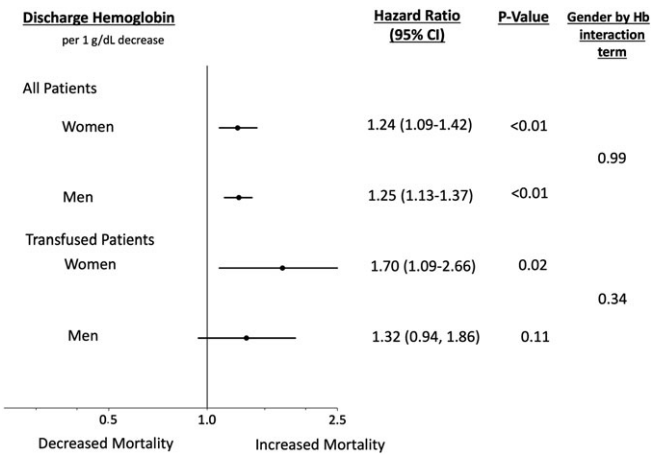

FIGURE 2 Adjusted associations between discharge Hb with 12-month mortality in women and men. Models are adjusted for patient demographics, comorbidities, clinical characteristics, and medication use. Only the 473 patients who had a blood transfusion were included in the sensitivity analysis. Interaction term is for gender*discharge Hb. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid (aspirin); CABG, coronary artery bypass grafting; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; GI, gastrointestinal; GP, glycoprotein; Hb, hemoglobin; HF, heart failure; HTN, hypertension; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease

4 | DISCUSSION

In this population of patients hospitalized with AMI, discharge Hb was associated with 12-month mortality. The relationship was similar in women and men. Importantly, the relationship between discharge Hb and mortality was linear, or continuous, suggesting no clear threshold Hb value at which the association with mortality abruptly changes in women or men.

Our study adds to the evidence of the importance of anemia during AMI hospitalization in several ways. First, our study confirms prior studies suggesting that lower discharge Hb is associated with worse outcomes.[5,14] Patients with lower discharge Hb levels were less likely to be discharged on dual antiplatelet therapy, which likely contributes to higher mortality. Discharge Hb is an ideal marker for prognosis, as it is routinely measured in patients hospitalized with AMI and it is potentially modifiable. Notably, most patients in our cohort (84.6%) had some decline in their Hb during AMI admission. Further, bleeding events following AMI are associated with poor outcomes.[15–17] Therefore, future research is needed to determine if efforts to improve discharge Hb levels, such as strategies to predict and minimize bleeding, will improve outcomes for all patients after AMI.

Second, our study enhances previous literature in its assessment of whether gender differences exist in the association between discharge Hb and outcomes. Women are known to have higher rates of anemia associated with AMI, higher risk of bleeding with acute coronary syndrome, and an overall worse prognosis after AMI.[1,18–21] Similar to differences noted in prior studies, our findings suggest women were less likely to receive guideline-indicated medications on arrival, particularly antiplatelet agents, anticoagulants, and glycoprotein IIb/IIIa inhibitors, or undergo invasive procedures such as angiography, PCI, or CABG (Table 1).[22,23] Yet, to our knowledge, our study is the first to demonstrate that a lower Hb value at discharge is equally associated with poor outcomes in women and men. Therefore, our findings support using discharge Hb as a marker for poor prognosis in all patients after AMI.

Finally, our study is unique in that we tested whether the relationships between discharge Hb and mortality was nonlinear, or suggestive of a threshold value at which the association abruptly changes. Our tests for nonlinearity were nonsignificant, supporting a continuous relationship between decreasing levels of discharge Hb with poor outcomes. Therefore, our study suggests that any fall in Hb is associated with worse outcomes and challenges the clinical paradigm of using specific Hb thresholds to define anemia of prognostic importance. Our study also suggests that Hb thresholds may be triggering differences in interventions such as transfusion. For example, despite equal rates of bleeding events, women had nearly twice the rate of blood transfusions compared with men. We hypothesize this difference may be due to a higher likelihood of women presenting with lower Hb levels or more frequently reaching a Hb level below a clinical threshold value prompting transfusion. Given the uncertainty as to whether transfusions in AMI patients are beneficial, further studies are needed to understand whether efforts to increase discharge Hb levels in AMI patients, including transfusion, improve long-term mortality.[2,24,25]

4.1 | Study limitations

Several limitations should be considered when evaluating the findings of this study. First, although we controlled for many variables related to sources of potential blood loss, including bleeding events and revascularization procedures, other sources of unmeasured Hb decline likely exist that could affect discharge Hb. Second, we were unable to assess the lowest Hb value during admission, as the registry only captures admission and discharge levels. However, discharge Hb is routinely captured, reflects the level after interventions to optimize outcomes have been rendered, and has been shown to be a valuable prognostic marker. Finally, we only examined the relationship between discharge Hb and mortality. Future studies examining the relationship with Hb levels after discharge are needed to compare whether longitudinal trends in Hb are similarly associated with outcomes.

5 | CONCLUSION

Following AMI, lower discharge Hb levels, a potentially modifiable variable, were associated with increased 12-month mortality. Importantly, these relationships are similar in women and men. The relationship between discharge Hb and mortality is continuous or linear, suggesting no threshold value where outcomes worsen. Future studies are needed to determine whether efforts to increase discharge Hb levels improve outcomes for patients after AMI.

Conflicts of interest

The authors declare no potential conflicts of interest.

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