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Consequences of anemia in geriatric hip fractures: how low is too low?

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ABSTRACT

Background The transfusion threshold for low hemoglobin (Hgb) in geriatric patients with hip fractures is widely debated. In certain populations, low Hgb is associated with poor outcomes. Our objective was to evaluate the relationship between lowest Hgb and outcome to identify the Hgb threshold where poor outcomes were more prevalent.

Methods This retrospective cohort study included consecutive patients with hip fractures, aged ≥60 years, evaluated at two level 1 trauma centers from 2018 to 2021. Patients who did not undergo operative fixation or had a length of stay <1 day were excluded. The primary endpoint was adverse outcome defined as the composite of myocardial infarction, stroke, new-onset arrhythmia or death. We compared lowest Hgb and possible confounders between patients with and without adverse outcomes. Classification and regression tree (CART) analysis was performed to identify the threshold for Hgb where adverse outcomes were more prevalent. Multivariate analysis was performed.

Results We evaluated 935 patients. Mean age was 80±10 years; admission Hgb was 12.5±1.7 g/dL. Diabetes was present in 20%, and 20% had coronary artery disease. Adverse outcomes were noted in 57 patients (6.1%). CART identified ≤7.1 g/dL as the Hgb threshold where adverse outcomes were more prevalent (15% vs. 4.1%, p<0.001). Additionally, a greater number of adverse outcomes were noted in the subgroup of patients having both a hemoglobin ≤7.1 g/dL and advanced age (age >79 years (22%)). After controlling for age, American Society of Anesthesiologist Physical Status Classification (ASA), antiplatelet medication, admission Hgb, time to operation and blood transfusions, lowest Hgb ≤7.1 g/dL remained a risk factor for adverse outcomes.

Conclusions In geriatric patients with isolated hip fractures, Hgb ≤7.1 g/dL is associated with a significantly higher rate of adverse outcomes. This risk was most pronounced in patients older than 79 years; particular care should be taken in this demographic.

Level of evidence/study type Level III/prognostic and epidemiological.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Variability in practice patterns exists regarding the threshold to transfuse geriatric patients after hip fracture. A better understanding of anemia-related complications and when they occur could better guide this practice.

WHAT THIS STUDY ADDS

⇒ The incidence of complications varied by age and reached its highest level in patients older than 79 years and a hemoglobin cut-off value of 7.1 g/dL.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The challenges of an aging population require institutions in the USA to consider the development of age-specific transfusion protocols after geriatric trauma.

INTRODUCTION

As our society ages, the number of geriatric patients presenting to trauma centers after a fall is ever increasing. Hip fractures are one of the most common injuries sustained in this population accounting for more than 300 000 hospital admissions, annually.[1] Care for these patients is complicated by increased frailty and a higher rate of medical comorbidities which increase the risk of perioperative complications. In addition, the prevalence of anemia is high, resulting in a greater need for perioperative blood transfusions.[2] The adverse sequelae of blood transfusions have been widely documented and include cardiogenic complications, surgical site infection, 30-day mortality, and 1-year readmission.[3–6] Restrictive transfusion strategies are therefore more widely accepted.

Studies evaluating anemia in geriatric patients with hip fracture have been performed and some advocate for a higher transfusion threshold in this patient population. Geriatric patients have a higher risk of frailty and their physiologic reserve may not tolerate a restrictive transfusion practice.[7] One meta-analysis of restrictive versus liberal transfusion strategies in older adults found that liberal transfusion strategies might produce better outcomes in this patient population.[7] A second meta-analysis investigated the effects of transfusion thresholds ranging from 7 g/dL to 10 g/dL in elderly patients undergoing orthopedic surgery.[8] They found that a restrictive policy led to an increased risk of ischemic events or acute kidney injury.

The exact hemoglobin (Hgb) value where the benefit of preventing anemia-related complications outweighs the risks associated with a transfusion remains unclear in the geriatric population. Given this uncertainty, clinicians may be hesitant

to comply with restrictive blood transfusion strategies in this patient population. Therefore, our hypothesis was that adverse events are only increased in geriatric patients with hip fracture who sustain Hgb levels less than 7.0 g/dL. We sought to answer this by identifying the Hgb threshold where adverse events were more prevalent.

METHODS

This retrospective cohort study identified geriatric trauma patients, aged 60 years or older who sustained an isolated hip fracture and underwent surgical repair at two level 1 trauma centers from 2018 to 2021. These patients were admitted to the trauma service with a specialized geriatric trauma program (G60). The G60 program includes a dedicated, multidisciplinary team of nurses, trauma surgeons, physical therapists, occupational therapists, social workers, case managers and a geriatrician when needed. We coordinate care with multidisciplinary rounding on all trauma patients over the age of 60 years to ensure that we are addressing all aspects of their injury, recovery and post-hospitalization needs. Patients were excluded if they died within 24 hours of hospital admission or transferred to another hospital. The primary endpoint evaluated was the incidence of adverse outcomes defined as the composite of ischemic stroke, myocardial infarction (MI), new-onset cardiac arrhythmia, or death. We defined new-onset cardiac arrhythmia as an arrhythmia identified on ECG, other than sinus tachycardia or sinus bradycardia, not present at admission. Data collected included demographics, Hgb at admission, lowest Hgb, and Hgb value prior to transfusion, American Society of Anesthesiologists (ASA) score, time to operating room (OR), estimated blood loss (EBL) in OR, prior usage of anticoagulants or antiplatelet medications, reversal medications, transfusion requirements, length of stay, and study outcomes. Patients were followed until hospital discharge.

Patients were stratified into two groups based on the occurrence of an adverse clinical outcome (ie, ischemic stroke, MI, new-onset cardiac arrythmia, or death) and clinical variables were compared. To identify the threshold Hgb value associated with an adverse outcome, classification and regression tree (CART) analysis was performed. Variables associated with an adverse outcome on univariate analysis along with the threshold for Hgb identified via CART were entered into a multivariate model. Variables that were significant on multivariate analysis were retained as predictors of adverse clinical outcomes. These independent predictors were then analyzed via CART to identify subgroups where adverse outcomes were more prevalent.

To compare continuous data that were normally distributed, Student's t-test was used, whereas Mann-Whitney U was used for data that were skewed. Categorical data were compared using either Pearson's X^2 test or Fisher's exact test as appropriate. Multivariate analysis was performed by logistic regression (backward, stepwise approach). Data are presented as mean±SD, median (IQR) or n (%). A p value of <0.05 defined statistical significance. SPSS, V.26 (IBM) was used for all statistical analyses.

RESULTS

There were 1095 patients screened for inclusion and 935 were included. The average age at presentation was 80±9.5 years, the most common comorbidities were coronary artery disease (20%) and diabetes mellitus (20%), and the median time to surgical fixation was 20 (14–26) hours (table 1).

The lowest Hgb observed was 8.8±1.8 g/dL. Blood transfusions were administered in 298 patients (32%). The median amount of blood transfused was 1 (1–2) units and the median time to blood transfusion was 2.3 (1.5–3) days.

Table 1 Demographics

Variable	Value (n=935)
Age (years)	80±9.5
Sex (% male)	293 (31)
Body mass index (kg/m²)	24.1±5.2
ISS	9±0
History of coronary artery disease	187 (20%)
History of diabetes mellitus	187 (20%)
History of chronic kidney disease	137 (15%)
History of liver disease	22 (2.4%)
History of stroke	127 (14%)
Time to surgical fixation (hours)	20 (14–26)
ASA score	3 (3–3) n=934
Estimated blood loss	
<100 mL	385 (41%)
100–500 mL	530 (57%)
>500 mL	20 (2.1%)
Anticoagulant pre-injury	132 (14%)
Antiplatelet pre-injury	327 (35%)
Anticoagulant reversal	27 (2.9%)
Received red blood cell transfusion	298 (32%)
Admission hemoglobin (g/dL)	12.5±1.7
Preoperative hemoglobin (g/dL)	11.7±1.8
Lowest hemoglobin (g/dL)	8.8±1.8

ASA score 1–5, where 1=minimal risk and 5=extreme risk of death with or without surgery.
ASA score, American Society of Anesthesiologists physical status classification system; ISS, Injury Severity Score.

An adverse outcome was observed in 57 (6.1%) patients (table 2). The most commonly observed adverse outcome was new-onset cardiac arrhythmia. Of the patients with arrhythmia, 76% experienced adverse hemodynamic sequelae, requiring drug or electrical therapy. CART analysis identified 7.1 g/dL as the Hgb threshold where adverse outcomes were more prevalent (15% vs. 4.1%, p<0.001). Adverse outcomes stratified by lowest Hgb range are displayed in figure 1. In the subgroup of patients with coronary artery disease (n=187), 13 (7%) had an adverse event. Adverse outcomes were more prevalent when lowest Hbg was ≤7.1 (14.6% vs. 4.8%; p=0.029). There was no difference in outcomes using an Hgb threshold <8 (9.1% vs. 5.1%; p=0.278) in patients with coronary artery disease.

Variables associated with an adverse outcome on univariate analysis are displayed in table 3. After controlling for age, ASA score, admission Hgb, antiplatelet medication pre-injury, time to surgical fixation and lowest Hgb ≤7.1 g/dL via multivariate analysis, lowest Hgb ≤7.1 g/dL was retained as a predictor for an adverse outcome (table 4).

Subgroups, identified through CART analysis, where an adverse outcome was more prevalent, are displayed in figure 2. The highest prevalence of adverse outcomes was noted in patients with a lowest Hgb ≤7.1 g/dL, age >79 years and ASA score >3 (44%).

DISCUSSION

The safest and most optimal transfusion threshold for geriatric trauma patients has been widely debated. Geriatric patients have

Table 2 Outcomes

Adverse outcomes (composite endpoint)	57 (6.1%)
Arrhythmia	41 (4.4%)
Atrial fibrillation	N=31
Atrial flutter	N=3
Ventricular tachycardia	N=1
Non-sustained ventricular tachycardia	N=3
Pulseless electrical activity	N=1
Supraventricular tachycardia	N=2
Acute myocardial infarction	6 (0.6%)
Cerebrovascular accident	6 (0.6%)
Death	10 (1.1%)
Length of stay (days)	4.6 (3.4–6)

a higher risk of coronary artery disease and other comorbidities which increase their risk of cardiovascular complications.[7] Recommendations from the ASA Task Force on Perioperative Blood Management suggest a restrictive transfusion strategy may be safely used but were unable to recommend a specific universal trigger.[9] Guidelines from the American Academy of Orthopedic Surgeons support a blood transfusion threshold of no higher than 8 g/dL in asymptomatic patients with postoperative hip fracture.[10] Similarly, recent guidelines from the Association for the Advancement of Blood and Biotherapies recommend a red blood cell (RBC) transfusion threshold of 7 g/dL, but clinicians may choose a threshold of 7.5 g/dL in patients undergoing cardiac surgery and 8 g/dL in patients undergoing orthopedic surgery, or those with cardiovascular disease.[11] There is no strong biological basis though, suggesting different effects with a threshold of 7 g/dL versus 8 g/dL in most populations, although randomized controlled trial (RCT) evidence is not available for all patient categories. These recommendations from many different governing bodies may encourage clinicians to transfuse patients if Hgb levels fall below 8 g/dL. Conversely, data from RCTs recommend transfusions in asymptomatic patients be held unless Hgb levels fall below 7 g/dL.[12 13] This information leaves clinicians challenged with when to actually transfuse blood based on Hgb values if a patient has no other indications for transfusions. In this large, retrospective study, we observed a higher prevalence of adverse outcomes in geriatric patients with isolated hip fracture aged 79 years and older, who sustained an Hgb value of ≤7.1 g/dL. There was no difference in adverse outcomes in those aged 60–78 years who sustained an Hgb value of ≤7.1 g/dL. This supports the evidence for restrictive transfusion strategies in most geriatric patients but could imply the need for age-based transfusion protocols.

We used a composite endpoint to characterize adverse events which consisted of MI, ischemic stroke, new-onset cardiac arrhythmia, and death. Each of these conditions has been associated with anemia in the perioperative setting. The most common adverse outcome observed in our cohort was new-onset cardiac arrhythmia. Anemia has been previously shown to be a predictor of new-onset atrial fibrillation in non-cardiac surgery.[14]

Our threshold for Hgb where adverse events became more common was identified using CART analysis, a useful method for identifying thresholds with continuous data where two mutually exclusive groups can be formed. Subgroups were identified and groups were formed based on lowest Hgb and age where adverse outcomes were most prevalent. The group at greatest risk were those with an Hgb ≤7.1 g/dL, age >79 years and ASA score >3. This Hgb value of 7.1 g/dL is consistent with restrictive transfusion policies that are instituted at many centers. In contrast, patients who were greater than age 79 years had an alarmingly high rate of adverse outcomes when Hgb fell below 7.1 g/dL (approximately a 3.5-fold increase). Strong efforts should be taken to avoid anemia in this subpopulation.

Interestingly, our primary outcome may have been influenced by the use of RBC transfusions. Specifically, differences in risk were observed based on our identified Hgb threshold (≤7.1) and receipt of a transfusion. The highest risk was noted in patients with Hgb ≤7.1 who were not transfused. Although this was not statistically significant, this is likely due to the small number of patients in this cohort (n=6). The next highest-risk group was patients with Hgb ≤7.1 who were transfused (OR=4.8), but

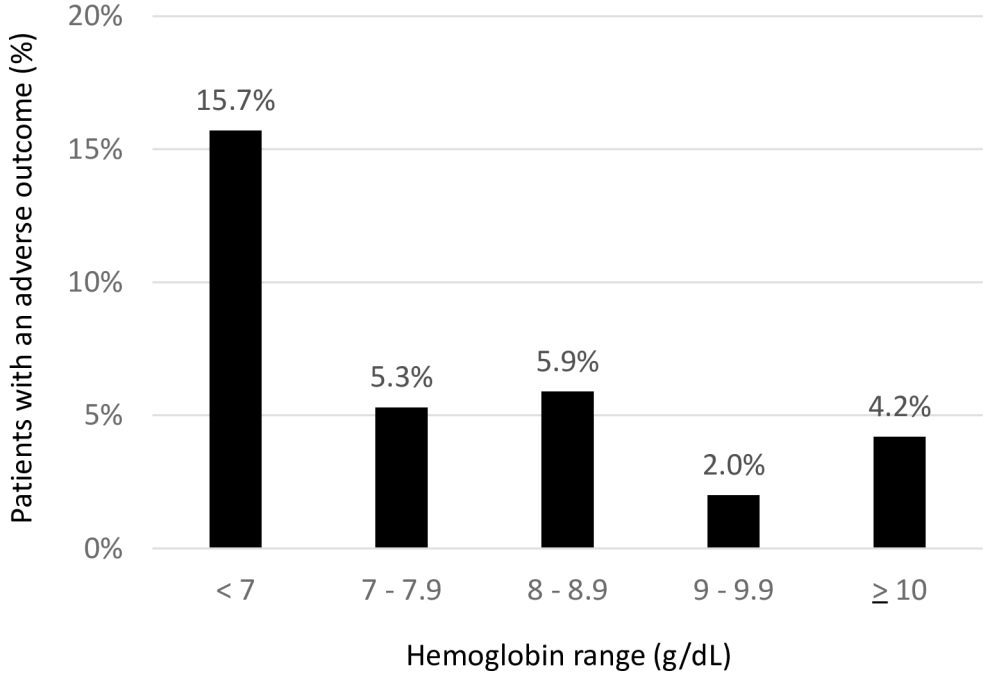

Figure 1 Adverse outcomes stratified by hemoglobin range.

Table 3 Adverse outcomes: univariate analysis

Variable	No adverse outcome (n=878)	Adverse outcome (n=57)	P value
Age (years)	80±9.5	86±8	<0.001
Sex (% male)	272 (31)	21 (37)	0.355
Body mass index (kg/m^2)	24.2±5.3	23.4±4.4	0.248
ISS	9±0	9±0	1.00
History of coronary artery disease	174 (20%)	13 (23%)	0.585
History of diabetes mellitus	174 (20%)	13 (23%)	0.585
History of chronic kidney disease	127 (15%)	10 (18%)	0.524
History of liver disease	20 (2.3%)	2 (3.5%)	0.639
History of stroke	119 (14%)	8 (14%)	0.918
Time to surgical fixation (hours)	20 (13–25)	23 (18–23)	0.003
ASA score	3 (3–3)	3 (3–4)	<0.001
Estimated Blood Loss			
<100 mL 100–500 mL >500 mL	358 (41%) 501 (57%) 19 (2.2%)	27 (47%) 29 (51%) 1 (1.8%)	0.616
Anticoagulant pre-injury	125 (14%)	7 (12%)	0.681
Antiplatelet pre-injury	298 (34%)	29 (51%)	0.009
Anticoagulant reversal	25 (2.8%)	2 (3.5%)	0.678
Receipt of a blood transfusion	262 (30%)	36 (63%)	<0.001
Units of blood transfused	1 (1–2) n=262	2 (1–3) n=36	0.016
Admission hemoglobin (g/dL)	12.6±1.7	11.7±2	<0.001
Preoperative hemoglobin (g/dL)	11.7±1.8	10.7±1.7	<0.001
Lowest hemoglobin (g/dL)	8.8±1.7	7.9±1.7	<0.001

ASA score, American Society of Anesthesiologists physical status classification system; ISS, Injury Severity Score.

the group consisting of patients with Hgb >7.1 who received transfusions was also significant (OR=2.6). These data highlight the potential complications of liberal transfusion thresholds. We think a prospective study would better evaluate this relationship.

The optimal Hgb threshold for RBC transfusion in patients with hip fracture is unknown. One systematic review evaluated 10 trials involving 3968 patients who underwent orthopedic surgery (eg, hip fracture, hip or knee arthroplasty).[15] They demonstrated that a restrictive strategy (mostly Hgb <8 g/dL) was associated with an increased risk of cardiovascular events compared with a more liberal transfusion strategy (mostly Hgb >10 g/dL); Risk ratio=1.51 (1.08 to 2.1)). Subgroup analysis revealed this risk was most evident in patients who underwent hip fracture surgery versus elective arthroplasty (p=0.02 vs. p=0.07). A second systematic review evaluated restrictive versus liberal blood transfusion strategies in nine studies of patients specifically with hip fractures (n=3575).[16] In this analysis, there was no difference reported in mortality, but substantial variation existed with morbidity endpoints. Specifically, a restrictive transfusion threshold (which was defined as mostly an Hgb level

Table 4 Adverse outcomes: multivariate analysis

Model	Variable	OR	95% CI	P value
Base	Age	1.071	1.035 to 1.108	<0.001
	ASA score	1.895	1.098 to 3.270	0.022
	Admission hemoglobin	0.998	0.838 to 1.188	0.979
	Antiplatelet pre-injury	1.535	0.871 to 2.706	0.138
	Time to surgical fixation (hrs)	1.013	1.002 to 1.024	0.023
	Lowest hemoglobin ≤7.1 and no blood transfusion	7.831	0.785 to 78.117	0.079
	Lowest hemoglobin ≤7.1 and blood transfusion	4.638	2.248 to 9.572	<0.001
	Lowest hemoglobin >7.1 and blood transfusion	2.631	1.144 to 6.049	0.023
Final	Age	1.072	1.037 to 1.108	<0.001
	ASA score	1.961	1.146 to 3.357	0.014
	Time to surgical fixation (hrs)	1.013	1.001 to 1.024	0.027
	Lowest hemoglobin ≤7.1 and no blood transfusion	8.518	0.882 to 82.314	0.064
	Lowest hemoglobin ≤7.1 and blood transfusion	4.785	2.543 to 9.005	<0.001
	Lowest hemoglobin >7.1 and blood transfusion	2.633	1.205 to 5.758	0.015

Hosmer and Lemeshow X^2=5.228, p=0.733; c-statistic=0.776.
ASA score 1–5, where 1=minimal risk and 5=extreme risk of death with or without surgery.
ASA score, American Society of Anesthesiologists physical status classification system;

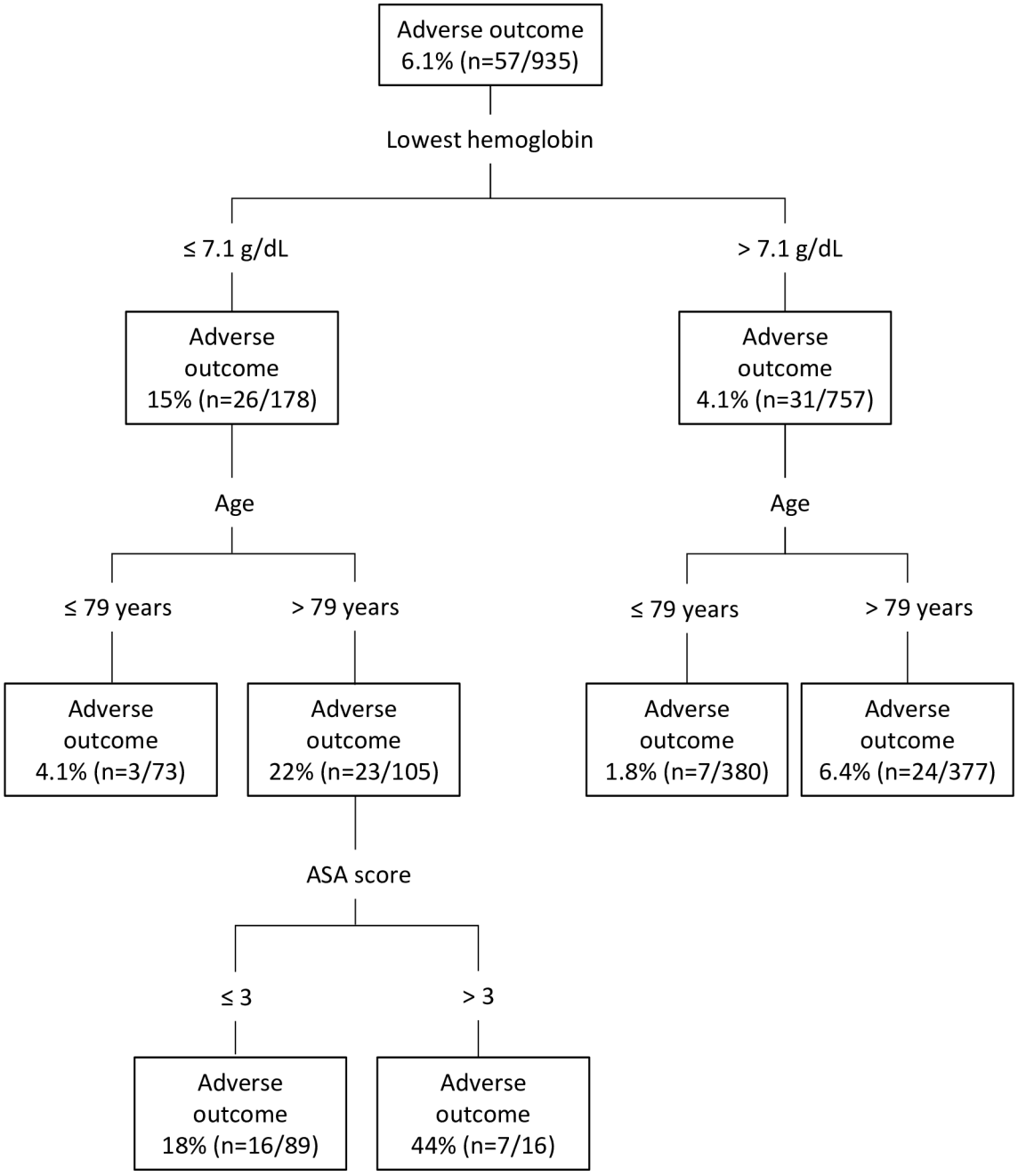

Figure 2 Adverse outcomes stratified across different subgroups using CART. Variables entered were age, lowest hemoglobin, time to surgical fixation, ASA score and antiplatelet pre-injury. ASA score, American Society of Anesthesiologists physical status classification system; CART, classification and regression tree.

of 8 g/dL or symptomatic anemia) was associated with higher rates of acute coronary syndromes, but a liberal transfusion threshold increased the risk of cerebrovascular accidents. It was concluded that clinicians adopt different transfusion strategies according to patient-specific scenarios rather than a transfusion trigger. A large study by Amin *et al* examined patient outcomes and blood utilization after instituting a restrictive transfusion protocol using an Hgb threshold of <7 g/dL and whether clinical outcomes were similar compared with a historical threshold of <8 g/dL.[17] There were 498 patients included and a significant decrease in transfusions was noted (51% vs. 33%, p<0.001). There was no difference in mortality, but cardiac morbidity was significantly lower with the restrictive strategy (22% vs. 12%, p=0.004). This difference remained significant on multivariate analysis (OR (95% CI)=0.45 (0.27 to 0.75)). Last, a large RCT compared a liberal transfusion strategy (Hgb threshold of 10 g/dL) with a restrictive strategy (Hgb <8 g/dL) on the incidence of death or an inability to walk across a room at 60 days after hip fracture surgery.[13] There were no differences noted between groups suggesting transfusions may be withheld in asymptomatic higher-risk patients. Collectively, these data illustrate the challenges in applying these data to the bedside given the heterogeneity in the study definitions (eg, thresholds for each transfusion strategy) and variance in the outcomes observed.

There are several limitations which should be acknowledged. First, this was a retrospective study so typical limitations inherent with this design would apply. Second, there was no transfusion protocol in place at either institution; thus, different transfusion

triggers were used throughout the study period. Confounding by indication would therefore exist. Next, transfusion-related adverse effects were not analyzed (eg, infectious complication, acute lung injury, etc) which would provide a more global assessment of risks and benefits of transfusion practices. Finally, these results may not be generalizable given that all patients with hip fracture were admitted to the trauma service with a well-established geriatric (G60) program.[18] Strengths of this study were the large sample size of 935 patients from two trauma centers committed to geriatric trauma. Lastly, the thresholds used to identify high-risk groups were formed using a multivariate statistical approach rather than predetermined operational definitions.

In conclusion, adverse events were more prevalent when Hgb values fell below 7.1 g/dL. This risk was also age related with higher adverse outcomes occurring in patients who were greater than age 79 years. Clinicians should consider appropriate interventions to maintain Hgb values above this level. It is possible that transfusion triggers should vary based on age group. When controlling for blood transfusions, we noted that adverse outcomes could be mediated by blood transfusions, leading us to question the use of early transfusion thresholds. Future studies are needed to refine transfusion thresholds in high-risk subpopulations including age, fracture patterns, and surgical approaches.

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