Is preoperative anemia a significant risk factor for splenectomy patients? A NSQIP analysis

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A B S T R A C T

Background: Prior literature has examined the association between preoperative anemia and complications across surgical settings; however, evidence is lacking for splenectomy patients. We investigated the association between preoperative hematocrit and 30-day postoperative outcomes in this population using a national database.

Methods: Patients who underwent splenectomy (2012–2017) were identified from the American College of Surgeons National Surgical Quality Improvement Program database. Analyses were performed for the overall cohort and elective versus emergent subsets, adjusting for transfusion among other covariates.

Results: Our sample included 5,580 patients. As hematocrit decreased, complication rates increased incrementally in both the univariate and multivariate analyses. Adjusted odds ratios (and 95% confidence intervals) for moderate anemia (26% ≤ hematocrit < 30%) as compared to no anemia (hematocrit ≥ 38%) were readmission = 1.5 (1.1–1.8), sepsis = 2.2 (1.6–3.0), and composite outcome = 1.8 (1.0–3.2); Parameter estimates (standard error, P value) for the moderate versus no anemia group were length of stay = 3.0 (0.5, P < .001) and days to discharge = 1.2 (0.3; P = .001).

Conclusion: Our results demonstrate a dose-response relationship between increasing degree of anemia and odds of various postoperative adverse outcomes after adjusting for several potential confounders. The subset analysis further suggests that elective splenectomy cases are more likely to have poor outcomes when in the presence of anemia or when transfusions are performed as compared to emergent cases. This suggests that the harm associated with transfusion may offset the benefit of optimizing anemia in an elective splenectomy case.

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B A C K G R O U N D

Preoperative anemia is a significant risk factor for postoperative morbidity and mortality in patients undergoing general surgery procedures [1]. Studies have shown varying degrees of association between preoperative anemia and adverse postoperative outcomes, including increased length of stay; rates of readmission, infectious complications, respiratory failure, cardiac events, and deep venous thrombosis (DVT); and poorer functional status [2–7]. In addition to anemia, perioperative transfusion is independently associated with poor postoperative outcomes including mortality [1,8]. Studies have investigated the role of preoperative anemia in the general surgery population and in specialized patient populations such as orthopedic, spinal, lung, hepatic, colorectal, and head and neck surgery; however, literature on the impact of anemia on surgical outcomes in splenectomy patients is lacking [9–15]. Anemia is a common clinical feature noted preoperatively in patients requiring splenectomy secondary to traumatic, hematologic, and oncologic etiologies [16–18]. Considering the risk of anemia in this population, it is important to clarify the relationship between preoperative anemia and postoperative outcomes in the splenectomy population as well as for general surgical patients to elucidate how anemia, perioperative transfusion, and outcomes are related. Our aim was to investigate the association between preoperative anemia and postoperative outcomes in splenectomy patients using a national database.

M E T H O D S

Subjects. This retrospective cohort study used the participant data file from the American College of Surgeons National Quality Improvement (ACS NSQIP) database, a nationally validated, surgical outcome-based database. Inclusion criteria included all adult patients (male and female) who underwent splenectomy between 2012 and 2017 enlisted in the
Exclusion criteria for this study included subjects with age <18 or ≥90 years old, preoperative hematocrit (HCT) <21%, or missing data variables.

Preoperative anemia was categorized into 4 classes based on preoperative HCT, including no anemia (≥38%), mild (30% to 37%), moderate (26% to 29%), and severe (21% to 25%). These were divided according to clinical reasoning and in accordance with prior studies [1,19]. Outcomes included 30-day postoperative mortality, readmission, length of stay, days from surgery to discharge, surgical site infection (including superficial, deep, and organ space infections), sepsis, deep venous thrombosis (or thrombophlebitis), and a previously implemented adverse composite binary outcome (consisting of myocardial infarction, cerebrovascular accident, progressive renal insufficiency, and death within 30 days) [19,20]. Progressive renal insufficiency was defined as a rise in creatinine of >2 mg/dL from preoperative value but with no requirement for dialysis within 30 days of the operation.

Statistical Analysis. Demographic and clinical variables were compared between hematocrit groups using $\chi^2$ or Fisher exact test for categorical variables and analysis of variance tests for continuous variables. To assess the association between preoperative anemia and postoperative outcomes, and account for potential demographic and clinical confounders, univariate and multivariate logistic and linear regressions were performed ($P$ value cutoff < .05). Subjects in the no anemia cohort had a significantly higher proportion of patients requiring emergent surgery ($P < .001$) compared to the other anemia groups. Table 1 and Figure 1 further detail the demographic and clinical characteristics of each anemia cohort.

* denotes statistical significance.
group were used as a reference group for mild, moderate, and severe categories. Odds ratios (ORs) and 95% confidence intervals (CIs) were provided for categorical variables. Parameter estimates, standard error (SE), and P values were provided for continuous variables. Results were also provided for each significant covariate of the multivariate regression models.

The multivariate analysis accounted for the following NSQIP variables: sex, age, American Society of Anesthesiologists (ASA) classification, congestive heart failure, disseminated cancer, diabetes, bleeding disorder, smoking, hypertension, chronic obstructive pulmonary disease, recent weight loss (>10% body weight loss in the past 6 months), preoperative dialysis, steroid use for chronic conditions, body mass index (using weight/height variables in kg/m²), preoperative transfusion (≥1 U of whole/packed red blood cells 72 hours prior to surgery), and intra/postoperative transfusion (within 72 hours of surgery start time).

The ACS NSQIP and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. All statistical analyses were conducted using the SAS Statistical Software (Version 9.4; SAS Institute Inc, Cary, NC).

RESULTS

Our cohort included 5,580 subjects in total, including 2,063 (37.0%) with no anemia (median HCT 41.3%), 2,035 (36.5%) with mild anemia (median HCT 34.0%), 833 (14.9%) with moderate anemia (median HCT 28.0%), and 649 (11.6%) with severe anemia (median HCT 23.9%) (Table 1; Fig 1). The overall median age of each group was 53 years for no anemia, 57 years for mild anemia, 60 years for moderate anemia, and 64 years for severe anemia (P < .001). Increasing levels of anemia were statistically associated with increasing frequency of open surgical approach (P < .001); increasing frequency of emergent splenectomy (P < .001); higher ASA class (P < .001); increasing BMI (P < .001); and higher frequency of other clinical comorbidities including history of smoking (P < .001), hypertension (P < .001), chronic obstructive pulmonary disease (P < .001), diabetes (P < .001), congestive heart failure (P < .001), bleeding disorder (P = .0022), recent weight loss (P < .001), preoperative transfusion (P < .001), intra/postoperative transfusion (P < .001), and dialysis use (P < .001). The stratified samples of patients requiring emergent and elective splenectomy included 1,761 (31.6%) and 3,819 (68.4%) subjects, respectively (Table 1). The mortality rate for each cohort was 1%, 2%, 4%, and 7% for the no anemia, mild anemia, moderate anemia, and severe anemia groups, respectively (Table 2).

Without accounting for covariates, increasing levels of anemia were statistically associated with greater odds of 30-day mortality, readmission, sepsis, DVT, and composite adverse outcome, as well as longer length of stay and greater days to discharge (Table 3). For example, for 30-day mortality, OR increased from 3.0 (CI 1.7–5.4) in the mild anemia cohort to 9.7 (CI 5.3–17.6) in the severe anemia cohort (Table 3). After accounting for covariates, increasing levels of anemia were no longer statistically associated with increasing odds of 30-day mortality or DVT. However, increasing levels of anemia did remain independently and statistically associated with increasing odds of readmission, sepsis, and composite adverse outcome, and greater length of stay and days until discharge (Table 4).

In regard to transfusion in the overall sample, preoperative transfusion was associated with lower odds of readmission (OR 0.6, CI 0.5–0.9), greater odds of sepsis (OR 1.9, CI 1.5–2.4), longer length of stay (1.7, SE 0.5, P < .001), and longer days to discharge (0.9, SE 0.3, P = .0012). Intra/postoperative transfusion was associated with greater odds of 30-day mortality (OR 2.5, CI 1.6–4.0), sepsis (OR 1.7, CI 1.4–2.1), and composite adverse outcome (OR 2.6, CI 1.8–3.9), as well as greater length of stay (2.1, SE 0.4, P < .001) and days to discharge (2.0, SE 0.2, P < .001) (Table 4).

| No anemia | Mild anemia | Moderate anemia | Severe anemia |
|-----------|-------------|-----------------|--------------|
| ≥ 38%     | ≤ HCT < 38% | ≤ HCT < 30%     | ≤ HCT < 26%  |
| No. of patients | 2,063 | 2,035 | 833 | 649 | 5,580 |
| Death | 15 (1) | 44 (2) | 35 (4) | 43 (7) | 137 (3) | <.001 |
| Readmission | 152 (7) | 222 (11) | 100 (12) | 96 (15) | 570 (10) | <.001 |
| Surgical site infection | 77 (4) | 89 (4) | 45 (5) | 33 (5) | 244 (4) | .1777 |
| Sepsis | 88 (4) | 194 (10) | 161 (19) | 212 (33) | 655 (12) | <.001 |
| Deep venous thrombosis | 55 (3) | 82 (4) | 35 (4) | 34 (5) | 206 (4) | .0083 |
| Composite | 21 (1) | 62 (3) | 47 (6) | 59 (9) | 189 (3) | <.001 |
| Length of stay | 3.00 (2.00–5.00) | 4.00 (2.00–7.00) | 6.00 (4.00–13.00) | 8.00 (5.00–15.00) | – | <.001 |
| Days to discharge | 3.00 (2.00–4.00) | 4.00 (2.00–6.00) | 5.00 (3.00–8.00) | 6.00 (4.00–9.50) | – | <.001 |

Table 2
Outcome frequency by anemia cohort

Table 3
Results of the univariate analysis

Results compare anemia severity groups with the no anemia group (HCT ≥ 38%). * denotes statistical significance.
In the stratified sample of elective cases accounting for covariates, mild anemia was associated with increased odds of readmission; moderate anemia was associated with increased odds of sepsis, greater length of stay, and greater days to discharge; and severe anemia was associated with increased odds of readmission, sepsis, DVT, and composite adverse outcome. Preoperative transfusion in this elective cohort was statistically associated with increased odds of sepsis (OR 4.1, 95% CI 2.2–7.7), longer hospital stay (3.2, SE 0.8, P < .001), and greater days to discharge (1.4, SE 0.4, P < .001). Intra/postoperative transfusion was associated with increased odds of 30-day mortality and composite adverse outcome. Preoperative transfusion in this elective cohort was statistically associated with increased odds of sepsis (OR 4.1, 95% CI 2.2–7.7), longer hospital stay (3.2, SE 0.8, P < .001), and greater days to discharge (1.4, SE 0.4, P < .001). Intra/postoperative transfusion was associated with increased odds of 30-day mortality and composite adverse outcome. Preoperative transfusion in this elective cohort was statistically associated with increased odds of sepsis (OR 4.1, 95% CI 2.2–7.7), longer hospital stay (3.2, SE 0.8, P < .001), and greater days to discharge (1.4, SE 0.4, P < .001). Intra/postoperative transfusion was associated with increased odds of 30-day mortality and composite adverse outcome.

**DISCUSSION**

In this retrospective cohort study of patients undergoing splenectomy, we demonstrated a dose-response relationship between degree of anemia and increasing odds of various postoperative adverse outcomes after adjusting for several potential confounders. Furthermore, the urgency of the case (elective or emergent) had a heterogenous effect on this association—the ORs of sepsis, readmission, DVT, and composite adverse outcome in anemic patients were higher in elective cases than in those undergoing emergent splenectomy. Our findings also demonstrated an association between preoperative transfusion and postoperative complications in the elective cohort. In patients who underwent intra- or postoperative transfusion, there was also an overall association with worse outcomes, which was more pronounced in the elective cohort as evidenced by greater ORs.

Prior literature has shown similar associations between pre- and postoperative transfusion and morbidity and mortality [8]. In the preoperative setting, Gabriel et al used a sample of noncardiac surgical cases from NSQIP to show an independent association between preoperative and perioperative transfusion with mortality. In patients who were transfused, there was no difference in outcomes associated with HCT level, suggesting that transfusion impacts outcome regardless of anemia. However, the study does not answer at which threshold the risks of transfusion offset those of anemia.

Other studies have compared liberal (hemoglobin < 10 g/dL) and restrictive (hemoglobin < 8 g/dL or symptomatic) transfusion guidelines in an attempt to discern at which point the harm of transfusion outweighs the benefits. Carson et al demonstrated no difference in mortality, inability to walk at 60-day follow-up, or in-hospital morbidity between liberal and restrictive transfusion groups [8, 21–25]. Additionally, Murphy et al focused on a cohort of cardiac patients and showed no difference in morbidity and health care costs between liberal and restrictive transfusion guidelines. These studies alongside others suggest that because conservative transfusion guidelines in postoperative anemia result in similar outcomes as liberal ones, there is limited benefit or possible harm associated with transfusion when hemoglobin is between 8 and 10 g/dL.
Table 6
Results of the multivariate analysis, emergent cohort

|                  | Mild anemia (30% ≤ HCT < 38%) | Moderate anemia (26% ≤ HCT < 30%) | Severe anemia (21% ≤ HCT < 26%) | Preoperative transfusion | Intra/postoperative transfusion |
|------------------|-------------------------------|-----------------------------------|---------------------------------|--------------------------|-------------------------------|
| 30-day mortality | 0.81 (0.37–1.76)              | 0.79 (0.34–1.81)                  | 0.82 (0.36–1.84)                | 1.19 (0.76–1.87)         | 1.69 (1.00–2.87)*             |
| Readmission      | 1.56 (0.93–2.63)              | 1.55 (0.88–2.72)                  | 1.67 (0.94–2.95)                | 0.68 (0.48–0.96)*        | 0.93 (0.67–1.28)              |
| Sepsis           | 0.92 (0.64–1.32)              | 1.14 (0.77–1.69)                  | 1.48 (1.00–2.17)*               | 1.19 (0.94–1.51)         | 1.35 (1.06–1.72)*              |
| Deep venous thrombosis | 1.84 (0.68–4.92) | 1.55 (0.51–4.31)                  | 1.55 (0.54–4.46)                | 1.69 (0.98–2.00)         | 1.01 (0.58–1.78)              |
| Composite        | 0.98 (0.47–2.02)              | 0.97 (0.45–2.10)                  | 1.05 (0.50–2.23)                | 1.27 (0.85–1.90)         | 1.73 (1.08–2.77)*              |
| Length of stay   | 1.20 (1.13, P = .2896)        | 2.70 (1.25, P = .0315)*           | 2.65 (1.27, P = .0370)*         | 0.77 (0.82, P = .3509)   | 1.42                           |
| Days to discharge| 0.67 (0.64, P = .2960)        | 1.20 (0.72, P = .0022)            | 1.47 (0.72, P = .0047)          | 0.01 (0.47, P = .9987)   | 2.06                           |

Results compare anemia severity groups with the no anemia group (HCT ≥ 38%). * denotes statistical significance.

The mechanism by which transfusion leads to poor outcomes is not fully elucidated. The current hypothesis suggests that red blood cell transfusion induces immunomodulation through the infusion of cytokines, lipids, and other soluble bioactive substances, resulting in transfusion-related lung injury and immunosuppression, which increase susceptibility to infection [24]. Furthermore, additional well-studied transfusion reactions, including ABO incompatibility and non-hemolytic febrile reactions may be contributing to the morbidity and mortality associated with transfusion in the surgical population.

The findings of this study have important clinical implications in management of patients undergoing splenectomy. Although increasing severity of anemia was associated with greater odds of adverse postoperative outcomes, transfusion itself, independent of anemia severity, was also associated with poor outcomes. If transfusion can in fact be harmful to these patients, then it raises the question—when should an anemic patient undergoing a splenectomy be transfused? Our results suggest that the urgency of the case may be a critical factor in deciding. The association between transfusion and adverse postoperative outcomes, based on the ORs, was significantly greater in elective cases than in emergent cases. This suggests to physicians that the harm associated with transfusion may offset the benefit of optimizing anemia in an elective splenectomy case. Future prospective, randomized control trials should further elucidate the relationship between anemia, transfusion, and outcomes in the splenectomy and general surgical population preoperatively.

There are several limitations to this study. First, our sample groups have many variables that are statistically significantly associated with the anemia cohort. This could suggest that our cohorts are inherently different. However, although the P values are statistically significant, many of the numerical values are quite close and these minimal differences would have little clinical applicability. For instance, in the statistically significant sex category, there is no trend with anemia severity, and the minimal differences are not clinically notable. Additionally, in using a large national database, our analysis was limited to certain data variables and a follow-up of 30 days. Because NSQIP does not provide dates of transfusion, we were unable to determine the temporal relationship between date of hematocrit draw and preoperative transfusion (within 72 hours). Furthermore, it was difficult to assess the relationship between transfusion with length of stay and days to discharge, as the need for a transfusion could prolong a hospital stay. Finally, causality between anemia, transfusion, and measured outcomes could not be established given the retrospective nature of our study.

In conclusion, our findings further inform clinical decision making in regard to transfusion for splenectomy patients with preoperative anemia. These results demonstrate that anemia and intra/postoperative transfusion are associated with increased odds of various 30-day postoperative complications. Our subset analysis suggests that elective splenectomy cases are more likely to have poor outcomes when in the presence of anemia or when transfusions are performed as compared to emergent cases. Thus, physicians should exercise caution in transfusing elective splenectomy patients with mild to moderate anemia, as the harm of transfusion may outweigh the benefit of correcting anemia in this population.

Author Contributions

Research, drafting, and editing of this original report manuscript were conducted by Alexandra Agathis, BA; Prerna Khetan, MPH; Daniel Bitner, MD; and Celia Divino, MD, of the Icahn School of Medicine at Mount Sinai. All authors have seen and approved the final version of the manuscript being submitted, and all authors fulfill the COPE requirements for authorship.

Conflict of Interest/Disclosures

Authors have no related conflicts of interest to declare.

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