

Disparities in the risk of septic events in patients undergoing splenectomy for hematological malignancies (D-ROSE-PUSH): a study based on ACS-NSQIP database

Short title/running head: Sepsis in splenectomy patients

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DISCLOSURE

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Esteemed editor,

Studies evaluating non-traumatic splenectomy in patients with myeloid and lymphoid malignancies reported particularly higher morbidity and mortality rates, ranging between 24 – 52 % and 2 – 18% respectively.¹⁻⁴ Infectious complications including sepsis have been reported to be significantly more common in patients with malignant indications for splenectomy.⁵ The goal of this analysis was to evaluate the risk of post-operative septic events in patients undergoing splenectomy for lymphoid and myeloid malignancies as compared to patients with non-malignant, benign indications.

Our study was a retrospective cohort study of the prospective validated American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database from 2008 to 2016. Cases with the Current Procedural Terminology® (CPT) codes 38100 and 38120 were included. These CPT codes included all the cases of total splenectomy, laparoscopic and open, that were not performed as add-on procedures. Cases with CPT codes 38101 (partial splenectomy) and 38102 (splenectomy as add-on procedure) were not included in the analysis. Only the index case was included for patients undergoing more than one procedure. Patients were not included more than once in the analysis.

The patient population was subsequently stratified based on whether the postoperative diagnosis was part of the pre-identified group of “malignant lymphoid and myeloid neoplasms/leukemia.” This group of diseases included the following International Classification of Disease Ninth Edition (ICD-9) diagnoses (200.X – 208.X) and International Classification of Disease Tenth Edition (ICD-10) diagnoses (C81.X – C96.X). This group of diagnoses includes lymphosarcoma, Hodgkin’s disease, other malignant neoplasms of lymphoid and histiocytic tissue, multiple myeloma, immunoproliferative neoplasms, lymphoid leukemia, myeloid leukemia, monocytic leukemia, and other leukemic diseases).

The primary outcome measure was the incidence of postoperative septic events, including sepsis and septic shock, at 30 days of the index surgery in the group with lymphoid and myeloid malignancy (neoplasms or leukemia as previously defined) compared with the group without lymphoid or myeloid

malignancy. Sepsis was defined per ACS-NSQIP based on the following criteria: (a) sepsis was considered present when a subject had evidence of systemic inflammatory response syndrome and either (i) positive blood culture (or clinical documentation of purulence or positive culture from any site for which there is documentation noting the site as the acute case of sepsis) or (ii) suspected preoperative clinical condition of infection or bowel infarction leading to the surgical procedure. Septic shock was defined as sepsis with documented organ and/or circulatory dysfunction. Both sepsis and septic shock were considered septic events. A multivariate logistic regression model for postoperative septic events at 30 days was created with adjusted odds ratios (OR_{adj}). Clinically relevant potential confounders in each separate model were considered for adjustments. Stepwise regression was performed with an entry level of 0.25 and a stay level of 0.15. The association was further evaluated across strata of age, sex, and emergency status. The interaction was assessed for the 30-day septic events outcome. All p values were 2-sided with level of significance <0.05 . Statistical analysis was done using Statistical Analysis System (SAS). In compliance with the guidelines of the American University of Beirut Institutional Review Board (IRB), ethical review was not needed for our analysis.

A total of 7,721 patients met the inclusion criteria and were included in the analysis. The mean age of the patients was 54.0 years (SD 17.69 years). 52.5% of patients were female. 4,081 (52.9%) of the procedures were done laparoscopically. Baseline characteristics are reported in *Supplementary Table 1*. There was no statistically significant difference in postoperative septic events between the patients who underwent splenectomy for lymphoid malignancy versus those who underwent splenectomy for other indications without adjusting for other factors. Unadjusted risk for 30-day postoperative septic events was not statistically significantly different ($OR_{unadjusted} = 1.16$ with a 95% CI of 0.85 – 1.57) between patients with lymphoid or myeloid malignancy and patients with benign indications for splenectomy. *Table 1* shows the non-stratified and stratified results on 30-day postoperative septic events across the different groups. For patients with lymphoid or myeloid malignancy undergoing splenectomy, the adjusted OR for postoperative septic events was 1.20 (95% confidence interval of 0.87 – 1.66) as compared to patients

with other postoperative diagnoses. Based on the adjusted OR, patients with myeloid and lymphoid neoplasms were not at a higher risk of postoperative septic events. When the subgroups were stratified by age, sex, and emergency status, females undergoing splenectomy for a malignant indication were at a statistically significantly increased risk of postoperative septic events with $OR_{adjusted} = 1.83$ (95% confidence interval of 1.12 – 2.99) when compared with females undergoing splenectomy for other indications.

In our analysis, the preoperative risk factors found to be associated with postoperative septic events included older age, age 65 years or older, male sex, functional dependence, and inpatient hospitalization status. Having a higher American Society of Anesthesiologists class was associated with higher risk for postoperative septic events. The use of general anesthesia did not affect the risk of postoperative septic events. Emergency cases were associated with two-fold increased risk of postoperative septic events. Perioperative transfusion, longer operative time, and open approach (versus laparoscopic) were associated with increased risk of postoperative sepsis. These results are similar to the findings of the study by Bagrodia et al evaluating morbidity and mortality following elective splenectomy.⁵ Patients with chronic heart failure and hypertension were at a higher risk of postoperative septic events. Pulmonary comorbidities including ventilator dependence and severe chronic obstructive pulmonary disease were associated with increased risk of postoperative septic events. These findings are similar to the findings by Neuwirth et al.² Smoking was not found to be associated with increased risk of postoperative septic events – a result consistent with findings in the literature.¹ Higher INR (greater than 1.4), lower hematocrit, and leukocytosis were associated with an increased risk of postoperative septic events. Diabetes mellitus, weight loss, and lower serum albumin were associated with higher risk of postoperative septic events; these results were consistent with findings in the literature.^{1,5}

Previous studies have established that elective splenectomy for malignant conditions has a higher complication rate than splenectomy for benign conditions.^{3,5,6} Our study validates the risk factors associated with infectious complications from previous studies.^{1,5} In our analysis, the adjusted risk for

postoperative septic events remains similar between the group undergoing splenectomy for malignant indications and the group undergoing splenectomy for benign indications. Our study did not find a differential effect of age on risk of postoperative septic events upon stratification. However, female patients undergoing splenectomy for lymphoid and myeloid neoplasms were at ~ 1.8-fold increased risk of postoperative septic events when compared to female patients undergoing splenectomy for benign indications. This differential effect had not been identified in previous studies.

The strengths of our study include the large, multicenter ACS-NSQIP database from which the data was extracted. The sample is thought to be representative of the pool of all the patients undergoing surgery in the United States, but there could exist aspects that the database does not accurately reflect. Another limitation is the 30-day postoperative follow-up. This relatively short period of follow-up captures most post-operative complications, especially those relevant to the outcomes of our study but may miss long-term outcomes. Potential missing confounders include preoperative vaccination status and antibiotic treatment in the postoperative period.

Our analysis suggests that, while pursuing measures to prevent infectious complications of splenectomy in patients undergoing the procedure for benign or malignant indications, special attention should be given to patients with the risk factors identified in this study including older patients with cardiovascular comorbidities, pulmonary comorbidities, renal comorbidities, malnutrition, need for perioperative transfusion, and coagulopathy. Among female patients, those undergoing splenectomy for malignant indications are at an increased risk as compared to females undergoing splenectomy for benign indications. The results shed light on another area of potential disparity in care and invites more prospective studies to evaluate this differential effect seen only in the female group.

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Table 1. Overall and stratified effects of surgical indication (malignant versus benign) on risk of postoperative septic events

	Septic events		<u>Unadjusted</u>		<u>Adjusted</u>	
	No	Yes	OR (95% CI)	p- value	OR (95% CI)	p- value
	n = 7329	n = 392				
Lymphoid/myeloid neoplasms (%)	823 (11.2)	50 (12.8)	1.16 (0.85 – 1.57)	0.35	1.20 (0.87 – 1.66)	0.26
Stratified analysis of patients with lymphoid/myeloid neoplasms						
Age						
<65 years (n=5241)	410 (8.2)	27 (10.9)	1.37 (0.91 – 2.07)	0.13	1.44 (0.93 – 2.24)	0.10
65+ years (n=2480)	413 (17.7)	23 (15.9)	0.88 (0.55 – 1.39)	0.57	1.01 (0.62 – 1.64)	0.98
Sex						
Male (n=3663)	457 (13.3)	28 (12.0)	0.89 (0.59 – 1.33)	0.57	1.02 (0.66 – 1.58)	0.93
Female (n=4048)	366 (9.4)	22 (13.8)	1.55 (0.97 – 2.46)	0.06	1.83 (1.12 – 2.99)	0.02
Emergency						
No (n=6549)	784 (12.5)	45 (17.1)	1.45 (1.04 – 2.01)	0.03	1.28 (0.90 – 1.81)	0.17
Yes (n=1172)	39 (3.7)	5 (3.4)	1.03 (0.40 – 2.68)	0.81	1.04 (0.38 – 2.79)	0.94