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Leukocytosis after distal pancreatectomy and splenectomy as a marker of major complication

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ABSTRACT

Background: The aim of this study was to analyze the associations between the degree of postoperative leukocytosis and major morbidity after elective distal pancreatectomy with splenectomy (DPS).
Methods: Retrospective review of patients undergoing DPS for pancreatic diseases (2013–2016). Receiver operating characteristic curves, Youden's index, and area under the curve were used to identify ideal lab cut-off values and discriminatory ability of postoperative white blood cell count to detect complications.
Results: 158 patients underwent DPS. Median age was 57 years (range, 22–90) and 53% of patients were male. POD3 absolute WBC count $\geq 16 \times 10^9$/L or an increase in WBC count $\geq 9 \times 10^9$/L from preoperative baseline was associated with major morbidity after DPS (AUC 0.7 and 0.7, respectively).
Conclusion: Postoperative day three leukocytosis $\geq 16 \times 10^9$/L or an increase in WBC of $\geq 9 \times 10^9$/L from preoperative baseline should raise clinical awareness for major postoperative complication after DPS.

Introduction

Distal pancreatectomy is performed for a variety of benign and malignant conditions involving the left side of the pancreas. Splenectomy is often performed concurrently with distal pancreatectomy given the spleen's intimate vascular relationship with the pancreatic tail. Regardless of procedural urgency, splenectomy generates a physiologic leukocytosis and thrombocytosis in the immediate postoperative period.[1–3] This physiologic response can add confusion to the postoperative clinical assessment for patients undergoing distal pancreatectomy with splenectomy (DPS).

Postoperative infectious complications and postoperative pancreatic fistula (POPF) following hepatopancreatobiliary surgery are exceedingly common and contribute significantly to procedure-specific morbidity, with rates ranging from 20 to 40%.[4–7] Early identification and intervention are critical in minimizing morbidity and improving the frequency of patients requiring rescue from mortality. Untoward deviation from expected postoperative recovery pathways are often alerted by elevations in circulating white blood cell count (WBC). However, differentiating physiologic from pathologic leukocytosis following splenectomy remains challenging.

Patients undergoing emergent splenectomy for traumatic indications experience the same physiologic elevations in WBC and platelet counts. Retrospective studies have established that operative blood loss, volume of resuscitation, and transfusion requirements are associated with postoperative complications following emergent splenectomy alone.[8,9] Patients with septic complications following splenectomy experience a profound and longer duration of postoperative leukocytosis.[2,3,10] Additional metrics such as platelet-to-WBC ratio, have been used to reliably delineate physiologic from pathologic complete blood counts.[8,11]

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The purpose of this study was to analyze the potential of routine laboratory metrics to predict postoperative complications in patients undergoing distal pancreatectomy with splenectomy for non-traumatic, elective operations.

Materials and methods

An institutional database was queried to identify patients undergoing distal pancreatectomy with splenectomy for any indication between January 2013 and December 2016. Patients under the age of 18 years old, pregnant patients, and imprisoned patients were excluded from review. The Indiana University Institutional Review Board (IRB) approved the conduct of this study, which remained compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Preoperative clinical factors were documented and included patient demographics, comorbidities, clinical diagnosis, and laboratory metrics. A compilation of each patient's comorbidities was calculated and recorded as a Charlson Comorbidity Index (CCI).[12] Intraoperative and postoperative variables were documented and included: ASA classification, duration of operation, operative blood loss (EBL), laboratory metrics, organ failure, infectious complications, postoperative pancreatic fistula, readmission, overall morbidity, and 90-day mortality.

Postoperative organ failure was defined according to the modified Marshall scoring system for organ dysfunction.[13] Postoperative pancreatic fistula was defined according to the International Study Group on Pancreatic Fistula.[14] Clinically relevant POPF (CR-POPF) was defined as grade B or C POPF.[15] Incisional and organ-space surgical site infections (SSI) were defined according to the Center for Disease Control (CDC) definitions.[16] Major morbidity was defined as any SSI, CR-POPF, organ failure, or hospital readmission. Overall morbidity was defined as any postoperative complication.

Absolute plasma WBC count, change in WBC count from preoperative baseline (ΔWBC), and platelet-to-WBC ratio (Plt:WBC) were evaluated daily from the time of operation through postoperative day five. Laboratory values are reported as mean values (+/− standard error of the mean, SEM) unless otherwise indicated. Student's t-test was used to compare mean lab values between patients with and without postoperative complications with p-values <0.05 accepted as statistically significant. Receiver operating characteristic (ROC) curves with Youden's index were used to identify optimal laboratory cut-off values and associated sensitivity and specificity. The area under curve (AUC) was used to determine the discrimination accuracy of each laboratory test.

Results

A total of 158 patients had complete data to include in the analysis. Surgical technique was open in 106 patients (67%), laparoscopic in 50 patients (32%), and robotic in 2 patients (1%). Demographic data, comorbidities, and perioperative variables are presented in Table 1. The most common indications for DPS were pancreatic adenocarcinoma (n = 33, 21%), chronic pancreatitis (n = 30, 19%), disconnected pancreatic duct syndrome (n = 28, 18%), pancreatic neuroendocrine tumor (n = 22, 14%), mucinous cystic neoplasm (n = 11, 7%), and intraductal papillary mucinous neoplasm (n = 8, 5%).

Overall morbidity in this surgical series was 37%, Table 2. Overall 90-day mortality was 3% (n = 5). A comparison of mean WBC on each postoperative day categorized by specific postoperative complications is shown in Table 3.

Table 1
Patient demographics and perioperative variables of interest.

Demographics	n = 158
Age, median (range)	57 years (22–89)
BMI, median (range)	28 kg/m^2 (15–54)
CCI, mean (+/− SEM)	3.0 (±0.2)
Male, n (%)	84 (53)
Hypertension, n (%)	91 (58)
Tobacco use, n (%)	78 (49)
Hyperlipidemia, n (%)	58 (37)
Chronic Pancreatitis, n (%)	54 (34)
Diabetes Mellitus, n (%)	47 (30)
Coronary Artery Disease, n (%)	23 (15)
COPD, n (%)	12 (8)
Perioperative variables	
ASA class, mean (+/− SEM)	2.9 (±0.03)
Estimated Blood Loss, mean (+/− SEM)	539.5 mL (±55.2)
Operative Duration, mean (+/− SEM)	217.5 min (±7.7)
Perioperative Transfusion, n (%)	35 (22)

Abbreviations: BMI – body mass index; kg – kilogram; m – meter; CCI – Charlson Comorbidity Index; COPD – chronic obstructive pulmonary disease; ASA – American Society of Anesthesiologists; SEM – standard error of the mean; mL – milliliter.

Procedure-specific outcomes

A total of 29 patients (18%) developed POPF. Clinically relevant POPF was seen in 15 patients (9%). There were no differences in any of the demographic and perioperative variables listed in Table 1 between patients with and without POPF or CR-POPF. When comparing patients with POPF to patients without POPF, the mean WBC was significantly higher on postoperative day three (POD3) in patients developing a POPF. Additionally, patients with CR-POPF had a significantly higher mean WBC on POD3 when compared to those without CR-POPF.

A total of 21 patients (13%) developed an SSI. Sixteen patients (10%) developed an organ-space SSI, four patients (3%) developed incisional SSI, and one patient developed both organ-space and incisional SSI (0.6%). There were no differences in any demographic or perioperative variables between patients with and without SSI. When comparing patients with SSI to patients without SSI, the mean WBC was significantly higher in patients developing SSI on POD2, POD3, POD4, and POD5.

Postoperative outcomes, major morbidity, and mortality

A total of 23 patients (15%) were readmitted within 90 days. Three patients were readmitted two times. The most common causes of readmission were failure to thrive (n = 8), intraabdominal abscess (n = 4), blood in surgical drain (n = 3), CR-POPF (n = 2), venous thromboembolism (n = 2), and portal vein thrombosis

Table 2
Postoperative outcomes.

Postoperative outcome	n (%)
Incisional SSI	5 (3)
Pneumonia	6 (4)
Urinary tract infection	7 (4)
Organ-space SSI	17 (11)
POPF	29 (18)
CR-POPF	15 (9)
Readmission	23 (15)
Overall morbidity	59 (37)
Major morbidity	30 (19)
90-day mortality	5 (3)

Abbreviations: SSI – surgical site infection; POPF – postoperative pancreatic fistula; CR-POPF – clinically relevant postoperative pancreatic fistula.

Table 3
Mean white blood cell count (10^9/L) with standard error of the mean on postoperative days one through five in patients with (+) and without (−) complications of interest.

	Postoperative pancreatic fistula			Clinically relevant postoperative pancreatic fistula			Surgical site infection			Hospital readmission		
WBC (SEM)	(−)	(+)	*P*	(−)	(+)	*P*	(−)	(+)	*P*	(−)	(+)	*P*
POD1 (SEM)	15.5 (0.6)	16.9 (1.2)	0.33	15.7 (0.6)	16.5 (1.3)	0.63	15.5 (0.6)	17.5 (1.1)	0.21	15.8 (0.6)	15.6 (0.9)	0.92
POD2	18.6 (0.6)	20.3 (1.3)	0.25	18.6 (0.6)	21.2 (1.9)	0.18	18.4 (0.6)	22.4 (1.5)	0.02	18.8 (0.6)	19.1 (1.3)	0.87
POD3	16.6 (0.6)	19.5 (1.5)	0.04	16.8 (0.5)	20.6 (2.5)	0.04	16.4 (0.6)	21.7 (1.8)	0.001	16.9 (0.6)	18.8 (1.7)	0.22
POD4	14.1 (0.6)	15.7 (1.4)	0.23	14.2 (0.5)	16.3 (2.0)	0.22	13.7 (0.5)	18.2 (1.5)	0.002	14.3 (0.6)	15.1 (1.2)	0.6
POD5	13.2 (0.6)	15.0 (1.2)	0.16	13.1 (0.6)	16.0 (1.6)	0.07	12.5 (0.5)	17.9 (1.5)	<0.001	13.4 (0.6)	14.5 (1.5)	0.43

Bolded values represent a statistically significant difference. Abbreviations: POD – postoperative day; WBC – white blood cell count; SEM – standard error of the mean.

(n = 2). Other single causes for readmission include pneumonia, pleural effusion, neutropenic fever, colitis, and a thromboembolic event from thoracic aortic aneurysm. Except for CCI, no differences were found in any demographic or perioperative variables between patients with and without readmission. Mean WBC on any postoperative day did not correlate with hospital readmission; however, patients requiring readmission had significantly higher mean CCI (4.1; SEM, 0.2) compared to patients not requiring readmission (2.8; SEM, 0.4), $P = 0.003$.

Major postoperative morbidity developed in 30 patients (19%). There were no differences in age, comorbidities, CCI, or perioperative variables between patients with and without major morbidity. When comparing patients with major morbidity to patients without major morbidity, the mean WBC was significantly higher in patients developing major morbidity on POD1-POD5, Fig. 1. A total of 5 patients (3%) died within 90 days of their operation. A significantly increased mean WBC count on POD1, POD3, POD4, and POD5 was observed in patients with 90-day mortality, Table 4. Causes of death included multisystem organ failure, intraoperative myocardial infarction complicated by multisystem organ failure, aortogastric fistula, post-discharge cardiac event, and hemorrhage from visceral artery pseudoaneurysm.

Metrics associated with postoperative complications

White blood cell count, the absolute change (ΔWBC) in WBC from the preoperative value, and the platelet-to-WBC ratio on POD1 and POD3 were evaluated to identify the metric able to most discriminate major complications using ROC with AUC, Fig. 2. The only two metrics achieving an AUC >0.7 included absolute WBC count and ΔWBC on POD3. Sensitivity, specificity, and AUC of these tests at the ideal cut-off point are shown in Table 5.

Table 4
Mean white blood cell count (10^9/L) with standard error of the mean on postoperative days one through five in patients with (+) and without (−) 90-day mortality.

	Mortality		
WBC (SEM)	(−) n = 153	(+) n = 5	*P*
POD1 (SEM)	15.5 (0.5)	23.1 (7.6)	0.01
POD2	18.8 (0.6)	21.4 (4.1)	0.42
POD3	**17.0 (0.5)**	**25.3 (2.5)**	**0.03**
POD4	**14.2 (0.5)**	**26.3 (2.7)**	**0.003**
POD5	**13.2 (0.4)**	**24.8 (4.1)**	**<0.001**

Bolded values represent a statistically significant difference.
Abbreviations: POD – postoperative day; WBC – white blood cell count; SEM – standard error of the mean.

Multivariable analysis

Multivariable analysis was performed to assess POD3 WBC of $\geq 16 \times 10^9$/L and POD3 ΔWBC $\geq 9 \times 10^9$/L as risk factors for major morbidity after DPS. Multivariable analysis controlled for age, CCI, BMI, comorbidities, operative indication (benign, malignant), operative technique (open, minimally invasive), and perioperative blood transfusion. This analysis found POD3 ΔWBC $\geq 9 \times 10^9$/L to be a significant risk factor for postoperative major morbidity ($P = 0.04$) with an odds ratio of 4.1 (95% confidence interval, 1.1–16.6).

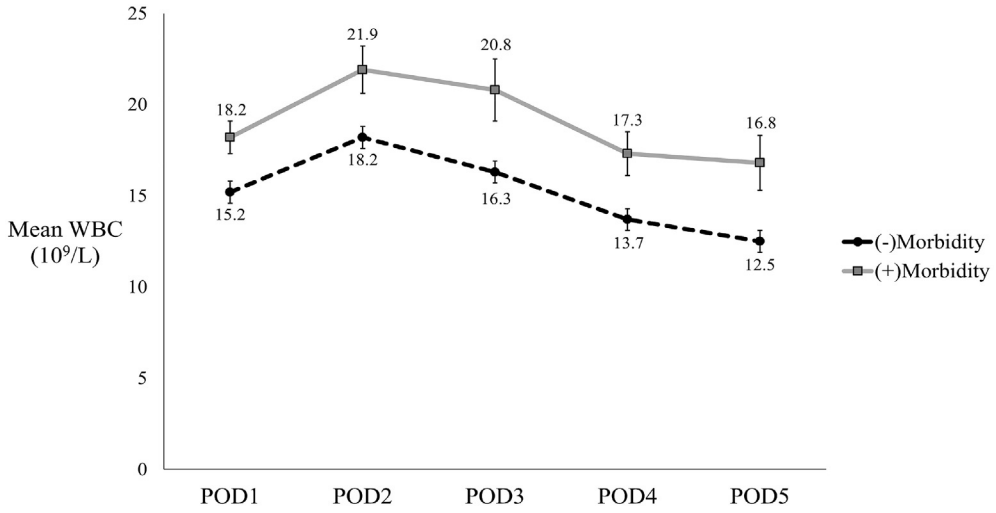

Fig. 1. Mean white blood cell count (+/− standard error of the mean) on postoperative days one through five in patients with and without major morbidity.
Abbreviations: WBC – white blood cell count; L - liter.

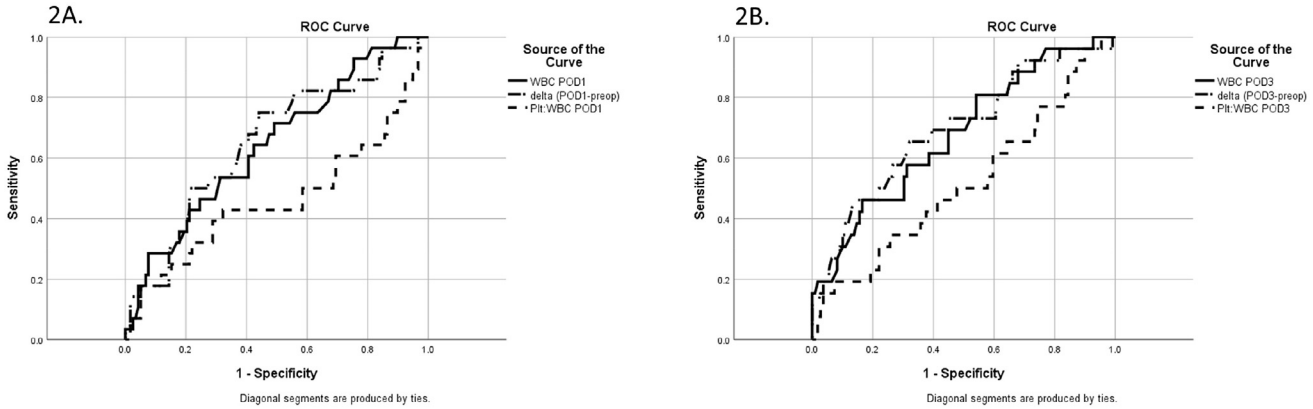

Fig. 2. Receiver operating characteristic (ROC) curve evaluating three metrics (WBC, ΔWBC, and Plt:WBC) on postoperative day one (Fig. 2A) and postoperative day three (Fig. 2B) to detect major morbidity.
Abbreviations: WBC - white blood cell; POD – postoperative day; Δ - delta; Plt - platelet.

Patients with POD WBC of $\geq 16 \times 10^9$/L were not at increase risk of postoperative major morbidity on multivariable analysis ($P = 0.2$).

Discussion

Physiologic leukocytosis following splenectomy can complicate the clinical picture during postoperative recovery. Studies evaluating splenectomy in trauma patients have associated the degree and duration of leukocytosis as well as the platelet-to-WBC ratio as useful metrics to heighten clinical suspicion for postoperative complications.[2,3,8,10] This observational study examined patients undergoing distal pancreatectomy with splenectomy for elective indications to determine if postoperative leukocytosis can discriminate pathologic from physiologic disease states. A significant difference in mean leukocytosis on POD3 existed between patients with and without clinically relevant postoperative pancreatic fistula, surgical site infection, and major morbidity. WBC counts of $\geq 16 \times 10^9$/L on POD3 and changes in WBC from preoperative value of $\geq 9 \times 10^9$/L were the optimal metrics to detect all-cause and procedure-specific major morbidity after distal pancreatectomy and splenectomy.

A significant difference in mean WBC count was identified at several time points during postoperative recovery; however, in each major complication category (CR-POPF, SSI, major morbidity), the mean WBC count was significantly higher on postoperative day three. Patients undergoing DPS for elective indications have a more profound elevation in WBC count in the setting of postoperative complications along with an upward trend for leukocytosis into postoperative day five. While these two associations had been reported previously in the setting of emergent splenectomy,[2,3,10] this current study correlates postoperative leukocytosis with complications for patients undergoing elective DPS. Significant elevations in WBC were noted among those patients experiencing 90-day mortality; however, given the causes of death, this metric likely is not clinically useful for predicting mortality as three patients experienced sudden death and two patients experienced immediate postoperative multisystem organ failure.

The combination of minimally invasive techniques for DPS and enhanced recovery after surgery (ERAS) protocols has led to shortened hospital stays and patient discharge often within 48 h after operation. Unfortunately, examination of blood count metrics on postoperative day one and two failed to identify any reliable predictors of complications in this study. Absolute WBC count, the change in WBC compared to preoperative baseline (ΔWBC), and platelet-to-WBC ratio (Plt:WBC) on POD1 was not associated with any postoperative complications. Similar to previous reports, associations between platelet-to-WBC ratio and complications do not become apparent until postoperative day five.[8] With the increased application of minimally invasive DPS and early discharge pathways, early postoperative metrics for predicting procedure-specific complications will need to be investigated. Consideration should be given to measuring C-reactive protein (CRP) on POD1 and POD2, as CRP has become a reliable metric in predicting complications and readmission after colorectal surgery.[17–19] Given the results of the current study, enhanced recovery after surgery pathways in elective DPS could consider routine outpatient complete blood count on POD3 to assist surgeons in the early detection of postoperative complications after discharge.

Two metrics from routine complete blood counts on postoperative day three can aid acute risk assessment for postoperative complication and hospital readmission for individual patients recovering from elective DPS, POD3 WBC $\geq 16 \times 10^9$/L and POD3 ΔWBC $\geq 9 \times 10^9$/L. Although these metrics correlate with postoperative complications, the sensitivity of these two metrics for detecting major morbidity is less than ideal for elective DPS. An upcoming institutional study is evaluating the use of these metrics

Table 5
Sensitivity and specificity of postoperative day three absolute white blood cell count and change in white blood cell count from preoperative baseline in detecting major morbidity.

Major Morbidity	POD3 WBC $\geq 16 \times 10^9$/L	POD3 ΔWBC $\geq 9 \times 10^9$/L	POD3 Plt:WBC <20
Sensitivity	0.70	0.70	0.24
Specificity	0.56	0.61	0.83
AUC (95% CI)	0.70 (0.58–0.80)	0.70 (0.59–0.82)	0.49 (0.36–0.62)
P	0.004	0.001	0.9

Abbreviations: POD – postoperative day; WBC – white blood cell; L – liter; Plt:WBC – platelet-to-white-blood-cell-count ratio; AUC – area under curve; CI – confidence interval.

combined with CRP to improve the ability to detect developing postoperative morbidity.

The retrospective design of this study introduces limitations inherent to its observational data acquisition. Serologic and blood count data for patients undergoing any testing after postoperative day five were not evaluated. Metrics on postoperative day one or two were not predictive of any postoperative complications within 90 days of operation. The sensitivity and area under the curve values were suboptimal for an ideal diagnostic test on postoperative day three. This may be the result of improved complication rates observed in this study compared to previous institutional reports, particularly improvements in POPF (25%–18%), CR-POPF (16%–9%), and readmission rates (27%–15%).[20] Larger volume studies may assist with improving the diagnostic utility of these metrics. Given the sample size, this study was unable to further analyze the discriminatory ability of POD3 WBC and POD ΔWBC within the subgroups of operative technique or operative indication.

Conclusion

Patients who develop major complications after elective distal pancreatectomy with splenectomy are more likely to have an increased and prolonged elevation in postoperative white blood cell count. On postoperative day three, leukocytosis $\geq 16 \times 10^9$/L and an increase in white blood cell count of $\geq 9 \times 10^9$/L from preoperative baseline should raise concern for major postoperative complications.

Author contribution

Conception and design: TKM, JRB, SQ, TC, EPC, AN, CMS, NJZ, MGH

Acquisition, analysis, and interpretation of data: TKM, JRB, SQ, AJL, TC, MGH

Drafting and revising: TKM, JRB, SQ, AJL, TC, EPC, AN, CMS, NJZ, MGH

Final approval of work: TKM, JRB, SQ, AJL, TC, EPC, AN, CMS, NJZ, MGH

Agreement to be accountable: TKM, JRB, SQ, AJL, TC, EPC, AN, CMS, NJZ, MGH

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Declaration of competing interest

The authors declare no conflict of interest.

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