Preoperative leukocyte count and postoperative inpatient mortality in South African non-cardiac surgery patients

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Abstract

Background: Published studies investigating the relationship between preoperative leukocyte counts and postoperative inpatient mortality in South African (SA) non-cardiac surgery settings are scarce. This could have important implications for perioperative risk stratification in SA non-cardiac surgery settings. The aim of our study was to address this paucity in the literature.

Methods: We conducted an unmatched case-control study of patient data from the South African Surgical Outcomes Study. Data collected for each patient included demographic variables, comorbidities, procedure-related variables, and preoperative laboratory test results (including leukocyte counts). Local reference ranges were used to stratify preoperative leukocyte count into three categories: normal, leukocytopenia, and leukocytosis. The sample size for this study was 495 patients (case:control ratio of 1:3). Data were analyzed using appropriate univariate and multivariate statistical methods.

Results: Preoperative leukocytosis was associated with increased postoperative inpatient mortality (odds ratio: 1.95, 95% confidence interval: 1.05-3.63; p=0.034). Preoperative leukocytopenia was not associated with postoperative inpatient mortality (odds ratio: 0.40, 95% confidence interval: 0.05-3.40; p=0.400).

Conclusion: Preoperative leukocytosis is a risk factor for postoperative inpatient mortality in SA non-cardiac surgery patients. Studies evaluating the prognostic accuracy of preoperative leukocytosis for postoperative mortality in SA non-cardiac surgery settings are required.

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Introduction

Preoperative laboratory testing in non-cardiac surgery patients is required for effective patient management during the perioperative period.[1] Laboratory test results, when interpreted using appropriate reference ranges, can be used to diagnose subclinical preoperative comorbidity or predict poor postoperative outcomes in non-cardiac surgery patients. Tests such as leukocyte (white blood cell) counts are amongst the most common laboratory tests requested during the preoperative evaluation process.[1] The test involves the enumeration of leukocytes in the peripheral circulation.[2] The leukocyte count measures systemic inflammation and is standardized. The leukocyte count test is also widely available and inexpensive.[3]

Inflammation plays an important role in the pathophysiology of certain postoperative complications in non-cardiac surgery populations. Acute myocardial infarction in the perioperative period, which may afflict between 2% and 5% of non-cardiac surgery patients, might evolve as a result of inflammation and the actions of leukocytes, which destabilize coronary plaques. Destabilized coronary plaques might subsequently occlude the coronary vessels and compromise oxygen delivery to the myocardium, culminating in myocardial infarction.[4] A similar pathophysiology has been proposed for perioperative stroke.[5] As there is cardiovascular involvement in a substantial proportion of perioperative mortality,[6] it is likely that inflammation and leukocyte activity also play direct or indirect roles with regard to this patient outcome.

A large American study of non-cardiac surgery patients conducted by Bishop et al. reported that patients with elevated preoperative leukocyte counts (leukocytosis) were at a 52% higher risk of postoperative mortality when compared with patients who had normal preoperative leukocyte counts.[7] In the same study, low preoperative leukocyte counts (leukocytopenia) were associated with a 17% lower risk of postoperative mortality.[7] The relationship between preoperative leukocyte count and postoperative mortality in a South African (SA) surgical setting has not been adequately described. Due to differences in the clinical importance of several risk factors between SA and American surgical populations,[8] it might be inappropriate to apply the findings from American surgical populations in SA settings. Establishing the relationship between preoperative leukocyte count and postoperative mortality would have potential implications for perioperative risk stratification in SA non-cardiac surgery patients. Therefore, the aim of this study was to address this paucity in the literature.

Methods

Study Design and Setting

We conducted an unmatched case-control analysis of data collected during the South African Surgical Outcomes Study (SASOS), which was a 2014 surgical audit of SA public hospitals.[9]

Patients, Data, and Definitions

Data for almost 4000 adult SA non-cardiac surgery patients collected during SASOS is available to the public as a de-identified database.[9] Data collected during SASOS included patient age, gender, ethnicity, American Society of Anesthesiologists (ASA) score, comorbidity, preoperative laboratory test results (including leukocyte measurements), procedure data, and inpatient survival outcomes.[9] Rather than using the definitions of various leukocyte count categories from the study of Bishop et al. we chose to use the SA laboratory reference ranges provided by Lawrie et al. to define leukocyte count categories in this study.[10] Our reason for this is that there are ethnic differences in leukocyte count,[11] and laboratory reference ranges used in a predominantly Caucasian population (such as that in the United States) would not be applicable in a predominantly black African population (such as that in SA). The definitions for the various thresholds of preoperative leukocyte count used in this study were as follows: Leukocytopenia – <3.92 cells/mm^3 for males and <3.90 cells/mm^3 for females; Normal – 3.92 cells/mm^3 to 10.4 cells/mm^3 for males and 3.90 cells/mm^3 to 12.60 cells/mm^3 for females; Leukocytosis – >10.4 cells/mm^3 for males and >12.60 cells/mm^3 for females. Cases were defined as patients who died in hospital following their surgical procedure. Controls were defined as patients who were discharged alive from hospital following their surgical procedure. Patients with incomplete datasets were omitted.

Sampling and Data Analysis

The sample size required for this study was 495 patients (case:control ratio = 1:3, 99 cases and 396 controls). The required number of cases and controls were selected from the SASOS database using a random number generator, following the exclusion of patients with incomplete datasets. Random selection of cases and controls is recommended to reduce bias in case-control studies.[12] Data were analysed using univariate (chi-squared test or Fisher's exact test for categorical data) and multivariate (unconditional logistic regression model) statistical methods. These statistical methods have been recommended for the analysis of data in unmatched case-control studies.[12] Results for the univariate statistical analysis are presented as frequencies and percentages, or medians with interquartile ranges (IQR). Results for the multivariate statistical analysis are presented as odds ratios (OR) with 95% confidence intervals (CI). A p-value <0.05 was considered to be a statistically significant result. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp, USA).

Ethical approval

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, SA (Protocol: BE002/18).

Results

The characteristics of the study sample are shown in Table 1. The median age of the study sample was 43.0 (IQR: 30.0-60.0) years. A total of 260/495 patients (52.5%) were female. Non-white patients comprised 88.9% of the study sample (440/495 patients). A total of 345/495 patients (59.7%) had an ASA score >2. Current smoking was reported for 74.9% of the study sample (371/495 patients). The prevalence of comorbidity in the study sample ranged from 0.4% for cirrhosis, to 51.5% for anemia. Miscellaneous comorbidity was reported for 39.6% of the study sample (196/495 patients). A total of 324/495 patients (65.5%) had normal preoperative leukocyte counts, 29.7% (147/495 patients) had preoperative leukocytosis, and 4.8% (24/495 patients) had preoperative leukocytopenia. Non-communicable disease was the indication for surgery in 247/495 patients (49.9%). Urgent/emergent surgery was performed in 286/495 patients (57.8%). Major surgery was performed in 138/495 patients (27.9%). A total of 351/495 patients (70.9%) had their surgeries performed under general anaesthesia.

Case and control groups differed statistically with respect to several variables investigated in this study, including age, ASA score, cardiovascular disease, metastatic cancer, HIV, renal impairment, preoperative anemia, preoperative leukocyte count, urgent or emergent procedures, and major surgery (Table 1).

The results of the multivariate statistical analysis are shown in Table 2. Statistically significant multivariate associations were observed between the following characteristics and postoperative inpatient mortality: Increasing age (OR: 1.04, 95% CI: 1.02-1.06; p<0.001), ASA score >2 (OR: 4.92, 95% CI: 2.65-9.14; p<0.001), renal impairment (OR: 6.45, 95% CI: 1.83-22.74; p=0.004), urgent/emergent surgery (OR: 2.71, 95% CI: 1.37-5.38; p=0.004), and major surgery (OR: 2.65, 95% CI: 1.36-5.14; p=0.004). A statistically significant multivariate association between preoperative leukocytosis and postoperative inpatient mortality was also observed (OR: 1.95, 95% CI: 1.05-3.63; p=0.034). No such multivariate association could be established between preoperative leukocytopenia and inpatient mortality (OR: 0.40, 95% CI: 0.05-3.40; p=0.400).

Table 3 shows the impact of preoperative leukocyte count on other reported outcomes reported in the SASOS dataset. Statistically significant differences across categories of leukocyte count were noted for both unplanned critical care admission and postoperative length of stay. Leukocytosis was associated with an increase in unplanned admissions to a critical care unit when compared with the other categories of leukocyte count. Leukocytosis was also associated with increased postoperative length of stay when compared with the other categories of leukocyte count.

Discussion

We report univariate and multivariate statistical associations between preoperative leukocytosis and postoperative mortality in this study. The results from our multivariate statistical analysis suggest a 95% higher risk of postoperative mortality associated with preoperative leukocytosis when compared with normal preoperative leukocyte counts. Although our overall finding of a higher risk of postoperative mortality in patients with preoperative leukocytosis is in agreement with the findings of Bishop et al.,

Table 1. Distribution of characteristics in the study sample and results of the univariate statistical analysis*

Characteristic	Subcategory	All patients (n=495)	Cases (n=99)	Controls (n=396)	p-value
Age in years (IQR)	N/A	43.0 (30.0-60.0)	56.0 (39.0-65.0)	40.0 (29.0-58.0)	<0.001
Gender					0.177
	Male	235 (47.5)	53 (53.5)	182 (46.0)	
	Female	260 (52.5)	46 (46.5)	214 (54.0)	
Ethnicity					0.721
	White	55 (11.1)	12 (12.1)	43 (10.9)	
	Non-White	440 (88.9)	87 (87.9)	353 (89.1)	
ASA score >2					<0.001
	Yes	150 (30.3)	69 (69.7)	81 (20.5)	
	No	345 (69.7)	30 (30.3)	315 (79.5)	
Current smoker					0.324
	Yes	124 (25.1)	21 (21.2)	103 (26.0)	
	No	371 (74.9)	78 (78.8)	293 (74.0)	
Cardiovascular disease					0.030
	Yes	23 (4.6)	9 (9.1)	14 (3.5)	
	No	472 (95.4)	90 (90.9)	382 (96.5)	
Metastatic cancer					<0.001
	Yes	23 (4.6)	12 (12.1)	11 (2.8)	
	No	472 (95.4)	87 (87.9)	385 (97.2)	
Cirrhosis					0.360
	Yes	2 (0.4)	1 (1.0)	1 (0.3)	
	No	493 (99.6)	98 (99.0)	395 (99.7)	
Chronic obstructive pulmonary disease					0.528
	Yes	33 (6.7)	8 (8.1)	25 (6.3)	
	No	462 (93.3)	91 (91.9)	371 (93.7)	
HIV					0.042
	Yes	78 (15.8)	9 (9.1)	69 (17.4)	
	No	417 (84.2)	90 (90.9)	327 (82.6)	
Diabetes					0.050
	Yes	53 (10.7)	16 (16.2)	37 (9.3)	
	No	442 (89.3)	83 (83.8)	359 (90.7)	
Renal impairment					<0.001
	Yes	21 (4.2)	15 (15.2)	6 (1.5)	
	No	474 (95.8)	84 (84.8)	390 (98.5)	
Preoperative anemia					<0.001
	Yes	255 (51.5)	70 (70.7)	185 (46.7)	
	No	240 (48.5)	29 (29.3)	211 (53.3)	
Other comorbidity					0.024
	Yes	299 (60.4)	50 (50.5)	249 (62.9)	
	No	196 (39.6)	49 (49.5)	147 (37.1)	
Preoperative leukocyte count					<0.001
	Leukocytosis	147 (29.7)	52 (52.5)	95 (24.0)	
	Leukocytopenia	24 (4.8)	1 (1.0)	23 (5.8)	
	Normal	324 (65.5)	46 (46.5)	278 (70.2)	
Indication for surgery					0.229
	Non-communicable disease	247 (49.9)	42 (42.4)	205 (51.8)	
	Injury/Trauma	145 (29.3)	32 (32.3)	113 (28.5)	
	Infectious disease	103 (20.8)	25 (25.3)	78 (19.7)	
Urgent/emergent surgery					<0.001
	Yes	286 (57.8)	79 (79.8)	207 (52.3)	
	No	209 (42.2)	20 (20.2)	189 (47.7)	
Major surgery					<0.001
	Yes	138 (27.9)	46 (46.5)	92 (23.2)	
	No	357 (72.1)	53 (53.5)	304 (76.8)	
General anaesthesia					0.235
	Yes	351 (70.9)	75 (75.8)	276 (69.7)	
	No	144 (29.1)	24 (24.2)	120 (30.3)	

*Results expressed as frequencies (%) or medians (IQR). IQR: Interquartile range, N/A: Not applicable, ASA: American Society of Anesthesiologists

Table 2. Results of the multivariate statistical analysis

Clinical Characteristic	Subcategory	OR (95% CI)	p-value
Age (per year increase)	N/A	1.04 (1.02-1.06)	<0.001
Gender	Male	1.03 (0.55-1.92)	0.928
	Female	Reference	-
Ethnicity	White	0.73 (0.29-1.84)	0.511
	Non-white	Reference	-
ASA score >2	Yes	4.92 (2.65-9.14)	<0.001
	No	Reference	-
Current smoker	Yes	0.87 (0.43-1.76)	0.696
	No	Reference	-
Cardiovascular disease	Yes	0.75 (0.18-3.14)	0.693
	No	Reference	-
Metastatic cancer	Yes	1.84 (0.44-7.67)	0.402
	No	Reference	-
Cirrhosis	Yes	1.01 (0.04-23.40)	0.993
	No	Reference	-
Chronic obstructive pulmonary disease	Yes	0.34 (0.09-1.29)	0.112
	No	Reference	-
HIV	Yes	0.39 (0.09-1.63)	0.196
	No	Reference	-
Diabetes	Yes	0.53 (0.14-1.95)	0.529
	No	Reference	-
Renal impairment	Yes	6.45 (1.83-22.74)	0.004
	No	Reference	-
Preoperative anemia	Yes	1.44 (0.77-2.69)	0.254
	No	Reference	-
Other comorbidity	Yes	0.65 (0.18-2.36)	0.507
	No	Reference	-
Preoperative leukocyte count	Leukocytosis	1.95 (1.05-3.63)	0.034
	Leukocytopenia	0.40 (0.05-3.40)	0.400
	Normal	Reference	-
Indication for surgery	Non-communicable disease	0.66 (0.30-1.42)	0.287
	Injury/Trauma	1.57 (0.69-3.56)	0.285
	Infectious disease	Reference	-
Urgent/emergent surgery	Yes	2.71 (1.37-5.38)	0.004
	No	Reference	-
Major surgery	Yes	2.65 (1.36-5.14)	0.004
	No	Reference	-
General anaesthesia	Yes	1.73 (0.82-3.63)	0.148
	No	Reference	-

IQR: Interquartile range, N/A: Not applicable, ASA: American Society of Anesthesiologists, OR: Odds ratio, CI: Confidence interval.

Table 3. Impact of leukocyte count on other outcomes reported in the SASOS dataset*

Outcome	Leukocytosis (n=147)	Leukocytopenia (n=24)	Normal (n=324)	p-value
Unplanned critical care admission	33 (22.4)	1 (4.2)	32 (9.9)	0.001
Median postoperative length of stay in days	5.0 (2.0-15.0)	3.0 (1.0-12.3)	3.0 (1.0-8.0)	<0.001

*Results expressed as frequencies (%) or medians (IQR). IQR: Interquartile range. Data analyzed using the chi-squared test and the Kruskal-Wallis test.

our study reports a higher magnitude of risk associated with preoperative leukocytosis. Another difference between our study and that of Bishop et al. was that we did not report a reduction in the risk of postoperative mortality in patients with preoperative leukocytopenia, while Bishop et al. reported a 17% reduction in the risk of postoperative mortality in patients with preoperative leukocytopenia.[7] Our findings are suggestive of potential variations in the importance of certain perioperative risk factors between SA and overseas surgical populations.[8]

There are two potential explanations for the difference in findings for leukocytopenia and postoperative mortality between the current study and that of Bishop et al. Firstly, rather than excluding patients with missing data from the final analysis (as per the current study), Bishop et al. used multiple imputation techniques to account for missing laboratory data.[7] There is a possibility that some of missing laboratory data was incorrectly imputed, thereby raising some concern about the estimates of risk obtained from the regression models in the study from Bishop et al.[7] Secondly, the study of Bishop et al. excluded patients with ASA>3, while these patients were included in the current study.[7] The exclusion of patients in poor physical condition in the study of Bishop et al. may have introduced bias toward a "healthier" population into their regression analysis, thereby casting doubts on their findings for leukocytopenia.[7]

As the leukocyte count is a component of the ubiquitous "full blood count test",[1] our findings raise further interest in the prognostic utility of preoperative leukocytosis in resource-limited settings. Furthermore, perioperative risk reduction by correcting preoperative leukocytosis should be explored. It might be beneficial to initiate preoperative statin therapy in SA patients with preoperative leukocytosis. Statin therapy is known to downregulate the inflammatory response, of which leukocytes are an important component.[13] In addition, several clinical studies conducted elsewhere have reported that perioperative mortality is lower in patients who receive statin therapy, whereas a higher rate of poor postoperative outcomes is observed when statin therapy is withdrawn.[14]

All other characteristics besides preoperative leukocyte count were included in the multivariate statistical analysis in order to account for possible confounders. This was in accordance with current methodological approaches for the analysis of data in unmatched case-control studies.[12] While we found independent multivariate statistical associations between some of these characteristics and postoperative mortality, we advise caution in interpreting these results as this study was specifically designed to detect potential statistical associations between preoperative leukocyte count and postoperative mortality. Therefore, it is possible that our study is not adequately powered to detect valid statistical associations between other variables and postoperative mortality. Additional characteristic-specific analyses of the SASOS dataset should be conducted to investigate the relationship between other characteristics of interest and postoperative mortality.

Our study did have limitations. While we attempted to control for as many potential confounders as possible, we were limited to the variables collected as part of the SASOS database.[9] For instance, the data collection during SASOS did not include medication use and this could not be included as a confounder in our analysis. Specific hospital information and information related to mortality risk for types of surgery could also not be investigated as this information was not available in the public use SASOS dataset. In addition, we only report on inpatient postoperative mortality as follow-up in surgical patients discharged from hospital was not conducted during SASOS.[9] Also regarding the study outcome, the specific cause of death was not reported in the SASOS dataset. Rather, this study reports all-cause mortality. However, the identification of specific, clear-cut causes of death following surgery was also noted as a challenge in the study of Bishop et al.[7] Research studies which incorporate solutions to these limitations are required.

Conclusion

We found preoperative leukocytosis to be a risk factor for postoperative mortality in SA non-cardiac surgery patients. We did not observe any statistical association between preoperative leukocytopenia and postoperative mortality in SA non-cardiac surgery patients. We recommend further research be performed to confirm our findings, address the limitations of our study, and evaluate the diagnostic accuracy of preoperative leukocyte counts in resource-limited settings such as SA.

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