Perioperative lymphocytopenia predicts mortality and severe complications after intestinal surgery

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Background: Patterns of white blood cells differential count with low lymphocyte number have been associated with poor outcome following sepsis, burns and trauma. Lymphocytopenia, measured preoperatively or in response to surgical stress, may affect complications after bowel resection.

Methods: Clinical characteristics and white blood cells differential count values, measured both pre- and post-operatively of a cohort of patients submitted to intestinal resection and anastomosis from June 2014 to June 2017 in our General Surgery Division, were retrospectively analyzed. Multivariate logistic regression was used to determine the dependence of mortality and postoperative complications from the clinical characteristics of patients and white blood cells differential count values.

Results: A total of 301 consecutive patients were studied; 165 (54.8%) were male; mean age was 70 years. Overall, the rate of in-hospital 30-day mortality was 4%. Post-operative morbidity was observed in 124 (41.2%). On multivariate analysis, age adjusted Charlson Comorbidity Index, low preoperatively lymphocyte count, high preoperative monocyte count, high postoperative neutrophil count and anastomotic leak were independently associated with increased in-hospital mortality. Preoperative lymphocytopenia and rectal resection were independently associated with high morbidity rate, while low postoperative lymphocyte count was associated with an increased risk of anastomotic leak.

Conclusions: Perioperative lymphocytopenia is associated with 30-days mortality, severe complications and anastomotic leak after bowel resection surgery. These routinely available laboratory data could help to identify patients at high-risk for developing complications.

Keywords: Intestinal surgery; mortality; lymphocytopenia; lymphocyte count; postoperative complications

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Introduction

Both cellular and humoral immune mechanisms play an important role in the systemic response to surgical injury and tissue healing, especially after procedures requiring visceral resections (1). Major surgery induces an activation of the hypothalamus-hypophysis-adrenal axis, followed by a spleen rapid mobilization of neutrophilic granulocytes and their massive influx in the bloodstream together with blood lymphocyte depletion. This reversible deficit of lymphocytes in the blood is caused by a redistribution of these cells into primary and secondary lymphatic organs, which happens in few hours (2). The recovery of lymphocyte count in peripheral blood takes approximately 36 to 72 hours. At present, there is no clear association, demonstrated in clinical settings, between postoperative complications and immune impairment of the patients. Nevertheless, some previous exploratory experiences are intriguing (3,4). Peripheral blood total lymphocyte count, assessed by differential automated count, has been found to be a valuable predictor of survival in patients with advanced cancer, both at baseline and after different pharmacologic treatment (5,6).

We hypothesized that major complications after abdominal surgery were associated with impaired immune response of the patients. The aim of this exploratory retrospective study is to verify whether postoperative mortality, postoperative morbidity and anastomotic leak (AL) are associated with a selected pattern of white blood cell (WBC) differential count, in patients who underwent abdominal surgery with bowel anastomosis without diverting stoma. In order to examine their real prognostic significance, we assessed the WBC differential count parameters together with major clinical variables, which are known to affect postoperative outcomes.

Methods

Inclusion and exclusion criteria

After local Ethics Committee approval (protocol 0016932/17U), clinical, pathologic and laboratory data of patients who underwent consequentially lower gastro-intestinal surgery (urgent or elective) in our General Surgery Division since June 2014 to June 2017 were retrospectively collected and analyzed. All patients received bowel resection (any intestinal segment: jejunum-ileum, colon or rectum) and anastomosis. Patients submitted to intestinal resection with concomitant diverting stoma or patients who underwent a Hartmann's procedure were excluded. In addition, patients with history of neo-adjuvant radio/chemotherapy or lymphoma/leukemia were excluded from the study.

Data collection and selection of variables

Written informed consent for data collection was obtained from each patient. Population, laboratory, intra- and post-operative data were collected by the investigators from the hospital electronic records of the General Surgery Division.

Routine demographic variables were obtained, including age at time of surgery and gender. Age-adjusted Charlson comorbidity index (ACCI) score of each patient was calculated (7). Clinical, operative, and pathological characteristics were collected, including type of resection (small intestinal, colonic or rectal resections), operative time, presence of bowel obstruction, peritonitis or intestinal ischemia, diagnosis of inflammatory bowel disease (IBD) and use of steroids. In case of colorectal cancer, tumor stage was registered. Complete blood count (CBC) at baseline (by blood samples taken within one month before surgery in elective procedures and at the time of admission in urgent surgery) and values taken on postoperative days (24–72 hours) were registered. In case of more than one postoperative value being available, the median value was calculated. Laboratory parameters included absolute neutrophil count, absolute lymphocyte count and absolute monocyte count. Overall 23 predictors of interest were selected: age, gender, ACCI, urgent operation, bowel obstruction, peritonitis, intestinal ischemia, colorectal cancer, cancer stage I–II, cancer stage III–IV, IBD, steroid therapy, operation time, small bowel resection, right hemicolectomy, left hemicolectomy, rectal resection, pre- and postoperative lymphocyte count, pre- and postoperative monocyte count and pre- and postoperative neutrophil count.

Outcomes

The primary clinical outcome was post-operative mortality; secondary outcomes were postoperative morbidity and occurrence of AL. Postoperative mortality was defined as in-hospital death occurring within 30 days after surgery. Therapeutic procedures for treatment of complications, reoperations, unplanned admissions to ICU, were registered and classified according to the Clavien-Dindo grading (8). All patients with a Clavien-Dindo grade II or lower were considered to have developed a minor complication, while those with a Clavien-Dindo grade III or higher were considered to have suffered a major complication. Deaths were excluded from the analysis of post-operative morbidity.

AL was graded according to International Study Group of Rectal Cancer (ISGRC) criteria as follows: AL requiring no active therapeutic intervention (grade A), AL requiring active therapeutic intervention but manageable without re-laparotomy (grade B) and AL requiring re-laparotomy (grade C) (9). Of interest, ISGRC proposed a grading

Table 1 Clinical and operative characteristics of the patients.

Characteristic	Value, N=301
Age, years, mean ± SD	70±14
Male, n (%)	165 (54.8)
Age-adjusted CCI (>5), n (%)	140 (46.5)
Urgent/emergency operation, n (%)	177 (58.8)
Bowel obstruction, n (%)	89 (29.6)
Peritonitis, n (%)	59 (19.6)
Intestinal ischemia, n (%)	29 (9.6)
Colorectal cancer, n (%)	180 (59.8)
Stage I–II, n (%)	94 (31.2)
Stage III–IV, n (%)	86 (28.6)
Inflammatory bowel disease, n (%)	13 (4.3)
Steroid therapy, n (%)	12 (4.0)
Operation time (>150 min), n (%)	150 (49.8)
Small bowel resection, n (%)	95 (31.6)
Right hemicolectomy, n (%)	76 (25.2)
Left hemicolectomy, n (%)	100 (33.2)
Rectal resection, n (%)	30 (10.0)

system for AL in patients submitted to anterior resection for rectal cancer. We decided to adopt this classification system because it represents the most validated grading score in the literature and can be easily applied even when different types of intestinal anastomosis are taken in consideration. ALs were diagnosed clinically and confirmed by imaging. Because of their minor clinical significance, grade A leakages were not considered in our analysis.

Statistical analysis

Continuous variables were expressed as means ± standard deviations. Categorical variables were presented as frequencies and percentages. The outcomes of the study were expressed as dichotomous data and consequently, a logistic regression model was used for all of them. The multicollinearity of continuous variables was measured by Pearson correlation coefficients (coefficient >0.8 was considered indicative of high collinearity of two variables). Initial variable analysis was carried out with univariate logistic regression: all variables that were significant at P value <0.25 (Wald test) were considered for the multivariable model (10). The main effects model was built with a forward sequential logistic regression with selection of variables associated with a significant p value. To evaluate the relevance of potential confounders and clinically relevant interactions, likelihood ratio tests were performed between models with and without confounders and interactions (10). In the final regression model, the results were presented as odds ratio with 95% confidence interval and P value <0.05. The Hosmer-Lemeshow test was performed for assessing goodness of fit of the final model. The area under the receiving operating characteristic (ROC) curve was calculated to illustrate the ability of the multivariable logistic regression model to predict the primary outcome of the study. Statistical analysis was performed by using STATA® version 14 (StataCorp LLC, College Station, TX).

Results

During the study period (June 2014 to June 2017) 301 patients were retrospectively analyzed. The mean age of our sample was 70 years (range, 25–93 years). One hundred and sixty-five (54.8%) patients were males and ACCI mean value was 5 (range, 0–14 years). Colorectal cancer was the predominant indication for surgery (59.8%), with 86 (28.6%) patients having an advanced disease at presentation (stage III–IV). Urgent surgery was performed in 177 (58.8%) cases. Eighty-nine (29.6%) patients had bowel obstruction at time of surgery, while 59 (19.6%) patients had local or generalized peritonitis due to intestinal perforation. Left hemicolectomy was the most frequent procedure (100 cases, 33.2%). Mean operation time was 2.5 hours (range, 32 minutes to 9.25 hours) with 150 (49.8%) procedures lasting longer than 150 minutes. Twelve (4.0%) patients were taking steroids at the time of surgery, while 13 (4.3%) people had a history of IBD. Clinical and operative characteristics are listed in *Table 1*.

Postoperative mortality

Twelve people died within 30 days after surgical operation, resulting in an in-hospital postoperative mortality rate of 4%. Univariate analysis showed 11 variables associated with higher risk of postoperative mortality: age (P=0.008), ACCI (P<0.001), urgent/emergent operation (P=0.094), bowel obstruction (P=0.125), right hemicolectomy (P=0.217), AL (grade B,C) (P=0.004), preoperative lymphocyte count (P=0.100), preoperative neutrophil count (P=0.213),

Table 2 Variables associated with postoperative 30-day mortality

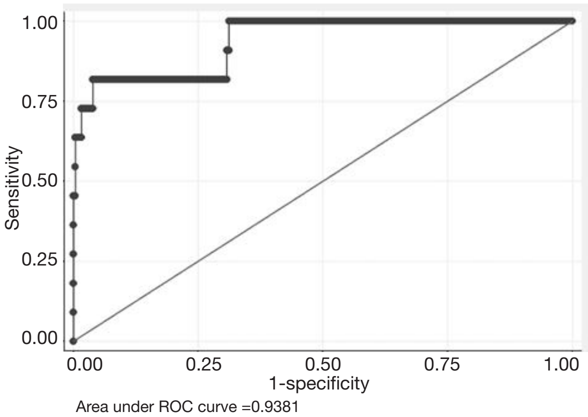
Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.10 (1.02–1.19)	0.008		
Male	1.68 (0.49–5.70)	0.405		
Age-adjusted CCI	1.54 (1.24–1.91)	<0.001	1.69 (1.20–2.36)	0.002
Urgent/emergent operation	3.10 (0.82–11.7)	0.094		
Bowel obstruction	2.48 (0.77 –7.91)	0.125		
Peritonitis	2.01 (0.52–7.76)	0.308		
Intestinal ischemia	–	–		
Cancer	2.07 (0.54–7.80)	0.283		
Stage I–II	1.10 (0.32–3.76)	0.873		
Stage III–IV	1.83 (0.56–5.94)	0.312		
Operative time (>150 min)	0.99 (0.99–1.01)	0.805		
Small bowel resection	1.10 (0.32–3.76)	0.873		
Right hemicolectomy	2.07 (0.65–6.60)	0.217		
Left hemicolectomy	1.51 (0.44–5.15)	0.513		
Rectal resection	–	–		
Anastomotic leak (grade B, C)	5.73 (1.71–19.1)	0.004	17.22 (2.60–113.97)	0.003
Pre-op lymphocyte count	0.39 (0.12–1.20)	0.100	0.11 (0.02–0.72)	0.021
Post-op lymphocyte count	1.19 (0.35–3.97)	0.776		
Pre-op neutrophil count	1.04 (0.97–1.11)	0.213		
Post-op neutrophil count	1.29 (1.12–1.48)	<0.001	1.32 (1.07–1.62)	0.008
Pre-op monocyte count	3.51 (1.31–9.38)	0.012	5.64 (1.13–28.03)	0.034
Post-op monocyte count	1.84 (0.89–3.78)	0.098		

preoperative monocyte count (P=0.012), postoperative neutrophil count (P<0.001), and postoperative monocyte count (P=0.098).

ACCI (OR =1.69; 95% CI, 1.20–2.36; P=0.002), AL (grade B,C) (OR =17.22; 95% CI, 2.60–113.97; P=0.003), low preoperative lymphocyte count (OR =0.11; 95% CI, 0.02–0.72; P=0.021), high preoperative monocyte count (OR =5.64; 95% CI, 1.13–28.03; P=0.034), and high postoperative neutrophil count (OR =1.32; 95% CI, 1.07–1.62; P=0.008) were significantly associated with 30-days mortality in the multivariate analysis (*Table 2*). The models that included the possible confounders present in the literature (age, urgent/emergent surgery, malignant tumor) were not more informative than the final model at likelihood ratio test. No significant interactions were present in the final model. The P value of the Hosmer-Lemeshow (goodness-of-fit) test was 0.657. The area under ROC curve of the multivariate regression model predicting postoperative mortality was 0.938 (*Figure 1*).

Postoperative morbidity

Postoperative morbidity was observed in 124 (41%) patients. Minor complications according to Clavien-Dindo classification occurred in 80 (27%) patients: 20 (7%) patients with grade I and 60 (20%) patients with grade II complications respectively. Major complications, graded as Clavien-Dindo III and IV, occurred in 44 (15%) patients, distributed as follows: 12 (4%) patients with grade III-a, 25 (8%) patients with grade III-b and 7 (2%) patients with



Variables	OR (95% confidence interval)	P value
Age-adjusted CCI	1.69 (1.20–2.36)	0.002
Anastomotic leak (grade B, C)	17.22 (2.60–113.97)	0.003
Pre-op lymphocyte count	0.11 (0.02–0.72)	0.021
Post-op neutrophil count	1.32 (1.07–1.62)	0.008
Pre-op monocyte count	5.64 (1.13–28.03)	0.034

Figure 1 Receiver-operating characteristic (ROC) curve analysis illustrating the ability of the multiple logistic regression model to predict 30 days postoperative mortality.

grade IV complications. Univariate analysis showed that age (P=0.219), male sex (P=0.029), operative time (P=0.097), small bowel resection (P=0.027), right hemicolectomy (P=0.070), rectal resection (P=0.019), pre-operative low lymphocyte count (P=0.019), postoperative low lymphocyte count (P=0.043) and postoperative high monocyte count (P=0.112) were statistically associated with major postoperative complications. In the multivariate analysis rectal resection (OR =2.83; 95% CI, 1.16–6.89; P=0.021) and low pre-operative lymphocyte count (OR =0.50; 95% CI, 0.27–0.93; P=0.029) were found to be independent variables associated with the development of grade III-IV complications (*Table 3*). The models with the possible confounders (age, urgent/emergent surgery, malignant tumor) were not more informative than the final model at likelihood ratio test. No significant interactions were present in the final model. The P value of the Hosmer-Lemeshow (goodness-of-fit) test was 0.275.

Anastomotic leak

Anastomotic leaks occurred in 37 (12%) patients (grade B and C). Of these 22 cases needed re-laparotomy (grade C), while 15 patients were treated by percutaneous drainage and antibiotics (grade B). Univariate analysis showed 12 variables associated with AL: male gender (P=0.249), ACCI (P=0.226), urgent/emergent operation (P=0.214), cancer (P=0.085), cancer stage I–II (P=0.096), operative time (>150 min) (P=0.027), small bowel resection (P=0.183), rectal resection (P=0.015), postoperative lymphocyte count (P=0.009), preoperative neutrophil count (P=0.039), preoperative monocyte count (P=0.110) and postoperative monocyte count (P=0.076). In the multivariate analysis low postoperative lymphocyte count (OR =0.31; 95% CI, 0.13–0.75; P=0.010) was significantly associated with developing a leak. It must be noted that rectal resection (OR =2.59; 95% CI, 0.99–6.76; P=0.051) was associated with a high risk of AL, with a borderline P value, very close to the conventional significance level (P=0.05), although odds ratio confidence interval contained the unit (*Table 4*). The models that included the possible confounders (age, urgent/emergent surgery, malignant tumor) were not more informative than the final model at likelihood ratio test. The P value of the Hosmer-Lemeshow (goodness-of-fit) test was 0.528.

Discussion

In this study, we investigated the relevance of WBC differential count patterns as independent risk factors of postoperative morbidity and mortality in patients who underwent intestinal resection and anastomosis, together with known clinical risk factors. We found that preoperative lymphocytopenia was independently associated with postoperative mortality and morbidity, while a low postoperative lymphocyte count was predictive of AL.

Many clinical variables seem to be involved in postoperative mortality after intestinal resection: advanced age, male sex, urgent surgery, cancer, total colectomy and AL (11-15). Even if large retrospective studies have assessed the postoperative mortality of colorectal surgery patients, nevertheless there is no clear consensus regarding major risk factors (11-15).

The possible confounders in the relationship between mortality/morbidity and WBC count parameters were tested in our model of multivariable regression: age, urgent surgery and malignant tumor. Moreover, we employed a restriction criterion for such conditions known to be cause of lymphocytopenia (neo-adjuvant radiotherapy or chemotherapy).

Differently from the majority of previous studies, urgent/

Table 3 Variables associated with postoperative morbidity (grade III–IV, according to Clavien-Dindo classification)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.01 (0.99–1.04)	0.219		
Male	0.48 (0.25–0.92)	0.029		
Age-adjusted CCI	1.05 (0.94–1.17)	0.359		
Urgent/emergent operation	1.02 (0.53–1.94)	0.941		
Bowel obstruction	1.01 (0.50–2.04)	0.976		
Peritonitis	0.73 (0.27–1.98)	0.543		
Intestinal ischemia	1.55 (0.59–4.05)	0.371		
Cancer	1.10 (0.57–2.12)	0.772		
Stage I–II	1.15 (0.58–2.27)	0.677		
Stage III–IV	0.95 (0.46–1.96)	0.909		
Operative time (>150 min)	1.00 (0.99–1.01)	0.097		
Small bowel resection	2.08 (1.08–4.01)	0.027		
Right hemicolectomy	0.48 (0.22–1.06)	0.070		
Left hemicolectomy	0.83 (0.38–1.77)	0.636		
Rectal resection	2.79 (1.18–6.58)	0.019	2.83 (1.16–6.89)	0.021
Pre-op lymphocyte count	0.48 (0.26–0.88)	0.019	0.50 (0.27–0.93)	0.029
Post-op lymphocyte count	0.44 (0.20–0.97)	0.043		
Pre-op neutrophil count	1.01 (0.94–1.07)	0.796		
Post-op neutrophil count	1.01 (0.90–1.11)	0.914		
Pre-op monocyte count	1.02 (0.38–2.74)	0.963		
Post-op monocyte count	0.31 (0.07–1.30)	0.112		

emergent surgery and age were associated with mortality at univariate analysis, but not at multivariate analysis (11-13). On the other side, we observed that ACCI and AL were significantly associated with in-hospital 30-day death, in accordance to two prior studies (14,15). The ACCI summarizes information about the presence of a number of medical conditions in order to create a single measure of comorbidity. It has showed a good ability to discriminate the outcomes, with a special regard to hospital mortality (16).

In the same way, a large amount of studies has been devoted to the study of AL and other postoperative complications after intestinal resection. In these studies, several clinical and biologic findings have been found to be associated with a higher risk of AL, including male sex, emergency surgery, rectal resection, operative time, steroid therapy, nonsteroidal anti-inflammatory drugs and obesity, showing a large variability in the results (17-20). In our analysis, rectal resection was significantly associated with both AL and postoperative morbidity.

In our retrospective study, we found that the introduction of the differential WBC count in the statistical analysis was able to identify a sub-set of patients who developed severe complications and death after surgery. Interestingly, fluctuations in WBC differential count showed the same or even a stronger value to predict poor outcomes compared to the traditional high-risk factors associated with mortality, morbidity and AL after intestinal surgery. In fact, patients showed different outcomes according to their immune status at baseline and their immune response to surgical trauma. Patients who had a normal immune pattern, represented by regular lymphocyte and monocyte count

Table 4 Variables associated with anastomotic leak (Grade B-C according to ISGRC criteria)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.01 (0.98–1.03)	0.439		
Male	0.66 (0.33–1.32)	0.249		
Age-adjusted CCI	1.07 (0.95–1.20)	0.226		
Urgent/emergent operation	0.64 (0.31–1.29)	0.214		
Bowel obstruction	0.62 (0.27–1.42)	0.261		
Peritonitis	0.90 (0.33–2.45)	0.839		
Intestinal ischemia	1.15 (0.37–3.53)	0.796		
Cancer	1.95 (0.91–4.21)	0.085		
Stage I–II	1.81 (0.90–3.66)	0.096		
Stage III–IV	1.06 (0.50–2.26)	0.868		
Operative time (>150 min)	1.01 (1.00–1.01)	0.027		
Small bowel resection	0.57 (0.25–1.30)	0.183		
Right hemicolectomy	1.10 (0.53–2.26)	0.792		
Left hemicolectomy	0.65 (0.27–1.56)	0.347		
Rectal resection	3.03 (1.23–7.43)	0.015	2.59 (0.99–6.76)	0.51
Pre-op lymphocyte count	0.73 (0.40–1.31)	0.300		
Post-op lymphocyte count	0.31 (0.12–0.75)	0.009	0.31 (0.13–0.75)	0.010
Pre-op neutrophil count	0.86 (0.74–0.99)	0.039		
Post-op neutrophil count	0.95 (0.84–1.07)	0.416		
Pre-op monocyte count	0.33 (0.08–1.28)	0.110		
Post-op monocyte count	0.23 (0.04–1.15)	0.076		

at baseline, postoperative recovery of lymphocyte count and usual increase of neutrophils at days 1 to 3, frequently had an uneventful postoperative course or developed mild complications (grade I–II, Clavien-Dindo classification). Differently, patients showing a low lymphocyte count and a high monocyte count at baseline, with a higher increase of neutrophils at days 1 to 3 were at higher risk of death at 30 days. Moreover, patients with low lymphocyte count at baseline frequently developed severe complications (grade III–IV, Clavien-Dindo classification), and those with postoperative lack of lymphocyte recovery in many cases developed AL (grade B-C).

The immune function can be measured in two different settings: at baseline, in a static condition, and after surgery, during a dynamic response (1). After an immediate decrease in circulating lymphocytes occurring within a few hours from surgical trauma, the recovery of the lymphocyte count in peripheral blood, together with the increase in neutrophils, begins approximately 24 hours after surgery (2,21). Thus, we chose the 24-hour period after surgery as the first time point to measure postoperative differential count, until day 3 (72 hours after surgery). After three days, in fact, surgical complications usually become clinically evident. Interestingly, patients with preoperative lymphopenia had a significantly higher incidence of complications and a higher death rate compared with those who had a normal lymphocyte level at admission.

Concerning immune response after surgery, our results support previous observations in trauma and septic patients where failure to normalize lymphopenia was associated with an increased mortality (22,23). In a recent study by Vulliamy *et al.*, persistent lymphopenia was an independent predictor of increased mortality in critically ill emergency surgical patients (3). This result reflects the concept that lymphocyte recovery in the first post-operative days could play an important role in the mechanisms of tissue repair and a primary role in patient healing. Thus, the evaluation of WBC differential count, especially lymphocyte count at baseline and after surgery, may allow surgeons to identify patients at high risk of death and postoperative complications in order to make the best individualized care decisions, both in elective and urgent settings. For example, the creation of loop ileostomy in patients' candidate for elective rectal resections and found with low preoperative lymphocyte count should be encouraged in order to reduce the risk of AL and severe morbidity. Moreover, considering the management of patients presenting with colorectal obstruction with impaired WBC count, the placement of self-expanding stents and delayed surgery should be considered a valuable alternative approach in order to reduce the incidence of postoperative complications and stoma rate.

Previous studies on neutrophil to lymphocyte (N/L) ratio explored the association between high N/L ratio and postoperative complications (24,25). A high postoperative ratio was found to be an easy calculable preoperative measure to possibly predict the outcome after abdominal and colorectal surgery. In our patients, a high postoperative neutrophil count was significantly associated with death, while lymphocyte count was predictive as a low value preoperatively. Indeed, the N/L ratio may confound the interpretation of different immune patterns of patient response to surgical trauma at different time points, thus its real value as a predictive factor of surgical outcome should be considered with caution. Furthermore, the introduction of N/L ratio in the regression model could lead to problems of collinearity in the statistical analysis.

As we reported above, a high preoperative monocyte count was found to be related to 30-days postoperative mortality at multivariate analysis. Despite many studies have identified a relationship between the peripheral blood monocyte count and the survival rate of colorectal cancer patients, there is a lack of evidence about the role of high preoperative monocyte count as a predictive marker of postoperative mortality in subjects submitted to intestinal surgery (26,27).

Our study results support the relevance of the WBC differential count as a crucial player and marker of postoperative outcomes in patients submitted to major intestinal surgery. In our patients, lymphocyte, monocyte and neutrophil count resulted to be more relevant than other known risk factors for complications such as age, male gender, urgency setting, operative time or malignancy (11-15,17-20). Accordingly, our final multivariate model is characterized by a considerable area under the ROC curve (0.93) determining a set of variables which are highly correlated with postoperative mortality (*Figure 1*). Nevertheless, it is necessary to underline some limitations of the present study. This is a retrospective collection of data and, although it represents the routine clinical practice, this makes our research less generalizable than a prospective one. All surgical interventions were performed both in elective and urgent setting and this could be considered a potential weakness of the study. However, as emerged from our results, urgent/emergent operation was not found to be significantly associated with mortality, death or AL in the multivariate analysis, thus its ability to influence the outcomes in our population should be considered with cautious. Moreover, not all the patients had continuously laboratory draws in the first, second and third postoperative days. Our in-hospital death rate was 4%, and this value does not differ significantly from the largest nationwide series for colorectal resections, reporting a postoperative mortality range from 2% to 8% (11-13). Although the comorbidity rate (41%) was in line with those reported in the literature (12,25,28,29), the incidence of AL was quite high compared to other studies (18,19). Some reasons could explain this higher rate of AL. First, half of the procedures were performed in an emergency setting and without stoma diversion (58.8%). Second, a large percentage of patients (47%) had an ACCI score greater than 5, which reflects a population at higher risk for surgical complications both in terms of ageing and of severe comorbidities.

Conclusions

Our study represents a common sample of daily surgical care and reflects demographic and public health resource challenges in the Western world. It refocuses the crucial role of immune status and immune response in healing processes in surgical patients. Furthermore, these results suggest that immune monitoring by a widely available, easily readable, and low-cost test, such as automated differential blood cell count may early add critical information on surgical patients risks and, once operated, even on clinical course. Patients having low lymphocyte counts were found to have a higher risk of developing major surgical complications and death, while postoperative lack of lymphocyte recovery was associated with a higher AL rate. In a short-term view, once validated, the evaluation of differential WBC count patterns may improve a tailored planning and monitoring of surgical strategy. In a future view, a therapeutic modification (30) of host immune patterns in response to major surgery may eventually represent an effective strategy to improve surgical outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Local Research Ethics Committee, the Socio-Sanitary Territorial Unit Of Monza (No. 0016932/17U). Informed consent for participation in the study was obtained either directly, or from a guardian of each patient.

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