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The Role of Pre-Operative Neutrophil-to-Lymphocyte Ratio in Predicting Post-Bariatric Surgery Related Complications

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ABSTRACT **Background:** Bariatric surgery has become the most common and effective therapeutic option for obesity. However, it is associated with morbidity and complications. Identification of predictors for surgical complications is an unmet need.

Objectives: To determine a simple non-invasive parameter that predicts early postoperative complications following bariatric surgery.

Methods: In this retrospective study of all patients who underwent elective bariatric surgery at Nazareth Hospital EMMS during a 4-year period (2015–2018). We collected clinical and laboratory parameters and determined predictors of complications.

Results: A total of 345 patients underwent bariatric surgery during the study period. Of the patients, 51 experienced early post-bariatric surgery complications as compared to 294 patients who had no complications. Univariate analysis revealed that neutrophil-to-lymphocyte ratio (NLR) (odds ratio [OR] 1.912, $P < 0.0001$) and platelet to lymphocyte ratio (OR 1.015, $P < 0.0001$) were associated with post-bariatric surgery complications. In a multivariate logistic regression analysis, only NLR remained a significant predictor (OR 1.751, 95% confidence interval 1.264–2.425, $P = 0.0008$) with a receiver operating characteristic curve for NLR of 0.8404.

Conclusions: We found that the NLR predicts post bariatric surgery early complications. Further prospective studies are needed to validate our findings.

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KEY WORDS: bariatric surgery, lymphocyte, neutrophil, neutrophil-to-lymphocyte ratio (NLR)

Obesity defined as a body mass index (BMI) of more than 30 kg/m^2, has become one of the leading epidemics worldwide and is associated with major morbidity, mortality [1], and disease including diabetes mellitus type 2, hypertension, ischemic heart disease, obstructive sleep apnea, and malignancy [2]. To date, bariatric surgery is the most effective treatment to obtain sustained weight loss with potential resolution of the associated co-morbidities [1,3]. The dramatic increase in obesity has led to an extensive increase of bariatric surgeries worldwide; however, the surgeries are associated with up to 17% in potential complications and a mortality rate ranging from 0.08 to 0.31% [4]. Therefore, finding clinical and laboratory markers that can identify patients with a potentially high risk of postoperative surgical complications is essential, and could minimize the complication rate, and improve outcomes. To date, most studies investigated patient characteristics and co-morbidities as predictors of short and long-term surgical complications [4-6].

Obesity is characterized by hypertrophied adipose tissue that induces the production of pro-inflammatory markers such as interleukin-6 and tumor necrosis factor-alpha, leading to the generation of chronic low inflammatory state [7]. Consequently, the levels of C-reactive protein (CRP) are elevated secondary to interleukin-6 [8]. Another simple available inflammatory marker is the neutrophil-to-lymphocyte ratio (NLR), which has been used as a prognostic marker in infectious diseases [9]. The NLR has been shown to be a significant parameter in several disease states including community acquired pneumonia, myocardial infarction, appendicitis, and cancers [10-13]. Furthermore, NLR is used as a prognostic marker to predict complications following a variety of major surgical procedures [14,15]. The aim of this study was to assess the role of NLR in predicting early post-operative complications following bariatric surgery.

PATIENTS AND METHODS

This retrospective cohort study was based on medical records of patients who were admitted to EMMS Nazareth hospital and underwent bariatric surgeries. All patients above 18 years of age were admitted for elective bariatric surgery if they fulfilled the eligibility criteria for bariatric surgery based on established

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clinical guidelines and had baseline complete blood count (up to 24 hours prior to the surgery), were included. The criteria for bariatric surgery at our institution are either BMI > 40 kg/m^2 or BMI > 35 kg/m^2 with associated co-morbidities, including diabetes mellitus, hypertension, and obstructive sleep apnea. Exclusion criteria included suspected infections one month prior to surgery, medications that could suppress the bone marrow such as immunosuppression, previous abdominal surgeries, and hematological diseases.

Medical records of eligible patients were reviewed and the following parameters were collected: demographics (age, gender), BMI, medical history, surgical history, chronic medication use, type of surgery performed (laparoscopic sleeve gastrectomy, gastric banding, or mini-gastric bypass surgery), and laboratory findings (complete blood count, neutrophils, lymphocytes, NLR, CRP, creatinine, blood urea nitrogen [BUN], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and albumin). Moreover, we assessed early postoperative (up to one month) complications such as bleeding, leak, wound infection, anastomotic stricture, and reflux esophagitis.

The study protocol conforms to the ethical guidelines of the 1975 declaration of Helsinki and was approved by the local ethics committee. Written informed consent was waived by the local ethics committee due to the retrospective non-interventional nature of the study.

PREOPERATIVE COMPLETE BLOOD COUNT AND NLR

Blood tests were performed one day prior to surgery. In cases of multiple complete blood count tests, the highest pre-operative value was recorded. The NLR was calculated by dividing the absolute neutrophil value by the absolute lymphocyte value.

STATISTICAL ANALYSIS

Univariate descriptive statistics were used to compare patients with and without early postoperative complications. Data were reported as mean ± standard deviation (SD) for quantitative continuous variables, and frequencies (percentages) for categorical variables. Univariate and multivariate logistic regression was used to estimate odds ratio (OR) of baseline factors and backward selection was used to select the final model. To select a cut-off for the NLR, the area under the receiver operating characteristic (ROC) curve (the c-statistic) and its 95% confidence intervals (95%CI) were determined. We used the Youden (J) index that is defined for the value with maximal sensitivity and specificity using ROC analysis to report the threshold above which an NLR value may predict early complications following bariatric surgery. The diagnostic accuracy of the two cut-off points was determined by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the likelihood ratio.

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

BASELINE DEMOGRAPHICS, LABORATORY RESULTS, AND ENDOSCOPIC CHARACTERISTICS

A total of 345 patients underwent bariatric surgery during the study period. Early post-bariatric surgery complications were found in 51 patients (group A) as compared to 294 patients who had no complications (group B). The most common complication was reflux esophagitis (29.5% of patients). Of 15 patients who developed esophagitis following the surgery, only 2 patients were previously diagnosed with esophagitis, which deteriorated after the surgery. The second most common diagnosis was surgical site bleeding (25.5% of patients).

The mean age, in years, in groups A and B were 36.5 ± 10.1 and 36.3 ± 10.7, respectively. There were 14 males in group A, and 57 males in group B. The types of the bariatric surgery performed were similar between the two groups: 14 patients (27.5%) underwent laparoscopic sleeve gastrectomy, 8 patients (15.7%) gastric banding, and 29 (56.8%) mini-gastric bypass surgery in group A as compared to 60 patients (20.4%), 52 (17.7%), and 181 (61.1%) in group B. There was no difference between the groups with respect to medical and surgical history (P = NS). Table 1 shows the baseline demographic characteristics of our cohort. Moreover, the laboratory parameters showed higher average NLR and platelets to lymphocyte ratio in group A as compared to group B (3.6 vs. 2.13 and 145.75 vs. 118.6). The rest of the laboratory results were comparable between the two groups. Table 2 displays the laboratory findings of our cohort.

PARAMETERS ASSOCIATED WITH EARLY POST-BARIATRIC SURGERY COMPLICATIONS ON UNIVARIATE AND MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

Using univariate regression analysis, two predictors of early post-bariatric surgery complications were identified [Table 3]. These findings were NLR (OR 1.912, 95%CI 1.445–2.531, P < 0.0001) and platelet to lymphocyte ratio (OR 1.015, 95%CI 1.008–1.022, P < 0.0001). There was no correlation of post-bariatric complications with any other laboratory parameters or with the type of surgery (P = NS). Table 3 shows the univariate regression analysis. In multivariate logistic regression analysis, only NLR was shown to be significantly correlated with early post-bariatric surgery related complications (OR 1.751, 95%CI 1.264–2.425, P = 0.0008). When examining several cutoff points for NLR that showed correlation with early postoperative bariatric surgery complications, we found the Youden index (J) for NLR of > 2.67 which is associated with sensitivity of 77% and specificity of 84%. The area under the ROC curve for NLR was 0.8404. We found that NLR of more than 3 was associated with specificity of more than 90% and positive predictive value of 55–67% for early post-bariatric surgery complications. A value of less than 2 was associat-

ed with high sensitivity and NPV of 92–100% and 97–100%, respectively [Table 4].

DISCUSSION

Identifying predictors of surgery complications are a main concern of surgeons especially before elective surgeries. Accurate predictors can lead to the optimal timing of intervention in attempt to minimize complication rate and improve outcome.

The primary aim of our study was to assess the association of NLR with early post-bariatric surgery related complications. In univariate analysis, the NLR and platelets to lymphocyte ratio showed a statistically significant association with these complications. However, using regression multivariate

Table 1. Demographics and laboratory characteristics of study cohort

Parameters	Group A	Group B
Number of patients	51	294
Age in years (mean ± SD)	36.5 ± 10.1	36.3 ± 10.7
Gender, n (%) • Male • Female	 14 (27.5) 37 (72.5)	 57 (19.4) 237 (80.6)
Body mass index (Mean ± SD)	44.2 ± 4.9	43.2 ± 4.5
Type of surgery, n (%) • Sleeve gastrectomy • Gastric banding • Mini-gastric bypass	 14 (27.5) 8 (15.7) 29 (56.8)	 60 (20.4) 52 (17.7) 181 (61.6)
Medical history, n (%) • Diabetes mellitus • Hypertension • Hyperlipidemia • Ischemic heart disease • Other	 4 (7.8) 7 (13.7) 3 (5.9) 0 13 (25.5)	 35 (11.9) 47 (16) 46 (15.7) 1 (0.34) 70 (23.8)
Surgical history, n (%) • Sleeve gastrectomy • Gastric banding • Mini-gastric bypass • Cholecystectomy • Laparotomy	 5 (9.8) 3 (5.9) 2 (3.9) 3 (5.9) 1 (1.96)	 18 (6.1) 13 (4.4) 4 (1.4) 32 (10.9) 9 (3.1)
Medications, n (%) • Statins • Aspirin • NSAIDS	 4 (7.8) 2 (3.9) 1 (1.96)	 26 (8.8) 13 (4.4) 3 (1)
Pre-operative gastroscopy findings, n (%) • Normal • Hiatal hernia • Peptic ulcer disease • Esophagitis • Gastritis • Duodenitis	 7 (13.7) 7 (13.7) 0 4 (7.8) 10 (19.6) 0	 82 (38.5) 61 (20.7) 1 (0.34) 24 (8.2) 72 (24.5) 3 (1)

NSAID = non-steroidal anti-inflammatory drugs, SD = standard deviation

Table 2. Laboratory characteristics of study cohort

Parameters	Group A	Group B
Leukocytes × 103/µl	6.7 ± 1.1	7 ± 0.9
Platelets × 103/µl	271.6 ± 54.3	271.7 ± 64.9
NLR	3.6 ± 2.16	2.13 ± 1.24
Platelets to lymphocyte ratio	145.7 ± 49.5	118.6 ± 38.3
Creatinine (mg/dl)	1.4 ± 9	1.3 ± 7.7
Blood urea nitrogen (mg/dl)	17.3 ±10.3	16.3 ± 8.8
ALT (U/L)	31.9 ± 23.1	29 ± 21.6
AST (U/L)	27.6 ± 30.1	23.2 ± 15.9
Albumin (gr %)	4.1 ± 0.37	4.1 ± 0.5

ALT = alanine aminotransferase, AST = aspartate aminotransferase, NLR = neutrophil-to-lymphocyte ratio

Table 3. Univariate analysis of parameters associated with early post-bariatric surgery related complications

Parameter	Odds ratio	95% confidence interval	*P* value
Age	1.002	0.975–1.031	0.87
Gender male vs. female	1.597	0.813–3.137	0.17
Body mass index	1.048	0.984–1.116	0.14
Sleeve gastrectomy	0.713	0.008–67.627	0.88
Gastric banding	0.481	0.005–46.701	0.75
Mini-gastric bypass	0.483	0.005–44.959	0.75
WBC	1.052	0.970–1.1	0.22
NLR	1.912	1.445–2.531	**< 0.0001**
Platelets	1.000	0.995–1.005	0.98
Platelets to lymphocyte ratio	1.015	1.008–1.022	**< 0.0001**
Creatinine (mg/dl)	1.011	0.982–1.041	0.45
BUN (mg/dl)	1.012	0.981–1.045	0.45
ALT (U/L)	1.006	0.993–1.019	0.35
AST (U/L)	1.010	0.995–1.025	0.19
Albumin (gr %)	1.086	0.498–2.367	0.84

Bold indicates significance
ALT = alanine aminotransferase, AST = aspartate aminotransferase
BUN = blood urea nitrogen, NLR = neutrophil-to-lymphocyte ratios,
WBC = white blood cells

Table 4. Neutrophil-to-lymphocyte ratio cutoff points with their corresponding descriptive statistics

NLR	Sensitivity	Specificity	PPV	NPV
3–8.4	10–60	90–100	55–67	85–93
2–2.9	65–90	53–88	25–49	93–97
1.2–1.95	92–100	10–48	16–24	97–100

NLR = neutrophil-to-lymphocyte ratio, NPV = negative predictive value, PPV = positive predictive value

analysis, this association was observed only for NLR with an OR of 1.912. Neutrophils and lymphocytes are components of white blood cells which play an important role in the regulation of the inflammatory microenvironment and they can be examined by peripheral blood measurable parameters. The NLR was reported as having prognostic roles in acute infectious diseases and sepsis [9,16,17]. Moreover, previous studies have demonstrated an important prognostic role of NLR in community acquired pneumonia, myocardial infarction, appendicitis, and several cancers (10-13). NLR has been used to predict complications following colorectal surgery [14], other urgent abdominal surgeries [15-17], and surgical interventions in patients with acute diverticulitis [18]. Da Silva reported that NLR one day postoperatively is a predictor of one-month worse outcome among patients who underwent bariatric surgeries [19].

To the best of our knowledge our study is the first to show NLR as a predictor of early complications using several cutoff points with their corresponding statistics for predicting such complications. To date, most of the studies focusing on NLR were conducted in the setting of cancer [20] and infectious states, which showed a positive correlation with worse prognostic outcomes. High NLR might be explained in part by an augmented inflammatory state and altered immunity associated with the aforementioned conditions. Obese patients are characterized by a low inflammatory state [7], and the role of NLR is also validated in the setting of bariatric surgeries as we demonstrated in our study. It is important to note that there is a lack of predictive biomarkers for post-bariatric surgery complications, and most of the predictive models were based on clinical criteria rather than laboratory parameters [21]. A previous study reported a nine parameter scale based on eight clinical parameters and one laboratory parameter (serum albumin) as a predictor for surgical complications in bariatric surgery patients [22]. However, with a ROC curve for NLR of 0.8404 and as the NLR is a simple available non-invasive parameter, given the accumulating evidence in its role in surgical procedures, the ratio between neutrophil and lymphocyte is more precise in predicting poor clinical and surgical outcome than either neutrophil or lymphocyte count alone [23]. Implementing the use of the NLR in the pre-operative work-up of obese patients who are scheduled to undergo bariatric surgeries could be beneficial.

LIMITATIONS

The main limitation of our study is its retrospective nature of data collection and that it was conducted in a single center. However the study had a relatively large cohort.

CONCLUSIONS

Our study clearly demonstrated that NLR has a strong correlation with early post-bariatric surgery related complications. We recommend incorporating our findings into the clinical assessment and patient risk stratification, and use it as part of a score to be developed for predicting early post bariatric surgery complications. Further prospective trials are warranted to confirm our preliminary findings.

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Capsule

Viable bacterial colonization is highly limited in the human intestine in utero

Mucosal immunity develops in the human fetal intestine by 11–14 weeks of gestation, yet **Rackaityte** et al. reported that whether viable microbes exist in utero and interact with the intestinal immune system is unknown. Bacteria-like morphology was identified in pockets of human fetal meconium at mid-gestation by scanning electron microscopy (n=4), and a sparse bacterial signal was detected by 16S rRNA sequencing (n=40 of 50) compared to environmental controls (n=87). Eighteen taxa were enriched in fetal meconium, with *Micrococcaceae* (n=9) and *Lactobacillus* ($n = 6$) the most abundant. Fetal intestines dominated by *Micrococcaceae* exhibited distinct patterns of T cell composition and epithelial transcription. Fetal *Micrococcus luteus*, isolated only in the presence of monocytes, grew on placental hormones, remained viable within antigen presenting cells, limited inflammation ex vivo and possessed genomic features linked with survival in the fetus. Thus, viable bacteria are highly limited in the fetal intestine at mid-gestation, although strains with immunomodulatory capacity are detected in subsets of specimens.

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Eitan Israeli

Capsule

An environmental path to autoimmunity?

Celiac disease, a gastrointestinal disorder caused by exposure to cereal gluten, is an autoimmune disorder. In a perspective, **Iversen** and **Sollid** discussed the path to autoimmunity from gluten ingestion. They also suggested that, like gluten in celiac disease, environmental agents may feature in the development of other autoimmune diseases, which is an interesting avenue for future research. Sensitivity to such factors may determine why some people develop autoimmunity, whereas others do not.

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Eitan Israeli

Capsule

Evolutionary dynamics in hematopoiesis

Cells accumulate mutations as we age, and these mutations can be a source of diseases such as cancer. How cells containing mutations evolve, are maintained, and proliferate within the body has not been well characterized. Using a quantitative framework, **Watson** et al. applied population genetic theory to estimate mutation accumulation in cells in blood from sequencing data derived from nearly 50,000 healthy individuals. By evaluating how mutations differ between blood cell populations, a phenomenon known as clonal hematopoiesis, the researchers could observe how recurrent mutations can drive certain clonal lineages to high frequencies within an individual. The risk of specific mutations, some of which are associated with leukemias, rising to high frequencies may therefore be a function of cellular selection and the age at which the mutation originated.

Science 2020; 367: 1449
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