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# Neutrophil-to-Lymphocyte Ratio as an Early Predictor for Major Complications After Metabolic Surgery

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***Background:*** In metabolic-bariatric fast-track surgery, patients are scheduled for discharge on postoperative day 1. The neutrophil-to-lymphocyte ratio (NLR) could be an inexpensive and rapid way to identify patients at risk of early complications. This study aimed to determine the predictive value of the NLR on early complications.
***Methods:*** Prospective data were collected of all patients undergoing primary metabolic surgery in a single center, between April 2018 and April 2019. The association between NLR, leukocyte count, hemoglobin, and C-reactive protein (CRP) was compared with early complications.
***Results:*** In total, 829 patients underwent primary metabolic surgery: 336 (40.5%) Roux-en-Y gastric bypass, 410 (49.5%) sleeve gastrectomy, and 83 (10.0%) one anastomosis gastric bypass. Major complications occurred in 34 (4.1%) patients, who had significantly higher levels of postoperative NLR ($p < 0.001$), delta-NLR ($p < 0.001$), leukocyte count ($p < 0.001$), and CRP ($p = 0.008$). The ideal cutoff points to predict complications after metabolic surgery were 6.73 for postoperative NLR (sensitivity 74% and specificity 70%) and 4.68 for delta-NLR (sensitivity 77% and specificity 75%).
***Conclusion:*** Postoperative NLR and delta-NLR were independently associated with early major complications after metabolic surgery. These markers may be useful to help identify patients who are at risk for complications, and can aid in the decision making for safe postoperative discharge on day 1 or early intervention.

**Keywords:** Roux-en-Y gastric bypass, sleeve gastrectomy, one anastomosis gastric bypass, mini gastric bypass, neutrophil-to-lymphocyte ratio, major complications, enhanced recovery

## Introduction

Due to the increasing rates of morbid obesity worldwide, metabolic surgery has become a frequently performed procedure. With the Enhanced Recovery After Bariatric Surgery (ERABS) protocols, patients are scheduled for discharge on postoperative day 1 to ensure efficient and patient-friendly care.[1] Nonetheless, metabolic surgery remains major abdominal surgery in a high-risk patient group due to obesity-related comorbidities. Therefore, alertness for early postoperative complications is warranted.

Surgical interventions in general are associated with a systemic inflammatory response, and the level of systemic inflammation has been shown to predict surgical complications. A commonly used inflammatory marker for complications after abdominal surgery is C-reactive protein (CRP).[2] However, CRP shows insufficient sensitivity on postoperative day 1 to detect major complications, due to high interpatient variability.[3,4] Therefore, a more sensitive early marker to aid in the detection of postoperative complications in metabolic surgery is needed.

Inflammation after surgery is characterized by a relative increase in circulating neutrophil levels compared to circulating lymphocytes.[5,6] The neutrophil-to-lymphocyte ratio (NLR) has been shown to correlate with organ dysfunction scores and the clinical course in critically ill patients.[7] The

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NLR could therefore turn out to be an inexpensive and rapid way to identify patients at risk of complications on postoperative day 1. Preoperative NLR as a marker for individual systemic inflammation levels is an independent predictor for complications following cardiac surgery, cardiac percutaneous interventions, elective abdominal surgery, and oncological resections.[8–11] With regard to metabolic surgery, one study found that an NLR of ≥10 on postoperative day 1 was associated with an increase in 30-day complications.[12] They recommended a prospective methodology with novel statistical techniques, such as receiver operating characteristics (ROC) analysis, to identify an optimal threshold for the bariatric surgical population.

The aim of this study was to determine the predictive value of the postoperative NLR on day 1 and delta-NLR on 30-day postoperative complications. We hypothesized that an increased NLR postoperatively on day 1 could better identify patients at higher risk of developing postoperative complications than CRP. We also hypothesized that an increased delta-NLR indicates an increased risk of overall complications better than the postoperative day 1 NLR. Furthermore, we aimed to determine ideal cutoff points for use of postoperative NLR on day 1 and delta-NLR in metabolic surgery practice.

## Methods

### *Design and data collection*

Data were collected prospectively from all included patients undergoing a primary metabolic surgical procedure between April 2018 and April 2019 in a single-center teaching hospital, and analyzed after all data was collected. Patients with a metabolic procedure in their medical history were not included, due to the increased risk of complications in revisional surgery.[13,14] The primary outcome measure was major complications within 30 days postoperatively, based on the guidelines described by Brethauer *et al.*: complications that resulted in a prolonged hospitalization (beyond 3 days), administration of anticoagulants, re-intervention, or reoperation (for example, anastomotic leak and postoperative hemorrhage).[15] The secondary outcome measure was readmission within 30 days postoperatively. Patient characteristics, obesity-related comorbidities, preoperative and 1 day postoperative laboratory results, major complication rates, length of hospital stay, and readmission rates were recorded.

### *Ethics and dissemination*

Written informed consent was obtained from all individual participants included in the study. The study protocol was conformed to the ethical guidelines of the Declaration of Helsinki as revised in 2013, and was approved by the institutional review board (IRB) and the regional Medical Research Ethics Committee TWOR, Rotterdam, the Netherlands (protocol number 2018–10).

### *Cohort*

All included patients were found eligible for metabolic surgery according to the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) guidelines and underwent laparoscopic Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (SG), or laparoscopic one anastomosis gastric bypass-mini gastric bypass (OAGB-MGB), depending on comorbidities and preference of the patient and surgeon.[16] The methods of the procedures were described in earlier publications.[17–19] All patients were treated according to the ERABS protocol with the intention to be discharged on postoperative day 1.[1] The ERABS protocol contained a checklist with discharge criteria divided in three categories. Category 1 anamnestic: patients had a VAS-score <4, no nausea, >1L fluid intake, adequate mobilization, no calf pain, and the patient should be willing for discharge. Category 2 physical: no abdominal tension, temperature <38.0, heart rate <100 bpm, oxygen saturation >95%, and if applicable, the drain production <30 mL/24 h. Category 3 laboratory results: hemoglobin (Hb) decrease <2 points, leukocytes $<14\times10^9$/L, and CRP <100 mg/L. Clinical examination was taken, and on indication, imaging was performed. Based on the checklist and the clinical opinion of the residence, and if needed the surgeon, patients were discharged. Patients were excluded from the study in case of conversion from laparoscopy to laparotomy. No power calculation was performed in this observational study.

### *Laboratory tests*

Neutrophil and lymphocyte counts were measured twice: first preoperatively on the intake day at the outpatient clinic of the department of Internal Medicine, and second in the ward on day 1 after surgery. The investigator verified if the blood samples were available, so there would be no missing data. The NLR calculation was not performed until all patients had undergone surgery and were discharged. As a result, the NLR could not influence the care pathway. The delta-NLR was calculated by subtracting the preoperative NLR from the postoperative NLR, leading to a positive result in case of an increase in NLR. Laboratory parameters were determined at the hospital's Department of Clinical Chemistry according to the standard procedures. Blood cell counts were measured on DxH800 analyzers (Beckman Coulter) and CRP was measured on the Architect c8000 (Abbott).

### *Statistical analysis*

All analyses were performed using SPSS (PASW) 25 software (SPSS, Inc., Chicago, IL). Multivariable logistic regression analysis was used to estimate the relationship between the occurrence of major complications and the NLR (preoperative, postoperative, and delta), leukocyte count, Hb, and serum CRP, adjusting for baseline characteristics, comorbidities (hypertension, type two diabetes and hypercholesterolemia), type of surgery, duration of surgery, and time between surgery and blood draw. Independent T-tests were used for analyzing the relationship between specific types of complications and NLR (preoperative, postoperative, and delta), leukocyte count, Hb, and serum CRP. ROC curves were constructed for NLR (preoperative, postoperative, and delta), leukocyte count, Hb, and serum CRP on major complications. For all values with an area under the curve (AUC) >0.70, the optimal cutoff value for predicting postoperative complications was determined. Multivariable logistic regression analysis was used to estimate the relationship between readmission and NLR (preoperative, postoperative, and delta), leukocyte count, Hb, and serum CRP, adjusting for the same baseline characteristics as described above. Results were evaluated at a significance threshold of $p < 0.05$ (two sided).

## Results

Between April 2018 and April 2019, 829 patients underwent primary metabolic surgery, of whom 336 (40.5%) RYGB, 410 (49.5%) SG, and 83 (10.0%) OAGB-MGB. The mean (±standard deviation) duration of surgery was 47.4 ± 13.2 min for RYGB, 33.9 ± 9.3 min for SG, and 43.0 ± 13.6 min for OAGB-MGB. The median (±SE) length of hospital stay for the complete cohort was 1.17 ± 0.03 days. Table 1 shows baseline characteristics by type of procedure and for the complete cohort.

In total, 34 (4.1%) major complications occurred within 30 days postoperatively: 16 postoperative hemorrhages (1.9%, range of hours between procedure and event 14–105), 4 stricture problems—2 of the gastrojejunostomy and 2 of the entero-enterostomy requiring a reintervention (0.5%, range of days between procedure and event 2–21), 3 anastomotic leakages requiring a reintervention (0.4%, range of hours between procedure and event 33–246), and 13 other complications (1.3%, perforation of the small intestine, persistent vomiting due to GERD that needed gastroscopy, atrial fibrillation that needed cardioversion and the administration of anticoagulation, admission on intensive care unit because of diabetic ketoacidosis, and prolonged hospitalization).

Postoperative day 1 NLR and delta-NLR were significantly higher in patients with major complications compared to patients without (respectively, 9.47 ± 3.96 vs. 5.74 ± 2.55, $p < 0.001$, and 7.04 ± 3.47 vs. 3.38 ± 2.38, $p < 0.001$). A similar trend was observed for postoperative leukocyte count (respectively, 13.69 ± 4.38 vs. 11.821 ± 2.93, $p = 0.019$) and CRP (respectively, 32.91 ± 21.03 vs. 23.36 ± 19.67, $p = 0.006$) (Fig. 1). No significant differences were found for patients with or without complications in preoperative NLR (respectively, 2.37 ± 0.97 vs. 2.38 ± 1.17, $p = 0.956$) and Hb (respectively, 7.86 ± 1.00 vs. 8.19 ± 0.73, $p = 0.067$).

After correcting for baseline characteristics, comorbidities, time between surgery, and blood draw on postoperative day 1, there were significant associations between major complications and higher levels of postoperative NLR (odds ratio [OR]: 1.416, 95% confidence interval [CI]: 1.273–1.579, $p < 0.001$), delta-NLR (OR: 1.496, 95% CI: 1.327–1.688, $p < 0.001$), postoperative leukocyte count (OR: 1.228, 95% CI: 1.118–1.361, $p < 0.001$), CRP (OR: 1.019, 95% CI: 1.005–1.033, $p = 0.008$), and lower levels of Hb (OR: 0.499, 95% CI: 0.305–0.814, $p = 0.005$). There was no significant association between major complications in preoperative NLR (OR: 0.983, 95% CI: 0.731–1.323, $p = 0.911$).

Although total complication rates were low, the predictive values were also studied with regard to specific complications. For postoperative hemorrhage, significant differences were found in postoperative NLR ($p = 0.004$), delta-NLR ($p = 0.006$), leukocyte count ($p = 0.032$), and Hb ($p = 0.001$), but no difference was found in preoperative NLR ($p = 0.585$) and CRP ($p = 0.864$). No significant differences were found for stricture problems in any of the laboratory results. For postoperative anastomotic leakages, significant differences were found in postoperative NLR ($p = 0.019$), delta-NLR ($p = 0.011$), and CRP ($p = 0.034$), but no differences were found in preoperative NLR ($p = 0.943$), leukocyte count ($p = 0.504$), and Hb ($p = 0.890$). For the other complications, significant differences were found in postoperative NLR ($p = 0.008$), delta-NLR ($p = 0.002$), leukocyte count ($p = 0.012$), and CRP ($p \leq 0.001$), but no differences were found in preoperative NLR ($p = 0.770$) and Hb ($p = 0.609$). Table 2 described the complications by type of surgery.

Additional analysis showed no significant difference in all the parameters within 30 days (data not shown).

The AUC according to ROC analysis for postoperative NLR and delta-NLR was 0.791 ($p < 0.001$) and 0.819 ($p < 0.001$), respectively. The ideal cutoff point for postoperative NLR was determined as 6.73, with a sensitivity of 74% and a specificity of 70%, and for the delta-NLR, it was determined as 4.68, with a sensitivity of 77% and a specificity of 75%. ROC curves of postoperative NLR and delta-NLR are shown in Figure 2. The AUC for preoperative NLR, leukocyte count, Hb, and CRP did not meet the criteria of an AUC of 0.7 (Table 3).

## Discussion

We studied the predictive value of the postoperative NLR for day 1, and delta-NLR for 30-day postoperative complications. Multivariable analyses demonstrated that the postoperative NLR and delta-NLR showed a correlation to postoperative complications in comparison with preoperative NLR. Considering this in addition to current used markers, the postoperative NLR with a cutoff point of 6.73 and the delta-NLR with a cutoff point of 4.68 may improve the process of identify patients at higher risk for early complications.

In 2017, Da Silva *et al.* found that an NLR ≥10 postoperatively was independently associated with the 30-day outcomes following metabolic surgery.[12] The concerning study included 737 patients undergoing an RYGB (88.6%) or SG (11.4%). The major complication rate was 6.4%. This study

Table 1. Baseline Characteristics

| | *RYGB* (N = *336*) | *LSG* (N = *410*) | *OAGB-MGB* (N = *83*) | *Total* (N = *829*) |
|---|---|---|---|---|
| Female, *n* (%) | 286 (85.1) | 317 (77.3) | 50 (60.2) | 653 (78.8) |
| Age (years), mean ± SD | 44.0 ± 10.5 | 39.4 ± 12.2 | 55.2 ± 7.0 | 43.0 ± 12.0 |
| Baseline BMI (kg/m$^2$), mean ± SD | 41.5 ± 4.2 | 43.5 ± 5.4 | 43.4 ± 6.0 | 42.7 ± 5.1 |
| History of hypertension, *n* (%) | 107 (31.8) | 96 (23.4) | 48 (57.8) | 251 (30.3) |
| History of T2D, *n* (%) | 53 (15.8) | 34 (8.3) | 39 (47.0) | 126 (15.2) |
| History of dyslipidemia, *n* (%) | 47 (14.0) | 38 (9.3) | 28 (33.7) | 113 (13.6) |

BMI, body mass index; LSG, laparoscopic sleeve gastrectomy; OAGB-MGB, one anastomosis gastric bypass-mini gastric bypass; RYGB, Roux-en-Y gastric bypass; SD, standard deviation; T2D, type 2 diabetes.

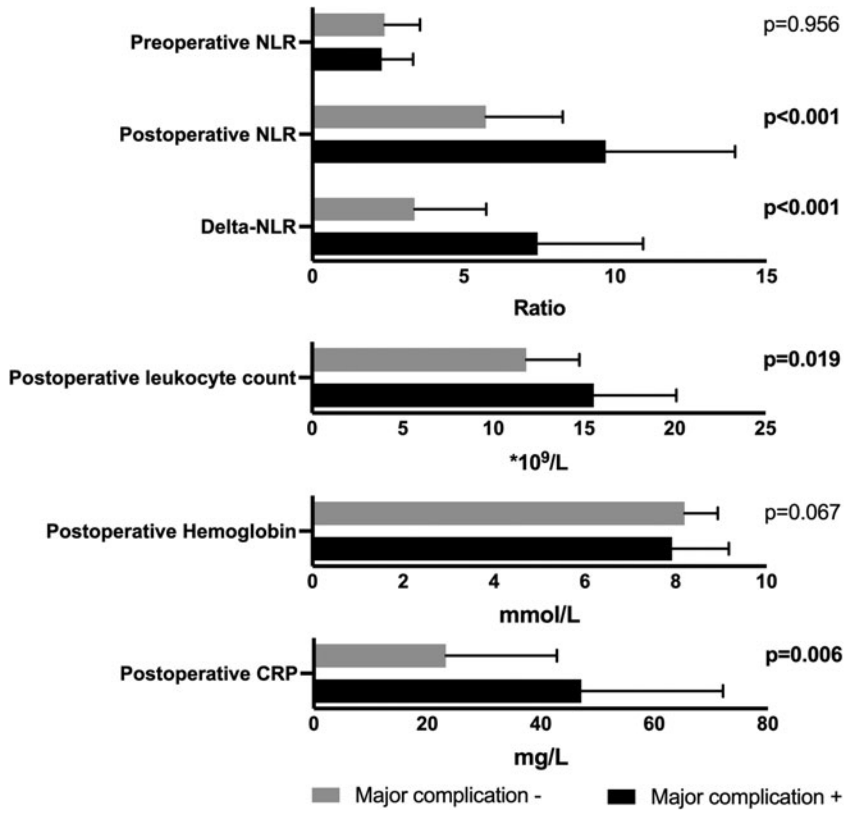


**FIG. 1.** Mean ± SD laboratory values divided by occurrence of major complication. BMI, body mass index; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristics; SD, standard deviation; T2D, type 2 diabetes.



reported a lower rate for major complications (4.1%), but shows a similar association. To predict postoperative complications, Da Silva *et al.* based the postoperative NLR cutoff value on previously published articles.[20] They recommended determining an optimal cutoff point for the postoperative NLR to predict postoperative complications after metabolic surgery. For our study population, the cutoff values of 6.73 for postoperative NLR and 4.68 for delta-NLR provided the best ratios of sensitivity and specificity.

Delta-NLR was not determined in earlier metabolic studies. By analyzing both delta-NLR and postoperative NLR, we could determine which parameter would be a more accurate predictor of major complications. We found that delta-NLR correlated slightly better with postoperative complications than postoperative NLR 0.812 ($p < 0.001$) versus 0.784 ($p < 0.001$). The calculated specificity of 71–75% may be acceptable, as the NLR is not intended to be used as a diagnostic test, but as part of an integrated set of clinical and laboratory parameters to enhance patient risk stratification and aid in the clinical decision making for discharge in a standardized way.[2] An elevated postoperative NLR or delta-NLR in an otherwise asymptomatic patient should not always warrant a prolonged hospital stay. The physician in charge should take the elevated laboratory values in consideration, but in the end rely on clinical experience.

Table 2. Major Complications by Type of Surgery

| | *LRYGB* n = *336* | *LSG* n = *410* | *OAGB-MGB* n = *83* |
|---|---|---|---|
| Hemorrhages, *n* (%) | 3 (0.9) | 11 (2.7) | 2 (2.4) |
| Stenosis, *n* (%) | 3 (0.9) | 1 (0.2) | 0 (0.0) |
| Anastomotic leakages, *n* (%) | 3 (0.9) | 0 (0.0) | 0 (0.0) |
| Other, *n* (%) | 3 (0.9) | 4 (1.0) | 4 (4.8) |

LRYGB, laparoscopic Roux-en-Y gastric bypass.

We also found a correlation between postoperative leukocyte count and complications, but the AUC was 0.615, with a cutoff value of 12.05, which had a low sensitivity (62%) and specificity (58%). Chiappetta *et al.* described the same result on postoperative day 1 after metabolic surgery.[21] Therefore, the postoperative leukocyte count may be of less value in comparison with the NLR to predict major complications.

Preoperative NLR levels have been shown to predict high-risk patients in other surgical areas.[7–10] A study by Mari *et al.* described that a higher preoperative NLR (1 day before surgery) significantly correlated with early postoperative complications after metabolic surgery.[22] They included 345 patients, of which 51 patients were with and 294 patients were without complications. However, esophagitis was the most common complication in the study (29.5%), which in our study was not a specific determent as major complication. In this study, preoperative NLR was mostly obtained weeks to months preoperatively, and was used as the patients NLR in a nonstressful situation, as a baseline value. We found that the preoperative NLR did not correlate with postoperative

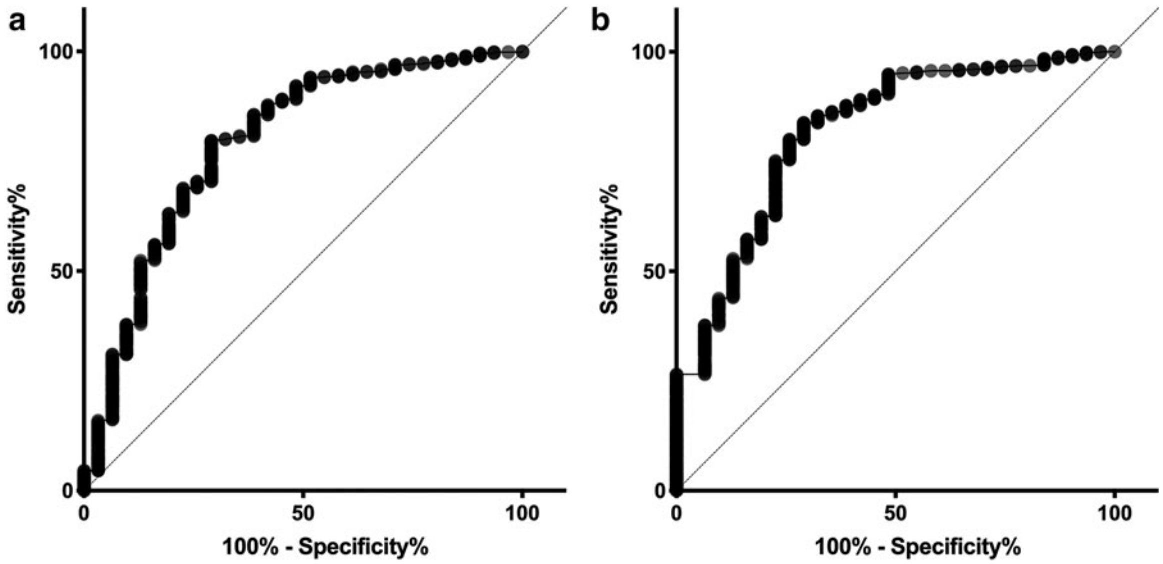


**FIG. 2.** **(a)** ROC curve of postoperative NLR of postoperative major complications. **(b)** ROC curve of delta-NLR of postoperative major complications.

major complications. In line with this outcome, neither the baseline characteristics nor the comorbidities correlated with the occurrence of major complications.

In this study, none of the patients were known to have systemic inflammatory diseases. As systemic inflammatory diseases influence the inflammatory markers such as CRP and NLR, these patients would deserve a separate analysis to determine the value of the NLR for detecting postoperative complications.

CRP as a predictive marker for complications on postoperative day 1 has been evaluated more thoroughly. Several studies have pointed out the insufficient sensitivity of postoperative day 1 CRP levels.[3,4] Other studies did find CRP to be a useful marker. Kröll *et al.* found that a CRP of <70 mg/L on postoperative day 1 can exclude early intra-abdominal infections with high accuracy in patients undergoing metabolic surgery.[23] A meta-analysis by Bona *et al.* concluded that a CRP value lower than 6.1 mg/dL on postoperative day 1, combined with reassuring clinical signs, could be useful to rule out early postoperative leak and complications after SG and RYGB.[24] In this study, there was also a correlation between elevated levels of postoperative day 1 CRP and major complication rates, but the AUC was relatively low, however.

Table 3. Characteristics of Receiver Operating Characteristics Curves for Postoperative Major Complications of Laboratory Results

| | *AUC* | *95% CI* | *Sig.* |
|---|---|---|---|
| Preoperative NLR | 0.524 | 0.420–0.627 | 0.639 |
| Postoperative NLR | 0.791 | 0.700–0.883 | <0.001 |
| Delta-NLR | 0.819 | 0.739–0.898 | <0.001 |
| Postoperative leukocyte count | 0.615 | 0.517–0.712 | 0.023 |
| Postoperative Hb | 0.602 | 0.489–0.715 | 0.047 |
| Postoperative CRP | 0.640 | 0.535–0.746 | 0.006 |

AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio.

The data were also analyzed with regard to specific complications. The postoperative NLR and delta-NLR were significantly higher in patients with postoperative hemorrhage, and the Hb significantly lower. The increased NLR in patients with hemorrhage could be explained by the upregulation of the innate immune system, and therefore more expression of myeloid leukocytes and their differentiation into neutrophils, among others, whereas the adaptive immunity will be downregulated, which means less expression of lymphocytes.[25] The NLR together with Hb, and heart rate[26] could be a strong tool to detect early hemorrhages. As expected, the NLR was not significantly different in patients with early strictures; they did not have an abdominal inflammation or high physical distress. In the remaining group of major complications, the postoperative NLR and delta-NLR were significant. A possible explanation could be the physical distress these patients had, due to a life-threatening event short after surgery, which increased the neutrophils and reduced lymphocytes.[27] It is helpful to intercept this group as well, given they require additional medical attention or procedures. Due to the low complication rate in this cohort, these results should be interpreted with caution.

No significant differences were found between NLR (preoperative, postoperative, and delta), leukocyte count, and CRP for readmission within 30 days. Most readmitted patients had no major complication, but had problems with pain regulation and nausea, which could explain no significant correlation was found.

Limitations of this study include a single-center design and a relatively low rate for major complications. This makes analyses of the subgroups more difficult. However, patient numbers are large enough to demonstrate the predictive value of the NLR for postoperative complications. In this study, we included three procedure types. As this was not a randomized study and there was no stratification, the patient characteristics were not equal between the three procedure types. However, we do not believe that this affected the results. As mentioned earlier, the baseline characteristics and presence of comorbidities were not shown to correlate with the occurrence of major complications. In the future, it could be interesting to investigate the effects of the difficulty or ease of the procedure, as technical difficulties during the procedure could potentially influence the postoperative laboratory results without indicating the presence of a postoperative complication. In our study, all the patients stayed overnight. Currently, more studies have shown that, for a select group of patients, metabolic surgery can be safe in daycare.[28] The NLR can rapidly increase following an acute infection within 6 h.[7] So even in daycare, the NLR might be of value. However, this should be analyzed in a prospective observational study, where new cutoff values should be determined. The discharge rules were used to help determine if the patient could be discharged. We compared the NLR with the other laboratory results from this checklist; we unfortunately did not include, for example, heart rate, which can be a predictor for hemorrhage. To include all predictors for day 1 discharge or same-day discharge, prediction models should be made in future research.

## Conclusion

In these times with the rise in bariatric procedures, more morbidly obese patients are exposed to the risk of a complication. ERABS protocols have proven their value in standardizing postoperative care, allowing for an early hospital discharge. However, there is need for a more sensitive predictive biomarker for early postoperative complications.[3] We believe that the NLR cannot replace the current parameters such as heart rate, leukocytes, Hb, and CRP, but should be an adjunct. Including the postoperative NLR and the delta-NLR may improve the process of identifying patients at higher risk for early complications. This could be an important information for the decision-making for safe day 1 discharge or early intervention.

## Author Disclosure Statement

No competing financial interests exist.

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