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ORIGINAL ARTICLE

Baseline neutrophil-to-lymphocyte ratio is associated with long-term T2D remission after metabolic surgery

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Abstract

Aims Metabolic surgery is considered as a therapeutic option for obese patients with type 2 diabetes (T2D). In order to identify novel laboratory variables that could improve the selection of patients who might greatly benefit from a surgical approach, we focused on the neutrophil-to-lymphocyte ratio (NLR) as a predictor of long-term T2D remission following metabolic surgery.

Methods Thirty-one obese patients with T2D included in this pilot study underwent Roux-en-Y gastric bypass or biliopancreatic diversion (BPD) at the Surgical Department of Genoa University, IRCCS Ospedale Policlinico San Martino in Genoa (Italy). Before surgery, serum samples were collected to evaluate blood count, glycemic profile, and circulating neutrophil degranulation products.

Results The median age was 56 years, median body mass index (BMI) was 32.37 kg/m^2, and median glycated hemoglobin was 8.4%. White blood cell count was in a range of normality, with a median NLR of 1.97. By a receiver operating characteristic curve analysis, NLR has been found to be significantly associated with T2D remission at 1, 3, and 5 years and the best cutoff of ≤ 1.97 has been identified by Youden index. When comparing study groups according to NLR cutoff, those with NLR ≤ 1.97 were older and underwent more often BPD. By a logistic regression analysis, NLR ≤ 1.97 has been found to predict T2D remission across 5 years, irrespective of baseline BMI.

Conclusions A baseline low NLR is associated with long-term T2D remission in obese patients undergoing metabolic surgery, suggesting that circulating inflammatory cells (i.e., neutrophils) might negatively impact on T2D remission.

Keywords Type 2 diabetes · Metabolic surgery · Neutrophil-to-lymphocyte ratio · Diabetes remission · Inflammation

Introduction

Recently, metabolic surgery has been included among glucose-lowering interventions for selected patients with type 2 diabetes (T2D) and obesity [1] mainly due to its quick and valid effect on hyperglycemia and glucose homeostasis. A large body of evidence accumulated both from randomized controlled clinical trials and from non-randomized observational studies demonstrates that metabolic surgery can reach better results in terms of glycemic control, reduction in cardiovascular (CV) risk factors, and both micro- and macrovascular complications in patients with T2D compared to lifestyle modifications and medical interventions [1, 2]. Pathophysiological mechanisms responsible for the beneficial effect of metabolic surgery on T2D are supposed to rely on a reduced insulin resistance and β-cell secretion recovery. Additional mechanisms, such as gut hormone release and gut microbiome, have been also postulated [3]. Moreover, a role for inflammation was hypothesized in a previous work from our group, in which an acute drop in metalloproteinase (MMP)-8 levels in the first month following bariatric

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surgery is positively correlated with a drop in leptin levels in the same period and was inversely associated with parameters of inadequate T2D control [4]. Additionally, we also tested C-reactive protein (CRP), a widely acceptable marker of low-grade inflammation, as a predictor of the beneficial effect of the metabolic surgery in T2D patients [5, 6].

Neutrophil-to-lymphocyte ratio (NLR) is widely used as a prognostic marker in the oncologic field [7–9], and in recent years, a predictive role was demonstrated also in the CV field, specifically for atrial fibrillation [10], coronary heart disease [11], and acute pulmonary embolism [12]. In the setting of bariatric surgery, NLR was previously considered as a predictor for 30-day post-surgery outcomes in order to distinguish patients potentially developing complications from those who could benefit from an early discharge [13].

In our pilot study, we aimed at investigating the role of NLR in long-term diabetes remission in a cohort of obese, T2D patients undergoing metabolic surgery, as defined by the American Diabetes Association [14].

Materials and methods

Clinical evaluation of patients

As previously described [5], 44 patients with T2D were recruited in a prospective cohort at the Surgical Department of Genoa University, Ospedale Policlinico San Martino in Genoa (Italy), from July 2007 to July 2009 to undergo Roux-en-Y gastric bypass (RYGBP) or biliopancreatic diversion (BPD). In this subanalysis of the previous study [5], we have considered only 31 patients, for whom all clinical records and blood samples across a 5-year follow-up period were available. Inclusion and exclusion criteria as well as the choice of the surgical technique were previously reported [5, 15, 16]. The Ethics Committee of IRCCS Ospedale Policlinico San Martino in Genoa (Italy) approved this protocol, performed in accordance with the guidelines of the Declaration of Helsinki. All patients gave written informed consent before being enrolled in the study.

The day before the surgical intervention, clinical characteristics, medications, and blood samples were collected in order to evaluate blood count, glycemic profile, and circulating neutrophil products of degranulation. Patients were then followed up until 5 years after surgery through outpatient visits, during which the assessment of anthropometric and blood parameters was performed.

Study endpoints

The primary endpoint of the present study was to determine whether NLR at the time of metabolic surgery (baseline) could predict the persistent remission of T2D at 1, 3, and 5 years after intervention. Secondary endpoints consisted in the assessment of potential associations between NLR and clinical characteristics of patients and inflammatory biomarkers. Two independent investigators who were blinded to biochemical analyses adjudicated the study endpoints, which were calculated based on data available for 31 patients.

Detection of biochemical and inflammatory biomarkers

Blood count and glycemic profile were evaluated by routine auto-analyzers. Serum levels of MMP-8, MMP-9, myeloperoxidase (MPO), and high-sensitivity CRP (hs-CRP) were measured by colorimetric enzyme-linked immunosorbent assay (ELISA) following the manufacturer's instructions (R&D Systems, Minneapolis, MN for all). Limits of detection were 62.5 pg/mL for MMP-8 and MPO, 31.25 pg/mL for MMP-9, and 15.625 pg/mL for CRP. Mean intra- and inter-assay coefficients of variation were $< 8\%$ for all markers measured by ELISA.

Statistical analysis

Analyses were performed using IBM Statistical Package for Social Science (SPSS) for Windows, version 23.0 (IBM CO., Armonk, NY) and MedCalc 12.5 (MedCalc Software, Ostend, Belgium). Categorical data were presented as absolute and relative frequencies and compared with Fisher's exact test according to NLR, while continuous variables were shown as median and interquartile range (IQR) and their comparison according to NLR was carried out by nonparametric Mann–Whitney *U* test. Ranked Spearman correlation coefficients were computed to establish correlations between NLR and clinical characteristics and inflammatory biomarkers. The prognostic ability of NLR was evaluated by a receiver operator characteristic (ROC) curve. The area under the curve (AUC) was given with 95% confidence interval (CI), and the cutoff point of NLR was calculated maximizing the sensitivity in accordance with the Youden index. The predictive ability of NLR toward 1-year, 3-year, and 5-year T2D remission was evaluated by a logistic regression and expressed with odds ratio (OR) and 95% CI. Stepwise backward elimination in the adjusted logistic regression (including age, gender, type of surgery, diabetes duration, previous antidiabetic therapy, baseline body mass index [BMI], baseline white blood cell [WBC] count, baseline fibrinogen, and baseline CRP) identified BMI and

Table 1 Baseline characteristics of the overall cohort

	$n=31$
Demographic	
Age, years (IQR)	56 (51–61)
Male, *n* (%)	26 (83.9)
Waist circumference, cm (IQR)	111 (103–130)
Weight, kg (IQR)	98 (86–116)
BMI, kg/m^2 (IQR)	32.37 (29.7–42.52)
Diabetes duration, years (IQR)	12 (8–16)
Type of surgical intervention	
RYGBP, *n* (%)	6 (19.4)
BPD, *n* (%)	25 (80.6)
Antidiabetic therapy	
Insulin, *n* (%)	16 (51.6)
Oral antidiabetic drugs, *n* (%)	15 (48.4)
Glycemic profile	
Fasting glycemia, mg/dL (IQR)	191 (155–248)
HbA1c, % (IQR)	8.4 (7.5–9.8)
Hematology	
WBC, $n\times10^9$/L (IQR)	7.21 (6.1–8.8)
Neutrophils, $n\times10^9$/L (IQR)	4.1 (3.5–5.6)
Lymphocytes, $n\times10^9$/L (IQR)	2.2 (1.9–2.8)
Monocytes, $n\times10^9$/L (IQR)	0.5 (0.45–0.6)
NLR (IQR)	1.97 (1.53–2.35)
Platelets, $n\times10^9$/L (IQR)	247 (224.5–281)
Neutrophil and inflammatory mediators	
MMP-8, ng/mL (IQR)	22.56 (6.16–37.38)
MMP-9, ng/ml	304.17 (140.15–767.49)
MPO, ng/mL	346.09 (200.20–661.98)
hs-CRP, µg/mL	3.31 (2.01–11.51)

Data are expressed as median (interquartile range [IQR]), number (n), or percentage (%)

BMI body mass index, *RYGBP* Roux-en-Y gastric bypass, *BPD* biliopancreatic diversion, *HbA1c* glycated hemoglobin, *WBC* white blood cells, *NLR* neutrophil-to-lymphocyte ratio, *MMP* metalloproteinase, *MPO* myeloperoxidase, *hs-CRP* high-sensitivity C-reactive protein

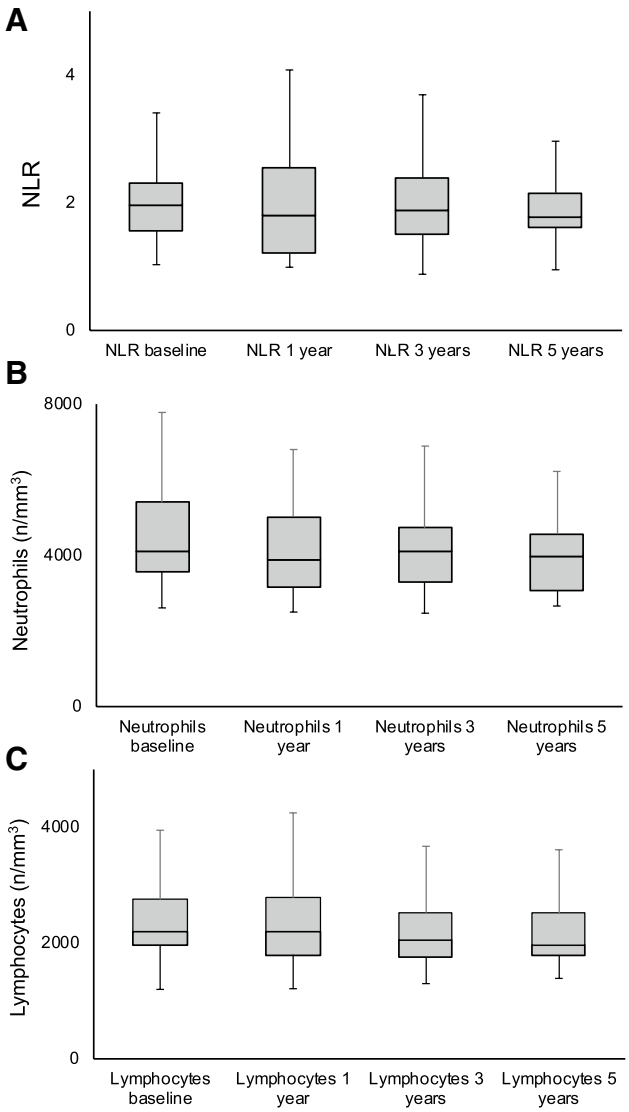

Fig. 1 Neutrophil-to-lymphocyte ratio (NLR) and neutrophil and lymphocyte counts. In the 5-year follow-up period, no statistically significant modification was found for NLR

previous antidiabetic therapy as independent risk factors for T2D remission. For all statistical analyses, a two-sided *p* value <0.05 was considered as statistically significant.

Results

Patients' characteristics

Clinical characteristics of the overall cohort at baseline are illustrated in Table 1. Median age was 56 (51–61), with a prevalence of males and a median duration of diabetes of 12 (8–16) years. Median BMI was 32.37 (29.7–42.52) kg/m^2, while median glycated hemoglobin (HbA1c) was 8.4% (7.5–9.8). WBC count was in a range of normality, with a median NLR of 1.97 (1.53–2.35), as depicted in Fig. 1a. Finally, levels of MMP-8, MMP-9, and MPO were 22.56 (6.16–37.38) ng/mL, 304.17 (140.15–767.49) ng/mL, and 346.09 (200.20–661.98) ng/mL, respectively (Table 1). The characteristics of the overall cohort across the whole follow-up period are reported in Supplementary Table 1. The ratio of T2D remitters to non-remitters during the follow-up period is shown in Supplementary Figure 1.

Baseline NLR and long-term T2D remission

In order to investigate the prognostic ability of NLR to predict long-term T2D remission, we performed a ROC curve analysis, by which NLR was found to show significant

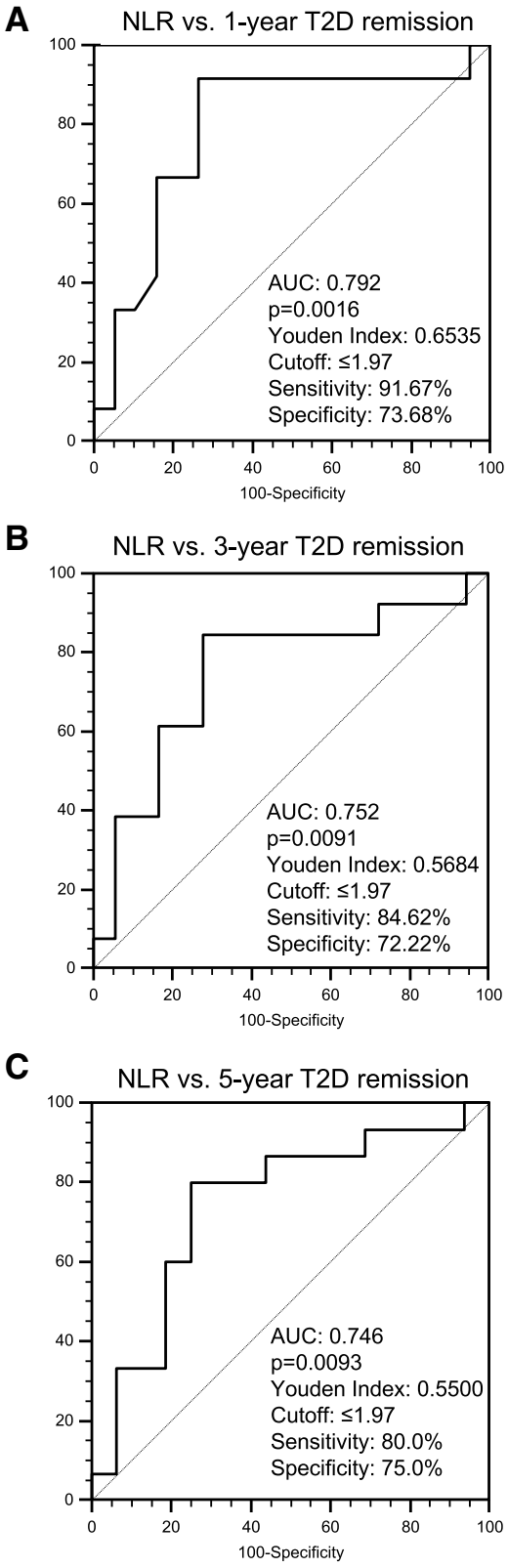

Fig. 2 Receiver operator characteristic curve analysis for neutrophil-to-lymphocyte ratio (NLR) toward T2D remission. **a** The prognostic ability of NLR toward T2D remission after 1 year from surgical intervention has been tested. A cutoff value of ≤ 1.97 has been identified. **b** The prognostic ability of NLR toward T2D remission after 3 years from surgical intervention has been tested. A cutoff value of ≤ 1.97 has been identified. **c** The prognostic ability of NLR toward T2D remission after 5 years from surgical intervention has been tested. A cutoff value of ≤ 1.97 has been identified

prognostic accuracy in the prediction of T2D remission at 1, 3, and 5 years (AUC 0.792 [95% CI 0.608–0.916], $p = 0.0016$, Fig. 2a; AUC 0.752 [95% CI 0.565–0.889], $p = 0.091$, Fig. 2b; AUC 0.746 [0.558–0.884], $p = 0.0093$, Fig. 2c, respectively). In accordance with the Youden index, a NLR cutoff of ≤ 1.97 was identified as the best cutoff point, with a sensitivity of 91.67, 84.62, and 80% and a specificity of 73.68, 72.22, and 75%, respectively, for each considered time point. When comparing the two study groups according to NLR cutoff, coinciding with median NLR of the overall cohort, we found that those with NLR ≤ 1.97 were older, underwent more often BPD compared to RYGBP, and presented with lower levels of neutrophils (Table 2). As depicted in Table 3, NLR is positively correlated with gender ($r = 0.392$, $p = 0.029$) and negatively with age ($r = -0.358$, $p = 0.048$). On the contrary, no statistically significant correlation was found for fasting glycemia, HbA1c, MMP-8, MMP-9, and MPO (Table 3). Interestingly, NLR did not show any significant modification during the 5-year follow-up period (Fig. 1).

By a logistic regression analysis, we tested whether NLR ≤ 1.97 was associated with the persistence of T2D remission across a 5-year follow-up period. Indeed, NLR ≤ 1.97 showed a persistent association with T2D remission at each time point, irrespective of BMI and previous antidiabetic therapy (OR 1.35, $p = 0.017$ at 1 year; OR 1.34, $p = 0.026$ at 3 years; OR 1.82, $p = 0.038$ at 5 years) that were considered as the only covariates as mentioned in paragraph 2.4 (Table 4).

Discussion

The main novelty of this paper is its contribute in verifying the use of NLR as a marker of T2D remission in a cohort of obese patients undergoing metabolic surgery. In this view, NLR can represent a valuable tool to help physicians in discriminating between long-term responders and non-responders to metabolic surgery.

Since T2D and its complications are known to provoke a low-grade inflammation and a derangement in the immune system, NLR can help clinicians in the detection of subclinical inflammation and endothelial dysfunction similar to CRP levels [17]. Interestingly, NLR combines two major components of the immune system: on the one side, high levels of neutrophils are a sign of an ongoing, non-specific inflammatory process and on the other side low levels of

Table 2 Baseline characteristics of the cohort according to neutrophil-to-lymphocyte ratio cutoff

	NLR ≤ 1.97 ($n = 16$)	NLR > 1.97 ($n = 15$)	p
Demographic			
Age, years (IQR)	60 (52–64.25)	53 (48–57)	**0.041**
Male, *n* (%)	15 (93.8)	11 (73.3)	0.129
Waist circumference, cm (IQR)	106 (103–128)	120.5 (97.5–133.75)	0.371
Weight, kg (IQR)	93 (85.25–109.87)	104 (94–130)	0.206
BMI, kg/m^2 (IQR)	32.27 (29.95–34.52)	39.84 (28.19–45.52)	0.502
Diabetes duration, yr. (IQR)	13 (8.5–19)	11 (3–15)	0.148
Type of surgical intervention			
RYGBP, *n* (%)	6 (37.5)	0 (0)	**0.010**
BPD, *n* (%)	10 (62.5)	15 (100)	
Antidiabetic therapy			
Insulin, *n* (%)	5 (31.3)	11 (73.3)	**0.020**
Oral antidiabetic drugs, *n* (%)	11 (68.8)	4 (26.7)	
Glycemic profile			
Fasting glycemia, mg/dL (IQR)	193.5 (174–245.25)	182 (147–301)	0.843
HbA1c, % (IQR)	8.3 (7.8–9.62)	8.6 (7.5–10)	0.968
Hematology			
WBC, $n \times 10^9$/L (IQR)	7 (5.64–8.33)	7.5 (6.3–9.9)	0.192
Neutrophils, $n \times 10^9$/L (IQR)	3.74 (2.92–4.18)	4.96 (4–6.2)	**0.007**
Lymphocytes, $n \times 10^9$/L (IQR)	2.33 (2.11–3.25)	2 (1.7–2.7)	0.085
Monocytes, $n \times 10^9$/L (IQR)	0.5 (0.42–0.6)	0.57 (0.44–0.6)	0.435
Platelets, $n \times 10^9$/L (IQR)	242.5 (228–287.75)	250 (213–278)	0.843
Neutrophil and inflammatory mediators			
MMP-8, ng/mL	24.00 (5.64–36.48)	14.58 (6.16–53.33)	0.892
MMP–9, ng/mL	303.97 (144.61–517.15)	328.84 (140.15–877.78)	0.626
MPO, ng/mL	418.87 (193.06–633.77)	335.90 (215.08–808.04)	0.953
hs-CRP, µg/mL	2.80 (1.86–9.67)	4.34 (2.75–20.66)	0.163

Data are expressed as median (interquartile range [IQR]), number (n), or percentage (%)

Statistically significant values are highlighted in bold character

BMI body mass index, *RYGBP* Roux-en-Y gastric bypass, *BPD* biliopancreatic diversion, *HbA1c* glycated hemoglobin, *WBC* white blood cells, *MMP* metalloproteinase, *MPO* myeloperoxidase, *hs-CRP* high-sensitivity C-reactive protein

lymphocytes show a relatively dysfunctional immune regulation or a quiescent immunity response. Hence, an impaired NLR is of help in reflecting the functional status of the immune system in a chronic disease such as T2D. As a further proof of it, a recent Dutch study confirmed the importance of NLR as a strong and independent risk indicator for mortality in the elderly population [18]. Of note, NLR is a widely accepted predictive marker in the CV field [10, 11], but it is still unclear whether it might be useful in T2D patients undergoing metabolic surgery. To date, NLR was evaluated in this setting only as predictor of 30-day outcome in terms of readmission, reoperation, and mortality when measured postoperatively at day 1 [13]. As well, since obesity is associated with an increased WBC count in humans, including neutrophils [19, 20], we might expect a pathophysiological relevance for these cells also in long-term complications. Actually, human adipose tissue is known to release pro-inflammatory cytokines and chemokines [21, 22] inducing neutrophilia via the demargination of intravascular neutrophils and enhancement of bone marrow granulopoiesis [19].

In our cohort, NLR did not correlate with hs-CRP levels (data not shown) or neutrophil degranulation products. A previous work from our group has shown that different neutrophil degranulation products are not always correlated. In fact, the acute abrogation of leptin levels following bariatric surgery was associated with a significant reduction in MMP-8 levels, but not in MMP-9 or MPO levels, particularly among T2D patients with morbid obesity [4]. Indeed, the acute MMP-8 drop did not lead to a concurrent reduction in the neutrophil count, but rather to a reduced degranulation, as demonstrated in in vitro experiments [4]. On this basis, the low-grade inflammation characterizing diabetes is

Table 3 Correlations between neutrophil-to-lymphocyte ratio and clinical data and circulating inflammatory biomarkers before metabolic surgery

NLR, % vs.		
	r	*p* value
Gender	0.392	**0.029**
Age	−0.358	**0.048**
Hypertension	0.040	0.832
BMI	0.128	0.492
Diabetes duration	−0.095	0.612
Antidiabetic therapy	−0.248	0.179
Fasting glycemia	0.213	0.251
HbA1c	0.160	0.389
C-peptide	−0.257	0.623
MMP-8	0.237	0.200
MMP-9	0.150	0.421
MPO	0.165	0.376

Correlations have been performed by Spearman's rank correlation coefficient

Statistically significant correlations are highlighted in bold character

NLR neutrophil-to-lymphocyte ratio, *BMI* body mass index, *HbA1c* glycated hemoglobin, *MMP* metalloproteinase, *MPO* myeloperoxidase

associated with a reduction in circulating pro-inflammatory cytokines and reactive oxygen species. Similarly, Dixon et al. [25] reported that a higher BMI was associated with a greater fall in the neutrophil count following bariatric surgery. These three studies included class III obese patients, while in our cohort only class I obese patients with T2D were enrolled. This difference might explain the different trends in neutrophil count that could be influenced by the release of pro-inflammatory cytokines proportionally to the extent of the adipose tissue [22]. However, Trottier et al. [26] showed that class III obesity did not greatly impair neutrophil functions, such as apoptosis and responsiveness to lipopolysaccharide stimulation, except for BMI > 50 kg/m^2.

A great concern may be raised when comparing the present results with prior ones from our group about inflammation [5, 6]. We previously found that high pre-surgery CRP levels were predictive of T2D remission and a decrease in visceral fat levels, thus suggesting that inflammation is a major driver of healing for these patients. In the current study, we report that a low baseline NLR is effective in predicting a durable remission of T2D irrespective of pre-surgery BMI and previous anti-diabetic therapy. In addition, the interplay between the adipose tissue, pancreatic β-cells, and systemic inflammation is likely to be more complicated

Table 4 Logistic regression illustrating the predictive value of pre-surgery neutrophil-to-lymphocyte ratio cutoff (NLR ≤ 1.97) toward type 2 diabetes remission across a 5-year follow-up period

	Unadjusted model			Adjusted model		
	OR	95% CI	*p* value	OR	95% CI	*p* value
T2D remission after 1 year						
NLR ≤ 1.97	1.41	1.12–1.77	**0.003**	1.35	1.06–1.73	**0.017**
Baseline BMI				0.84	0.69–1.03	0.101
Previous antidiabetic therapy				5.17	0.60–44.56	0.135
T2D remission after 3 years						
NLR ≤ 1.97	1.30	1.09–1.57	**0.004**	1.34	1.03–1.74	**0.026**
Baseline BMI				0.74	0.55–1.01	0.054
Previous antidiabetic therapy				1.68	0.19–15.13	0.642
T2D remission after 5 years						
NLR ≤ 1.97	1.28	1.08–1.52	**0.004**	1.82	1.03–3.21	**0.038**
Baseline BMI				0.43	0.17–1.08	0.071
Previous antidiabetic therapy				0.32	0.02–6.78	0.468

Statistically significant values are highlighted in bold character

OR odds ratio, *CI* confidence interval, *T2D* type 2 diabetes, *NLR* neutrophil-to-lymphocyte ratio, *BMI* body mass index

likely to be marginally driven by the innate immune system. In addition, the neutrophil count of patients at the time of surgery was within the normal range and a low NLR was shown to predict a long-lasting T2D remission.

While neutrophil count remained stable across 5 years in our cohort, Cunha et al. [23] reported a decrease of 10–20% 1 year after bariatric surgery and Roberts et al. [24] demonstrated that the normalization of the neutrophil count is than expected [27]. As well, some contrasting results on the role of CRP in metabolic surgery were already reported [28]. Although systemic inflammation as measured by CRP represents an important clue for the evaluation of T2D remission, CRP levels might especially reflect the inflammation of the adipose tissue, which greatly reduced after metabolic surgery. Indeed, the adipose tissue is an important source

of basal production of interleukin-6, which stimulates the hepatic production of CRP, a classical marker of systemic inflammation [29]. On the contrary, NLR might represent a better marker for systemic inflammation. Despite the human adipose tissue can induce neutrophilia via the release pro-inflammatory cytokines and chemokines [19], we did find that a low NLR is associated with diabetes remission among T2D patients sharing a low-degree inflammation. This aspect potentially underlies that a different behavior between systemic and local inflammations takes place as a consequence of metabolic surgery, thus needing to be further characterized in larger trials specifically testing this hypothesis.

Some limitations have to be acknowledged when reading our findings. First, the small sample size recruited at a single center may limit the generalization of our results. Accordingly, our patients were not such obese compared to other studies oft-quoted and BPD was the preferred surgical technique based on the expertise of our center. Second, current findings on a 5-year period follow-up may not take into account a possible relapse of T2D, so that further studies on a longer follow-up period including information on WBC and NLR are warranted. Finally, we did not have any fresh blood to test neutrophil and lymphocyte functions in vitro at the baseline or at the following timepoints, thus limiting our investigation toward the pathophysiological role of NLR in the setting of metabolic surgery.

Conclusions

A low pre-surgery NLR is associated with long-term diabetes remission among obese patients with T2D, suggesting that the inflammatory cell count (i.e., neutrophils)—but not their activation—might be considered as a marker of diabetes remission. Accordingly, no correlation was found between NLR and neutrophil degranulation products. Further studies are warranted in order to enlarge our knowledge about the role of the immune system as disease marker for diabetes remission following metabolic surgery, given the progressively increasing spread of this therapeutic strategy. Considering that NLR is an easy-to-measure and cheap parameter, our preliminary results might highlight interest in testing its clinical relevance in larger cohorts of patients.

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Authors' contributions NS, GBC, and FSP recruited patients and made the surgical intervention. ABona, LL, FC, AV, and FM analyzed samples by ELISA. ABono gave help for the statistical analysis. ABona wrote the manuscript. RC, FD, GA, DM, and FM read critically the manuscript and gave suggestions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in the study were conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all patients included in the present study.

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