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ORIGINAL ARTICLE

Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio Are Not Prognostic Biomarkers in Rectal Cancer Patients with Curative Resection

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Abstract

Background Actual predictors of survival and recurrence for rectal cancer patients undergoing curative resection mostly come from pathological data of surgical specimen. Recently, novel blood biomarkers have been proposed as useful tools in cancer patient management, but few and conflicting data have been reported in rectal cancer. We evaluated the prognostic relevance of preoperative platelet-to-lymphocyte (P/L) ratio and neutrophil-to-lymphocyte (N/L) ratio on survival and recurrence in patients undergoing laparoscopic curative resection for rectal cancer.

Methods All consecutive patients who referred for primary rectal disease to the Department of General Surgery in Cittadella (Italy) from June 2005 to September 2015 were retrospectively evaluated. Patients with metastatic disease at surgery were excluded. P/L and N/L ratios were calculated. For patients undergoing neoadjuvant chemo-radiotherapy, pre-treatment data were considered. Follow-up data were updated at December 2016.

Results One hundred fifty-two patients were included in the study, 49 (32%) received neoadjuvant chemo-radiotherapy. Both P/L and N/L ratios showed poor discriminative performance on 5-year OS and DFS. Time-dependent ROC curves showed no improvements in discriminative performance of P/L and N/L ratios when considering different time endpoints. Multivariable analysis identified CEA—rather than P/L or N/L ratios—as independent predictor of OS and DFS, adjusting for age, tumor stage, and postoperative morbidity.

Conclusion Neither P/L nor N/L ratios were associated with survival after rectal cancer surgery. Further studies on large series might provide insights on the role of these inexpensive blood biomarkers in rectal cancer.

Keywords Rectal cancer · Laparoscopy · Survival · Recurrence · Platelet-to-lymphocyte ratio · Neutrophil-to-lymphocyte ratio · Biomarkers

Introduction

Rectal cancer is one of the most common neoplasms worldwide.[1] Results of treatment for rectal cancer have significantly improved in the last 30 years thanks to the introduction of and the adherence to the oncological principles of total mesorectal excision (TME): removal of the mesorectum to allow for minimal pelvic recurrence.[2,3] In patients with local-advanced rectal cancer, TME combined with neoadjuvant chemo-radiotherapy has improved survival rate from 50% to over 70% in the last 30 years, and has reduced recurrence rate from 40% to less than 10%.[4,5]

Giuseppe Portale and Francesco Cavallin contributed equally to this work.

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In the last few years, several studies aimed to identify the subgroup of rectal cancer patients with unfavorable prognosis in term of survival and recurrence.[6,7] An important but controversial topic is the definition of markers that could be associated with those patients who might benefit from adjuvant therapy.[8] Most of the tools used by the clinicians to define "high-risk" rectal cancer patients rely on pathological examination of the surgical specimen, as depth of tumor invasion, nodal involvement, presence of distant metastases, perineural and lymphovascular invasion.[9–11] However, the main drawback is that these markers can only be assessed after surgery.

Peripheral blood biomarkers, such as platelet-to-lymphocyte ratio (P/L ratio) and neutrophil-to-lymphocyte ratio (N/L ratio), have been used to preoperatively assess the prognosis in some gastrointestinal solid cancers, emphasizing on the effect of inflammatory response in tumor growth and metastatic diffusion.[12–20] The precise role of cellular components of host inflammation (including platelets, lymphocytes, and neutrophils) in promoting/containing tumor progression is clearly not fully understood. However, the relationship between inflammation and cancer has been widely explored.[21] A few mechanisms of host-tumor-inflammation relationship have been suggested, involving platelets (having protumor/neoangiogenetic effect), neutrophils (reflecting host response to systemic inflammation), and lymphocytes (reflecting host antitumor forces). Therefore, the ratios platelets/lymphocytes and neutrophils/lymphocytes might express the equilibrium between protumor (inflammatory pathway) and antitumor (immune response) forces.[18,22]

Although several studies already published on the prognostic role of P/L and N/L ratios, they investigated heterogeneous events (overall survival, disease-free survival, time to recurrence) and reported conflicting results. Moreover, few data have been made available specifically on rectal cancer, so far.[23]

The aim of this study was to evaluate the role of P/L and N/L ratios as prognostic biomarkers of oncological outcomes—namely, overall and disease-free survival—after laparoscopic resection with curative intent of non-metastatic rectal cancer (LCRRC).

Materials and Methods

Patients

We evaluated all consecutive patients who referred for primary rectal adenocarcinoma to the Department of General Surgery in Cittadella (Italy) from June 2005 to September 2015. Data were retrospectively retrieved from a prospectively collected dedicated database. We excluded from this study patients not operated on by laparoscopy, those not operated with curative intent, those with metastatic disease at surgery, and those with rectal resection as part of pelvic exenteratio due to other non-rectal primary malignancies.

Preoperative Staging and Treatment

Preoperative cancer staging included endoscopic ultrasound, abdominal CT scan, and/or pelvic MRI. All patients with locally advanced tumor (cT3-4 and/or N+) of the mid/low rectum on preoperative examinations received a long course of neoadjuvant chemo-radiotherapy (CRT) with continuous venous infusion of 5-FU or capecitabine and radiation treatment directed to the pelvis (4500 cGy). Surgery usually followed 8 weeks after completing the treatment. Standard oncological principles of TME were applied for rectal cancer resection. The rectal dissection was carried out at least 5 cm below the lower edge of the tumor with partial mesorectal resection for high-rectal tumors (rectal anterior resection, RAR), while in case of mid-/low-rectal tumors the dissection was extended to the pelvic floor and a complete mesorectal resection was accomplished (low anterior resection, LAR). A diverting ileostomy or colostomy was performed in patients who had received preoperative CRT for a locally advanced mid-/low-rectal tumor and underwent a total mesorectal excision.

Variables

Platelets, neutrophils, and lymphocytes were analyzed in routine blood tests. Blood samples from each patient were obtained within 1 week prior to surgery, during preoperative evaluation tests. For patients undergoing neoadjuvant CRT, pretreatment hematologic data (1 week prior to CRT) were considered. Platelet-to-lymphocyte ratio was calculated as the absolute count of platelets divided by the absolute lymphocyte count. The neutrophil-to-lymphocyte ratio was calculated as the absolute count of neutrophil divided by the absolute lymphocyte count. Patient comorbidities were assessed using the American Society of Anesthesiologists (ASA) score[24] and the Charlson Comorbidity Index (CCI).[25] CCI calculation includes major comorbidities with different weight (1, 2, 3, or 6) according to their clinical relevance.

Follow-up

Patients were followed up routinely by the operating surgeon and seen at least once after discharge at 4 weeks after surgery and subsequently for oncological follow-up, on a regular basis, by the surgeon and/or oncologist with a combination of clinical examination, laboratory data, and radiological imaging. In the first 5 years after surgery, patients were seen every 6 months with CEA levels measured and thereafter yearly. Colonoscopy was performed at 12 and 48 months after surgery; abdominal CT scans and/or abdominal ultrasound every 6 months and then at 48 and 60 months; chest X-rays every

12 months for the first 5 years; chest CT scans every 12 months for the first 5 years.

Statistical Analysis

Continuous data were expressed as median and interquartile range (IQR). The correlation between continuous data was evaluated using Spearman rank correlation. The study endpoints were overall survival (OS) and disease-free survival (DFS), that were calculated according to proposed guidelines on cancer endpoints.[26] DFS and relapse-free survival (RFS) overlapped in the present study, because no second primary cancers occurred during follow-up.[27] Time-dependent receiver operating characteristic (ROC) curve analysis was used to assess the performance of P/L and N/L ratio in predicting survival outcomes.[28] A subgroup analysis was performed to evaluate the performance of P/L ratio and N/L ratio according to neoadjuvant therapy, adjuvant therapy, age, and tumor stage. Time-dependent ROC curve analysis was also used to assess the performance of potentially relevant hematologic data (CEA and CA19.9) and of single components of P/L ratio and N/L ratio (lymphocyte, neutrophil, and platelet count) in predicting survival outcomes. Two Cox regression model were estimated to identify independent predictors of 5-year OS and of 5-year DFS among P/L ratio, N/L ratio, CEA, and CA 19.9, adjusting for age, CCI, neoadjuvant treatment, pTMN stage, and postoperative morbidity. Time-dependent ROC curves were estimated using R package "survival ROC".[28] Statistical analysis was performed using R 3.3.2 software (R Foundation for Statistical Computing, Vienna, Austria).[29]

Ethics

The study was conducted according to the Helsinki Declaration and patients gave their consent to have their data collected for scientific purposes. The study was approved by the local Ethics Committee (4131/U15/17).

Results

Patient Characteristics

One hundred and fifty-nine patients who underwent laparoscopic resection of primary rectal cancer with curative intent were retrospectively evaluated. Seven patients were excluded, due to incomplete hematologic data on clinical charts (6 patients) or idiopathic thrombocytopenic purpura (1 patient with Werlhof's disease), thus 152 patients were included in the study. Patient characteristics are presented in Table 1. Median age was 70 years (IQR 59–76). One third of the patients received neoadjuvant CRT, 36 (23.7%) adjuvant chemotherapy. The completeness of TME was achieved in 143 out of 152 patients (94.1%), while the margin of the specimen was positive only in one patient (0.7%). Postoperative surgical complications occurred in 17 patients (11.2%), including ileus (6 patients), anastomotic leak (4 patients), abdominal collection (2 patients), colonic ischemia (2 patients), hemorrhage (1 patient), ileal volvulus (1 patient), and substenosis of the ileostomy (1 patient).

Table 1 Patient characteristics

No. of patients	152
Sex (M/F)	100:52
Age, years[a]	70 (59–76)
BMI, kg/m^{2}[a]	25.6 (23.4–28.3)
ASA score:	
- 1–2	99 (65.1)
- 3–4	53 (34.9)
Charlson comorbidity Index[a]	2 (2–3)
Neoadjuvant treatment, yes	49 (32.2)
Operative time, min[a]	210 (180–255)
Type of surgery	
- RAR	58 (38.2)
- LAR	86 (56.6)
- APR	7 (4.6)
- Total colectomy[b]	1 (0.6)
pTNM stage	
- 0 (post CRT)/Tis	17 (11.2)
- I	60 (39.5)
- II	39 (25.6)
- III	36 (23.7)
Lymph nodes removed, no.[a]	17 (13–23)
Adjuvant therapy	36 (23.7)

Data are expressed and no. (%) or [a] median (IQR), [b] In a patient with a previous right hemicolectomy

RAR rectal anterior resection, *LAR* low anterior resection, *APR* abdominoperineal resection

Hematologic Data

Hematologic data are presented in Table 2. Platelet and neutrophil count were correlated (rho 0.23, $p < 0.0001$), as well as P/L ratio and N/L ratio (rho 0.58, $p < 0.0001$). Age was not correlated with hematologic data (lymphocyte count: rho − 0.08, $p = 0.35$; neutrophil count: rho − 0.04, $p = 0.63$; platelet count: rho − 0.03, $p = 0.67$; N/L ratio: rho 0.02, $p = 0.81$; P/L ratio: rho 0.07, $p = 0.41$).

Survival

The 5-year OS was 78% and the 5-year DFS was 74%, with a median follow-up of 59 months (IQR 33–76). Nineteen

Table 2 Hematologic data

No. of patients	152
Lymphocyte count,[a] $\times 10^3/\mu L$	1.8 (1.4–2.2)
Neutrophil count,[a] $\times 10^3/\mu L$	4.2 (3.3–5.3)
Platelet count,[a] $\times 10^3/\mu L$	232 (194–276)
N/L ratio[a]	2.2 (1.7–3.1)
P/L ratio[a]	129 (99–165)
Lymphocytopenia present ($< 1.0 \times 10^3/\mu L$)	6 (4.0)
Neutrophilia present ($> 8.2 \times 10^3/\mu L$)	6 (4.0)
Thrombocytosis present ($> 450 \times 10^3/\mu L$)	5 (3.3)
CEA[a, b] (ng/mL)	2 (1.1–3.8)
CEA (> 5 ng/mL)[b]	25 (19.5)
CA 19.9[a, c] (U/mL)	10 (6–16)

Data expressed as no. (%) or [a] median (IQR). Data not available in [b] 24 and [c] 33 patients

patients (12.5%) had distant recurrence alone, and 7 patients (4.6%) had both local and distant recurrence.

Both P/L ratio and N/L ratio showed poor discriminative performance regarding 5-year OS (AUC: 0.45 and 0.47, respectively) and 5-year DFS (AUC: 0.48 and 0.47, respectively) (Fig. 1). Time-dependent ROC curves showed no improvements in discriminative performance of P/L ratio and N/L ratio regarding different time endpoints (1, 2, 3, 4, and 5 years; Fig. 2). AUCs of ROC curves are reported in Supplementary Table 1.

In addition, the single components of P/L ratio and N/L ratio had poor discriminative performance regarding 5-year OS (AUC: lymphocyte count 0.52, neutrophil count 0.47, platelet count 0.41) and 5-year DFS (AUC: lymphocyte count 0.52, neutrophil count 0.52, platelet count 0.42).

The discriminative performance of P/L ratio, N/L ratio, CEA, and CA 19.9 was compared in 119 patients who had complete hematologic data. All the hematologic parameters showed low discrimination regarding both 5-year OS and 5-year DFS (AUCs < 0.70; Fig. 3). Multivariable analysis identified CEA—rather than P/L ratio, N/L ratio, or CA 19.9—as independent predictor of both OS and DFS (Table 3), adjusting for age, Charlson Comorbidity Index, neoadjuvant treatment, pTMN stage, and postoperative morbidity.

Subgroup Analysis

The discriminative performance of P/L ratio and N/L ratio regarding 5-year OS and 5-year DFS was assessed in

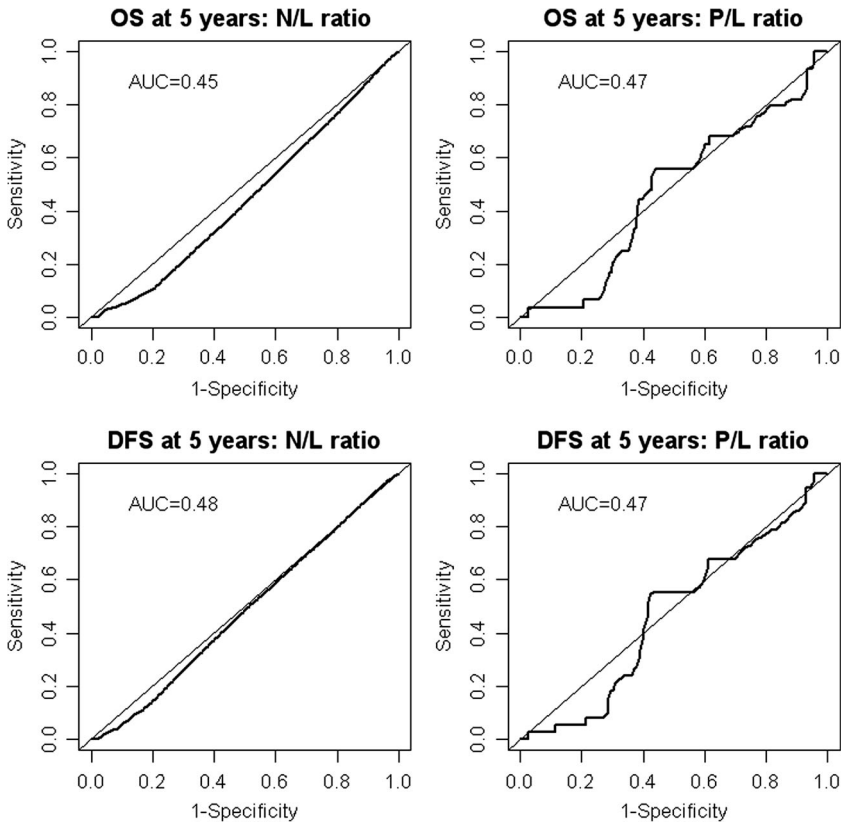

Fig. 1 Performance of P/L ratio and N/L ratio in predicting 5-year OS and 5-year DFS: ROC curves

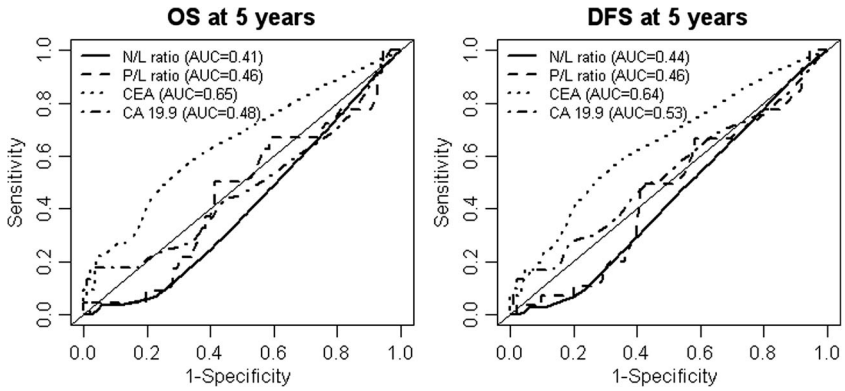

Fig. 2 Comparison of P/L ratio, N/L ratio, CEA, and CA 19.9 in predicting 5-year OS and 5-year DFS: ROC curves

subgroups of patients according to neoadjuvant therapy, adjuvant therapy, age, and tumor stage (Supplementary Table 2). The discriminative performance of P/L ratio and N/L ratio was low in any subgroup (Fig. 4).

Discussion

The present study aimed to assess the role of P/L and N/L ratios as prognostic markers after laparoscopic resection with curative intent of non-metastatic rectal cancer patients. These blood biomarkers are inexpensive and readily available as preoperative assessment in any rectal cancer patient.

Previous studies suggested a relationship between peripheral blood biomarkers, inflammatory pathway, and immune response.[18] In addition, these biomarkers might provide some advantages over the pathological prognostic evaluation (i.e., tumor invasion, nodal involvement, presence of distant metastases, perineural and lymphovascular invasion), because the latter is more expensive and can only be assessed after surgery.[8–11] The

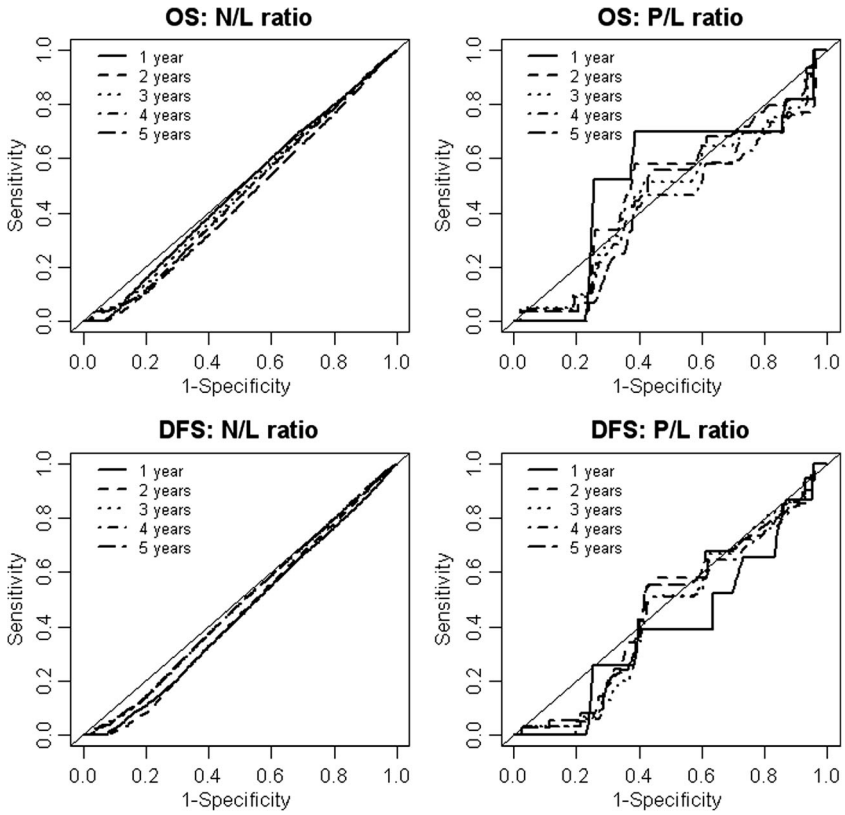

Fig. 3 Performance of P/L ratio and N/L ratio in predicting OS and DFS at 1, 2, 3, 4, and 5 years: ROC curves

Table 3 Effect of N/L ratio and P/L ratio on survival

	Univariate analysis		Multivariable analysis[a]	
	p value	HR (95% C.I.)	*p* value	HR (95% C.I.)
Overall survival				
N/L ratio	0.45	0.92 (0.74–1.14)	0.35	0.77 (0.46–1.33)
P/L ratio	0.73	0.99 (0.98–1.00)	0.69	1.00 (0.99–1.01)
CEA	*0.01*	1.01 (1.00–1.02)	*0.02*	1.02 (1.01–1.03)
CA 19.9	0.32	1.02 (0.98–1.06)	0.66	0.99 (0.94–1.04)
Disease-free survival				
N/L ratio	0.59	0.95 (0.79–1.14)	0.24	0.77 (0.51–1.18)
P/L ratio	0.59	0.99 (0.98–1.00)	0.47	1.00 (0.99–1.01)
CEA	*0.001*	1.01 (1.00–1.02)	*0.008*	1.02 (1.01–1.03)
CA 19.9	0.12	1.03 (0.99–1.06)	0.85	1.00 (0.96–1.04)

p values <0.05 are italized

HR hazard ratio, *C.I.* confidence interval

[a] Adjusted for age, Charlson Comorbidity Index, neoadjuvant treatment, pTMN stage, and postoperative morbidity

prognostic role of P/L ratio and N/L ratio has been investigated in gastrointestinal solid cancers[12–20], but few data and conflicting findings have been reported in rectal cancer.[23]

In our series, the discrimination of both P/L ratio and N/L ratio was poor regarding both 5-year OS and 5-year DFS. The analysis at different time points (1, 2, 3, 4, and 5 years) confirmed such poor discrimination even at short term. In addition, the single components of P/L ratio and N/L ratio (lymphocyte count, neutrophil count, and platelet count) showed poor discrimination as well. Multivariable analysis identified CEA as independent predictor of survival; nevertheless, CEA had low discrimination as showed by ROC curve analysis.

Our findings add to the few data available for P/L and N/L ratios in rectal cancer patients undergoing curative surgery and to the conflicting results of larger heterogeneous studies in which the subgroup of rectal cancer patients are usually less than 20%.[20]

To our knowledge, only two studies evaluated the prognostic effect of both P/L and N/L ratios in rectal cancer patients undergoing resection. Carruthers et al.[30] analyzed 115 UK patients undergoing preoperative chemo-radiotherapy and found that only N/L ratio (≥ 5) was significantly associated with OS, DFS, and time to local recurrence, with a nearly 3-fold difference in median survival between patients with and without elevated N/L ratio. Toiyama et al.[31] reported on 89 Japanese patients with locally advanced rectal cancer who underwent neoadjuvant chemoradiation treatment followed by TME surgery. Platelets and N/L ratio predicted OS, while platelets were the only biomarker independently predicting DFS and recurrence, along with lymph node involvement. In our series, subgroups analysis according to neoadjuvant therapy, adjuvant therapy, age, and tumor stage confirmed the poor discrimination of both P/L ratio and N/L ratio.

A recent systematic review reported the findings of four studies from Eastern countries that showed an association between N/L ratio and OS in rectal cancer,[23] but a recent Chinese study on 202 rectal cancer patients showed no prognostic role at all for N/L ratio.[32] In addition, a recent systematic review on P/L ratio did not find any significant association between P/L ratio and survival in rectal cancer patients.[20]

The limitations of the study include the retrospective design and the single institution series. However, selection bias has been avoided by the inclusion of all consecutive LCRRC that were performed during the study period. Moreover, the completeness of data has been achieved by standardized surveillance program with prospective collection of data in an electronic database and by updating follow-up information before the analysis, thus mitigating the common weakness of retrospective studies.

The strengths of this study rely in the inclusion of only rectal cancer patients, thus avoiding the analysis of a miscellaneous colorectal cohort, and in the sample size, which is one of the largest so far. In addition, all patients had a close clinical/radiological follow-up to properly assess survival and recurrence. Despite the two previous studies on rectal cancer included only patients receiving neoadjuvant therapy,[30,31] we included both patients with and without neoadjuvant treatment, in order to provide a "real" picture of the role of the biomarkers. For patients receiving preoperative CRT, we considered pre-treatment hematological values, to avoid the effects of systemic treatments on patient immunological status and on blood counts. Similarly, we included all stage III patients receiving adjuvant chemotherapy, because this treatment has become the standard of care for stage III patients. P/L ratio and N/L ratio have been evaluated as continuous variables without suggesting any cutoffs, in order to avoid the risk of dichotomizing continuous variable.[33] Finally, we performed a sub-analysis that confirmed the main findings in subgroups of patients according to neoadjuvant therapy, adjuvant therapy, age, and tumor stage. Our data confirmed the heterogeneity of findings on this topic in literature, with lack of agreement regarding the optimal cutoff value and the prognostic effect of P/L and N/L ratios. Interestingly, all but one of the previous studies were from Eastern populations (China, Korea, or Japan) and overall included less than 1000 patients, altogether. This might explain—at least in part—the differences with our results, but to date, it represents just a speculation.

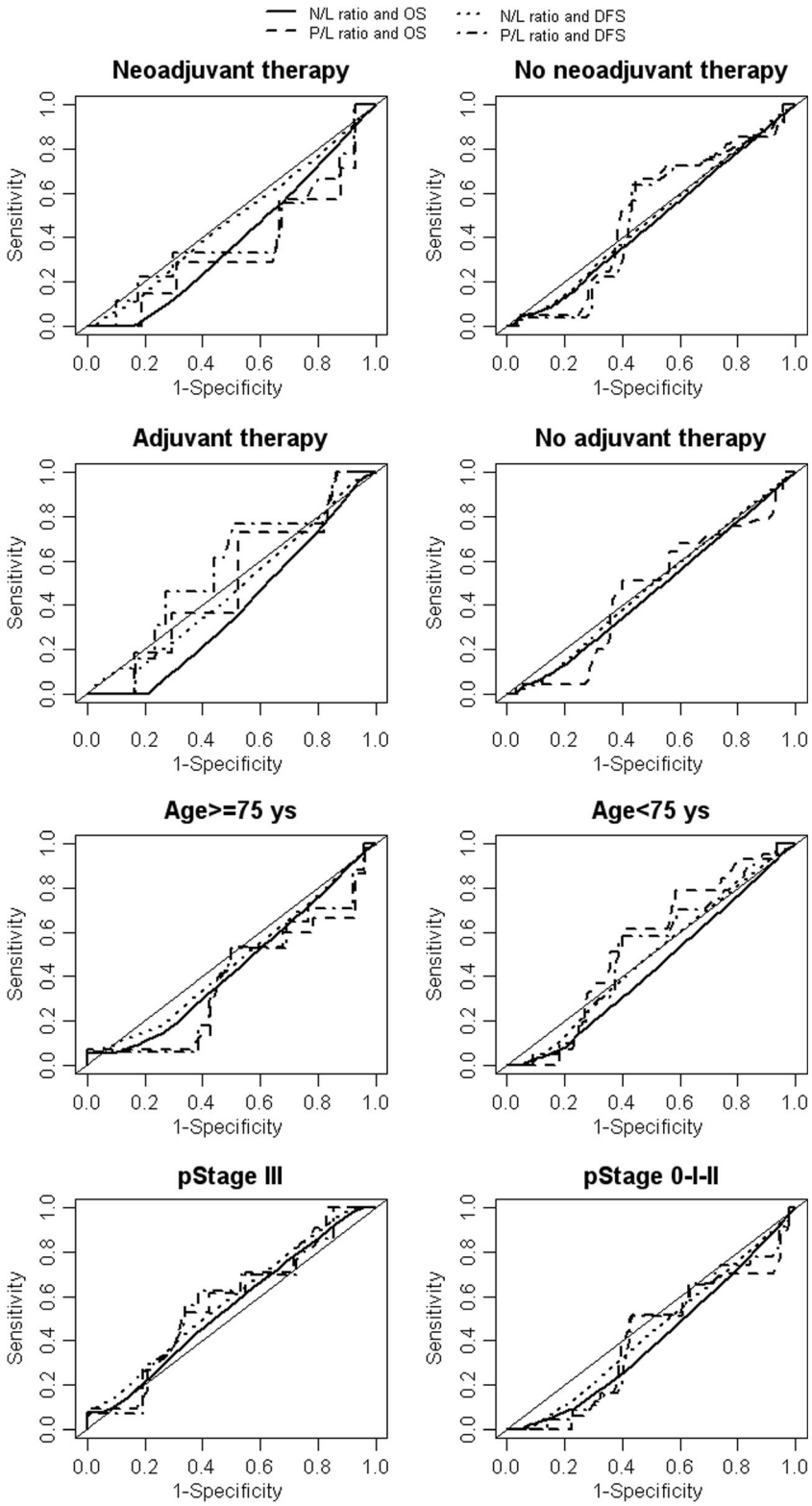

Fig. 4 Performance of P/L ratio and N/L ratio in predicting OS and DFS according to patient age, tumor stage, neoadjuvant therapy and adjuvant therapy: ROC curves

Conclusions

In conclusion, we reported one of the few and largest experience on the role of both P/L and N/L ratios as potential prognostic blood biomarkers for patients undergoing laparoscopic curative TME rectal cancer resection. Neither of these ratios significantly contributed as independent predictor of OS and DFS. Tumor features and postoperative pathological

cancer staging system currently remain the "gold" standard in defining prognosis and in suggesting postoperative management and surveillance programs in rectal cancer. Future studies on large series of rectal cancer patients might provide further knowledge on this topic and help clinicians in treatment decision making with the use of inexpensive blood biomarkers.

Authors' Contribution - Conception and design: G Portale, A Valdegamberi, F Cavallin, F Frigo, V Fiscon
- Acquisition of data: G Portale, A Valdegamberi, F Cavallin
- Analysis and interpretation of data: G Portale, F Cavallin, A Valdegamberi, F Frigo, V Fiscon
- Drafting of the manuscript: G Portale, F Cavallin, A Valdegamberi, F Frigo, V Fiscon
- Revising of the manuscript: G Portale, F Frigo, V Fiscon

Compliance with Ethical Standards

Conflict of Interest None of the authors has conflict of interest to disclose

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