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ORIGINAL ARTICLE

Prognostic role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with midgut neuroendocrine tumors undergoing resective surgery

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Abstract

Aim Several studies demonstrated the prognostic value of the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and platelet-to-white blood cells ratio (PWR) in different types of tumors. However, there is no information about a possible role of NLR, PLR and PWR as predictor of presence of metastasis or multifocal disease in patients undergoing surgery with curative intent for midgut NET. The aim of our study was to test the role of preoperative NLR, PLR and PWR as predictors of patients undergoing surgery with curative intent for midgut NET.

Methods We retrospectively enrolled seven foregut, 35 midgut and six hindgut NET patients with gastrointestinal neuroendocrine tumors operated in our Units from January 2005 to June 2016. Details about preoperative laboratory data, surgical operation, histology and follow-up were retrieved. Non-parametric statistics, ROC curve analysis and survival analysis were used.

Results NLR was significantly higher in patients with distant metastasis ($p = 0.04$). The ROC curve analysis indicated that a threshold value of NLR of 2.6 predicted the presence of peritoneal metastasis with a specificity of 100% and a sensitivity of 71% and an overall accuracy of AUC = 0.81 (95%CI: 0.59–0.94), $p = 0.05$. PLR and PWR was not be associated to metastasis but tended to be associated to multifocal disease.

Conclusion In patients with midgut NET, an impaired adaptive immune response, as suggested by a high NLR ratio, was associated to the presence of distant metastasis and in particular of peritoneal metastasis. This information may be helpful when planning the treatment of a patient with a midgut NET.

Keywords Midgut neuroendocrine tumors · Neutrophil-lymphocyte ratio · Platelet-lymphocyte ratio

Introduction

Neuroendocrine tumors (NETs) are rare neoplasms that comprise a heterogeneous group of lesions arising from cells of diffuse neuroendocrine system expressing neural markers such as synaptophysin or chromogranin [1]. An analysis of SEER database in the USA demonstrated an incidence of 5.25 per 100,000 people in 2004 [2], while in Italy, the incidence is 3–4 per 100,000 people in 1 year [3]. NETs are classified by site, histology, and staging [4]. The natural history and the therapy success differ by anatomic site of NETs [1]. Gastrointestinal- (GI-) NETs include foregut NET (esophagus, stomach, and proximal duodenum), midgut NET (from distal half of the duodenum to the proximal two-thirds of the transverse colon including appendix NET), [5] and hindgut NET [6, 7].

Surgery of midgut NETs is demanding because of the need for associated extensive node dissection and assessment of possible synchronous lesions [8]. Midgut NETs are often small, multifocal, and difficult to localize preoperatively, and can be overlooked during operative exploration. Indeed, either capsule endoscopy or small bowel enteroscopy may underestimate tumor burden [9]. Moreover, in a recent series, preoperative imaging understaged disease in 14/20 (70%) when compared with intra-operative findings [10]. In patients with multifocal primary tumors, peritoneal localization, and miliary liver metastases, no imaging modality was able to detect entire

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disease spread leaving to meticulous intra-operative abdominal examination the task to provide a complete disease resection [10]. Therefore, markers that may suggest the presence of multifocal or metastatic disease might alert the surgeon to heighten operative vigilance.

Peripheral blood neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), and platelet-to-white blood (PWR) cell ratio, which are indicators of systematic inflammatory response, were reported as independent unfavorable prognostic factors for malignant mesothelioma, soft tissue sarcomas, epithelial ovarian cancer, and breast cancer [11–14]. In a recent study, Kubo et al. indicated the preoperative NLR as prognostic predictor for cancer-specific survival of colorectal cancer patients [15]. Moreover, other studies explored the role of NLR as predictive of response to chemotherapy [16]. In a recent study, Salman et al. analyzed pre-chemotherapy values of NLR patients with gastrointestinal and pancreatic NET, indicating that significantly higher NLR and PLR were associated to an advanced stage and a worse progression-free survival [17]. However, to our knowledge, there is no information about a possible role of NLR, PLR, and PWR before surgery as predictor of presence of metastasis or multifocal disease.

The aim of our study was to test the role of preoperative NLR, PLR, and PWR as predictors of patients undergoing surgery with curative intent for midgut NET.

Patients and methods

Study design

In this retrospective study, we selected all the consecutive patients with diagnosis of GI-NET from the prospectively collected electronic database of the Regional Hospital "Ca′ Foncello," 31100 Treviso, Italy, that comprises 394 patients with histological diagnosis of NET from 1999 to 2016. We included in this study only patients who underwent resective surgery with curative intent for gastrointestinal NET and whom preoperative full blood count was available. Patients who had any kind of hematological disease was excluded from this study. Patients' characteristics and laboratory, diagnosis, treatment, and survival data were retrieved. Patients had given their consent to have their anonymized data collected, analyzed, and then published for scientific purposes. We divided the patients according NET origin (foregut, midgut, and hindgut) [18].

NET site, pathological features, and staging

The histological analyses on surgical specimen reported carcinoid histotype, synchronous adenoma or adenocarcinoma, grading, number of mitosis, Ki67 expression, chromogranin and synaptophysin expression, vascular invasion, total number of lymph nodes retrieved, and number of metastatic lymph nodes. The staging of neoplasia was established according to American Joint Committee on Cancer, 7th edition, for patients who underwent surgery after 2010 and according to the 6th edition for patients treated before 2010 [19].

Laboratory analysis

Blood samples were taken in fasting patients at admission for surgery and immediately sent to the laboratory for the analysis. The full blood count (FBC) was performed obtaining red blood cells (RBC), white blood cells (WBC), neutrophils, lymphocytic, and platelets counts. The NLR and PLR were then calculated, compared in the three groups, and tested as predictors of nodal, liver and peritoneal metastases, and multifocal disease. A dedicated sub-analysis was performed on the midgut NET group.

Follow-up

The follow-up protocol after resection for neuroendocrine tumors depends on staging, site of tumors, and hormone secretion. It included clinical examination every six months with serum chromogranin and a DOTATEC scan when required.

Statistical analysis

Statistical analysis was carried out with STATISTICA 5.1 software. The results are presented as median and IQR (interquartile range) unless otherwise specified. Non-parametric Mann–Whitney's U test for independent variables or Kruskal–Wallis ANOVA for multiple variables was used for comparison as appropriate. Kendall's correlation test was used to assess the association between variables. Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of the NLR, PLR, and PWR as predictors of nodal and distant metastases. Survival analysis was carried out with Kaplan–Meier methods and curves were compared with log rank test. A Cox proportional hazard model was created including NLR, presence of metastasis, and patients' age to estimate the covariate effect of the possible survival predictors. Statistical significance was set at $p < 0.05$.

Results

Patients' characteristics

In this retrospective surgical series, 48 patients underwent resective surgery with curative intent for GI-NET between 2005 and 2016. Their median age was 67 (53.5–74.0) years

and 26 of them were male. In 19 patients, there were signs of vascular invasion and in 26, there were nodal metastases. Eighteen of them had distant metastasis. Liver metastasis was observed in 15 patients and peritoneal metastasis was observed in four patients (a patient had both). In this cohort, seven foregut, 35 midgut, and six hindgut NET patients were included. All of them underwent stomach, bowel, or colonic resection and 14 of them underwent also to liver resection. At abdominal exploration, liver resection was not possible in a patient due to the extension of the disease. Peritoneal disease was treated with partial peritonectomy of the visible lesions. The characteristics of the patients are resumed in Table 1.

Pathological details and full blood count in different sites of gastrointestinal NET

In this cohort, the comparison of pathological characteristics of foregut, midgut, and hindgut NET showed a significantly higher Ki67+ and mitosis cell rate in foregut NET compared with midgut NET ($p = 0.0085$ and $p = 0.0054$, respectively). Moreover, synaptophysin positivity was significantly lower in hindgut NETs ($p = 0.007$). However, no significant difference was observed in terms of hematological features and in terms of NLR, PLR, and PWR. Pathological markers and full blood count according to different sites of gastrointestinal NETs are shown in Table 2.

NLR, PLR, and PWR as predictors of multifocal disease and metastasis in midgut NETs

In the midgut NET subgroup, we tested the three parameters, NLR, PLR, and PWR, as possible predictor of multifocal disease, distant metastasis, peritoneal and liver metastasis, and distant metastasis. Only NLR was significantly higher in patients with distant metastasis ($p = 0.04$). The ROC curve analysis indicated that a threshold value of NLR of 1.9 predicted the presence of distant metastasis with a specificity of 90% and a sensitivity of 71% and an overall accuracy of AUC = 0.75 (95% CI 0.55–0.90, $p = 0.018$), and a threshold value of NLR of 2.6 predicted the presence of peritoneal metastasis with a specificity of 100% and a sensitivity of 71% and an overall accuracy of AUC = 0.81 (95% CI 0.59–0.94, $p = 0.050$). PLR and PWR were not associated to metastasis but tended to be associated to multifocal disease. A threshold value of PLR of 48.4 tended to predict the presence of multifocal disease with a specificity of 45% and a sensitivity of 100% and an overall accuracy of AUC = 0.75 (95% CI 0.55–0.90, $p = 0.09$) and a threshold value of PWR of 32.3 tended to predict the presence of multifocal disease with a specificity of 52% and a sensitivity of 100% and an overall accuracy of AUC = 0.73 (95% CI 0.53–0.87, $p = 0.09$). ROC curve analysis is shown in Fig. 1.

The sub-analysis among patients who did not undergo preoperative CT confirmed that a threshold value of NLR of 2.6 predicted the presence of peritoneal metastasis with a specificity of 100% and a sensitivity of 82% and an overall accuracy of AUC = 0.86 (95% CI 0.63–0.97, $p = 0.01$). Moreover, in this subgroup of patients, a threshold value of PLR of 104.4 tended to predict the presence of multifocal disease with a specificity of 67% and a sensitivity of 88% and an overall accuracy of AUC = 0.78 (95% CI 0.55–0.93, $p = 0.08$). ROC curve analysis is shown in Fig. 2.

NLR, PLR, and PWR as predictors of overall survival

Overall survival analysis showed a trend toward a better survival in patients with low NLR compared with those with high NLR ($p = 0.09$). The threshold value we used was 2.63 as obtained to predict distant metastasis. PLR and PWR were not associated to overall survival. In a multivariable model including NLR, metastasis at diagnosis, and age, only high NLR and age were independent predictors of survival (HR = 4.71 (95% CI 1.18–18.80, $p = 0.02$) and HR = 1.06 (95% CI 1.00 to 1.13, $p = 0.03$), respectively). Survival analysis is shown in Fig. 3.

Discussion

Nowadays, it is widely accepted that immunological response to tumors has a role in development of cancer and in outcome of patients. The measurement of inflammatory index in blood sample can be used to predict the outcome and response to therapy in several kinds of solid tumor [20–22]. In a recent work, Salman et al. explored the role of pretreatment NLR and PLR in patients with GI and pancreatic NETs. The study evaluated the outcome of 132 patients and concluded that NLR and PLR are simple laboratory that can be used to identify NETs undergoing chemotherapy with a worse prognosis [17]. In our study, we tested and compared NLR, PLR, and PWR as possible predictors of presence of metastasis or multifocal disease in patients with midgut NETs undergoing surgical resection with curative intent.

In our series, the median lymphocyte count was particularly low, just above the lower threshold for the adult population. These data indicated that a relevant percentage of patients was below the normal values and thus could be defined as lymphopenic. More than 25% of the patients of our study group had metastasis at the moment of the operation and most of them was undergoing or had undergone chemotherapy. Classic chemotherapy for gastrointestinal NET includes alkylating agents such as temozolomide [23] and lymphopenia is one of the most often occurring side effect of this chemotherapy protocol [24]. Therefore, in our series, a subanalysis taking in account only patients who did not undergo

Table 1 Patients' characteristics

NET site	Parameters	Patients number	
Foregut 7 pts	Stage	1	T2N0M0
		1	T3N0M0
		1	T2N1M0
		2	T3N1M0
		1	T2N1M1
		1	T3N2M1
	Grading	4 G1; 1 G2; 2 G3	
	Synchronous adenocarcinoma	1	
	Carcinoid histotype	1	
	Liver metastasis (pts)	1	
	Peritoneal metastasis (pts)	1	
	Therapy	1 chemotherapy	
Midgut 35 pts	Stage	4	T1N0M0
		3	T2N0M0
		1	T3N0M0
		1	T2N1M0
		7	T3N1M0
		4	TxN1M0
		4	T2N1M1
		8	T3N1M1
		3	T4N1M1
	Grading	28 G1; 3 G2; 4 G3	
	Synchronous adenocarcinoma	5	
	Carcinoid histotype	8	
	Liver metastasis (pts)	13	
	Peritoneal metastasis (pts)	3	
	Preoperative therapy	5 chemotherapy; 3 somatostatin analogs	
Hindgut 6 pts	Stage	1	T2N0M0
		2	T2N1M0
		1	T1N0M1
		1	T3N1M1
		1	T4N0M0
	Grading	1 G1; 3 G2; 2 G3	
	Synchronous adenocarcinoma	2	
	Carcinoid histotype	1	
	Liver metastasis (pts)	2	
	Peritoneal metastasis (pts)	0	
	Preoperative therapy	2 chemotherapy	

preoperative CT was performed and it confirmed that NLR is a good predictor of peritoneal metastasis. Thus, the first take home message of this study is that some patients presents with lymphopenia that might be either associated to an advanced tumor stage or to chemotherapy prior to intestinal surgery.

In the last decade, several inflammatory markers have been investigated whether they can be used for a prognostic parameter independent of TNM stage in a variety of cancer population with mostly favorable results [25–28]. Several studies focused on the different components of the full blood count [29–31] and for this reason, we aimed to test and compare the diagnostic performance of NLR, PLR, and PWR as possible predictors of presence of peritoneal metastasis or multifocal disease in order to provide an easy tool to alert the surgeon of a possible diffuse disease while operating a midgut NET. In our series, only NLR was significantly higher in patients with metastasis and had a sufficient accuracy in the prediction of the presence of distant and peritoneal metastases in midgut NET patients. The concepts of the immune editing and immune surveillance well explain these data [32]. In fact, several studies revealed that cancer progression and prognosis are determined not only by tumor characteristic but also by host inflammatory response [33, 34]. In midgut NETs, a high NLR ratio (that indicated an impaired adaptive immune response) was associated to distant metastasis. An impairment might explain this observation secondary to the neoplasm immunoescape mechanism or by a metastatic spread due to the immunosurveillance failure. In any case, independent of the cause, NLR should be tested in larger groups to be used in NET staging before surgery.

In our series, PLR and PWR tended to be associated to the presence of multifocal disease and, a sub-analysis taking in account only patients who did not undergo preoperative CT confirmed that PLR tended to predict the presence of multifocal disease. As observed by several studies, midgut NET multifocality has no impact on survival or recurrence outcomes [35, 36] but the multifocality might make radical resection challenging. In our opinion, larger studies should aim to verify whether the mere tendency of PLR and PWR to be associated to multifocal disease, which we have observed in our series, is confirmed. The presence of an easy and cheap marker of multifocality might provide surgeons the awareness of a multifocal disease and of the need of extra care to examine the bowel to resect.

In our series, overall survival analysis showed a trend toward a better survival in patients with low NLR compared with those with high NLR, while PLR and PWR were not associated to overall survival. This observation is consistent with that observed in the case of other tumors. In fact, an elevated preoperative NLR was an independent predictor of worse survival after resection for brain metastases [37], early breast cancer [38], clear cell renal carcinoma [39], and other ones. In our series, multivariable analysis showed that high NLR and age were independent predictors of survival while the presence of metastatic disease not result to predict overall survival. The role of age in this

Table 2 Pathological details and full blood count in different sites of gastrointestinal NET. Comparisons were carried on with Kruskal–Wallis ANOVA for continuous variables and with chi-square test for dichotomous ones

NET site	Foregut NET		Hindgut NET		Midgut NET		
	Median (*n*)	IQR (%)	Median (*n*)	IQR (%)	Median (*n*)	IQR (%)	*p* value
Age (years)	70	56–75	63.5	56–68	66	53–75	0.6825
Ki67 (% cancer cell/5HPF)	35	16–55	12.5	6–42	2	1–3	0.0085
Mitosis (% cancer cell/5HPF)	17.5	5–25	1.5	1–2	1	1–2.75	0.0054
Chromogranin + (pts)	7	100%	4	66.6%	35	100%	0.0007
Synaptophysin + (pts)	7	100%	6	100%	32	91.5%	0.552
RBC (mL)	4.71	4.22–5.07	4.615	4.08–5.08	4.6	4.23–4.92	0.8754
WBC (mL)	7.15	633–7.38	7.49	5.95–11.45	6.36	5.26–7.96	0.7193
Neutrophils (mL)	4.49	4.15–5.14	3.8	3.72–5.39	3.51	2.42–4.64	0.1934
Lymphocytes (mL)	1.61	1.31–1.76	1.5	1.32–1.66	1.82	1.32–2.15	0.558
Platelets (mL)	249	156–298	299.5	201–401	224.5	183–282	0.5796
NLR	2.95	2.53–3.33	2.91	2.38–3.69	2.29	1.36–3.25	0.2982
PLR	49.11	32.30–69.08	63.58	51.42–102.04	75.395	42.83–86.35	0.5075
PWR	34.8	21.7–43.7	35.98	22.6–58.1	35.035	25.3–45.8	0.9495

model can be easily explained by the fact that we took in exam overall survival instead of disease-specific survival. This limit of the study was intrinsically due to its retrospective design and it is associated to the small sample size that prevented us to include other possible co-variables such as a more detailed tumor stage, tumor type, and tumor

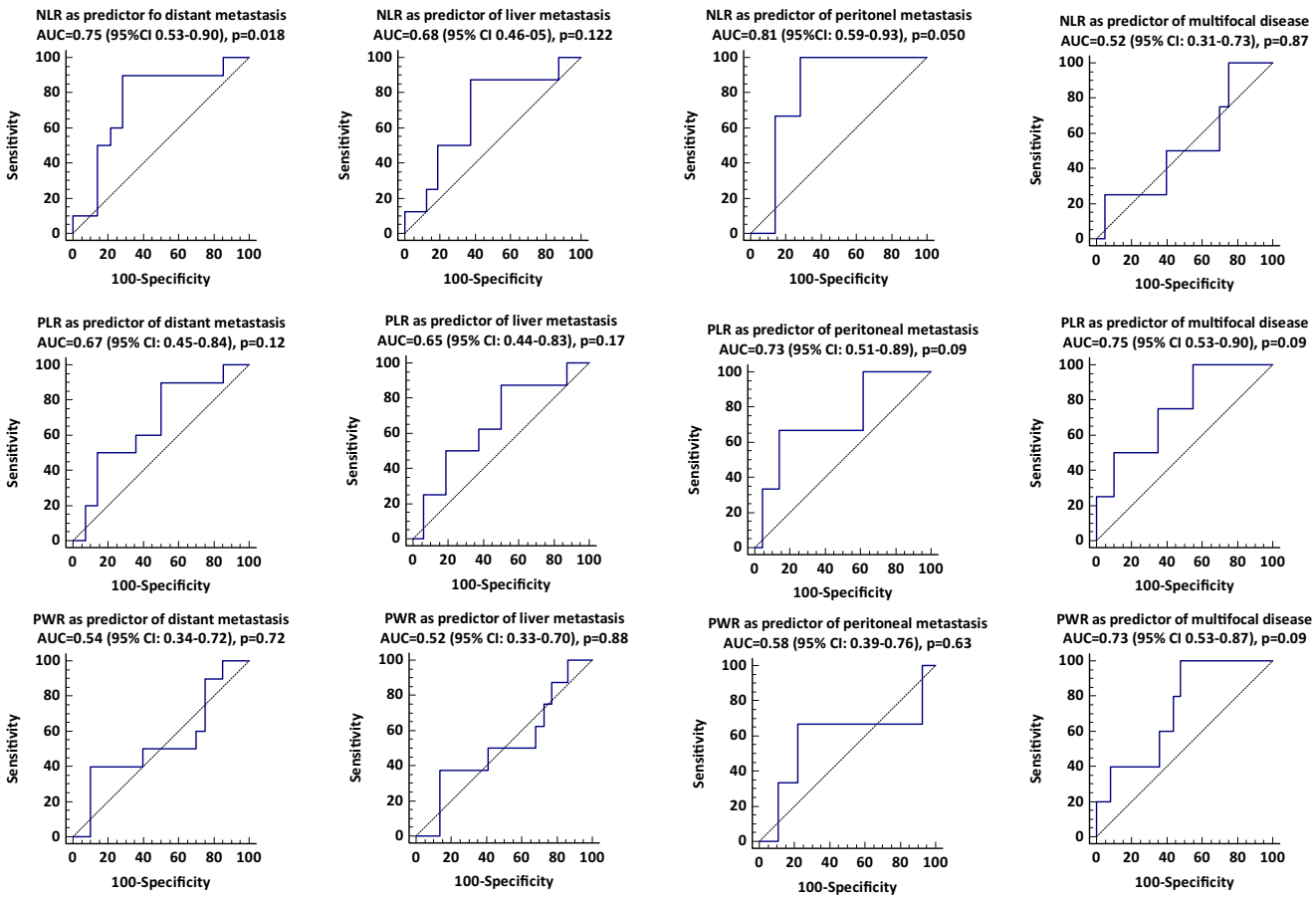

Fig. 1 The ROC curve analysis of NLR, PLR, and PWR as predictors of presence of distant, liver and peritoneal metastases, and of multifocal disease

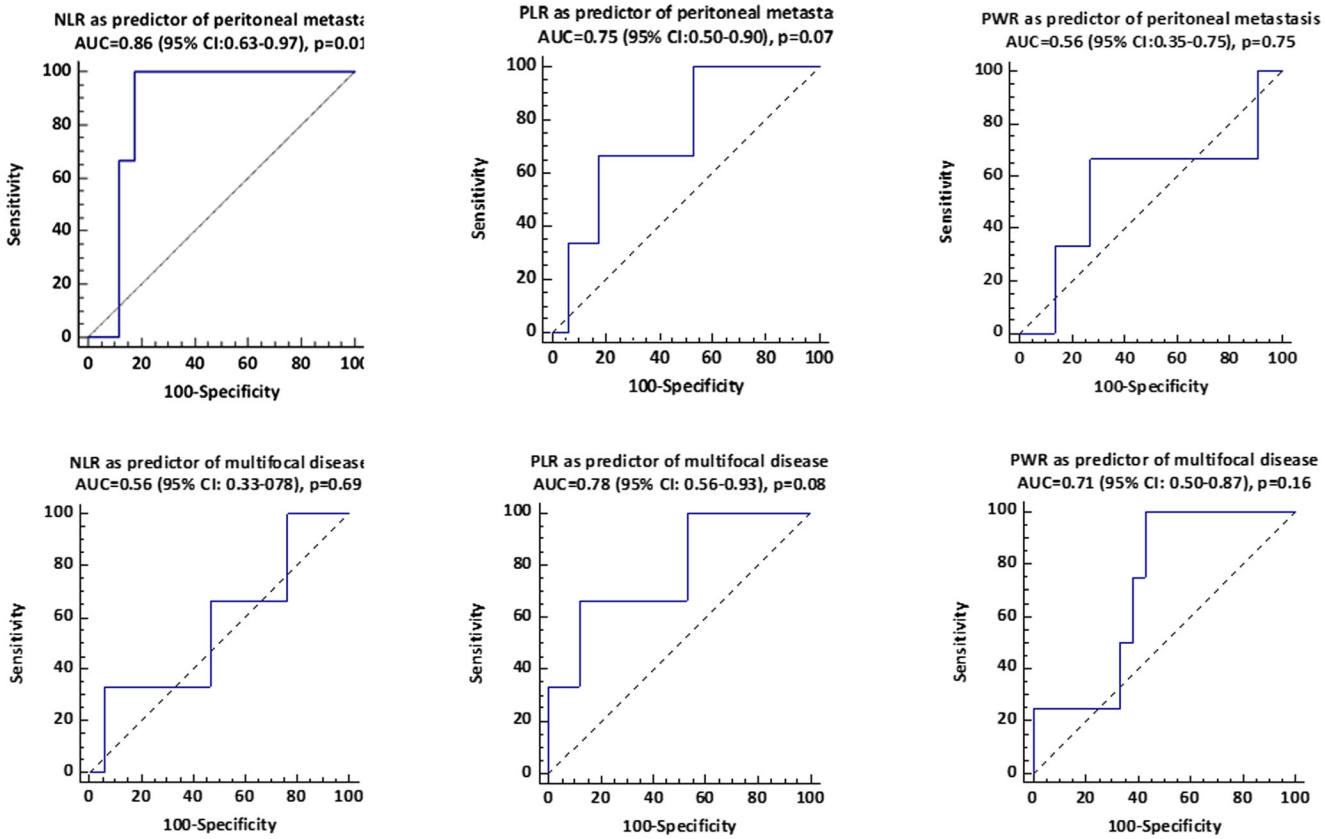

Fig. 2 The ROC curve sub-analysis among patients who did not undergo preoperative CT

treatment. On the other hand, these results confirmed those observed by Salman et al. using pre-chemotherapy values of NLR patients with gastrointestinal and pancreatic NET, indicating that there was a strong negative correlation between progression-free survival and NLR [17]. This is the only other study addressing the role of NLR in gastrointestinal NET but it is focused on pre-chemotherapy NLR and PLR values, while in the present study, pre-surgery values were taken in exam. This different time points may be the reason we did not find the same results about PLR.

The main limits of this study are the small sample size and the retrospective design of the study principally due to the rarity of gastrointestinal NET. These limits prevented to investigate further factors that might better define the immunological environment of gastrointestinal NET. In fact, further markers such as C-reactive protein/albumin ratio could have been tested [40].

In conclusion, several patients with gastrointestinal NET present with lymphopenia that might be associated to and advanced tumor stage or, alternatively, to chemotherapy prior to intestinal surgery. In patients with midgut NET, a high NLR ratio (that suggests an impaired adaptive immune response) was associated to the presence of distant metastasis and in particular of peritoneal metastasis. This information may be helpful when planning a surgical resection of a midgut NET. These findings cannot

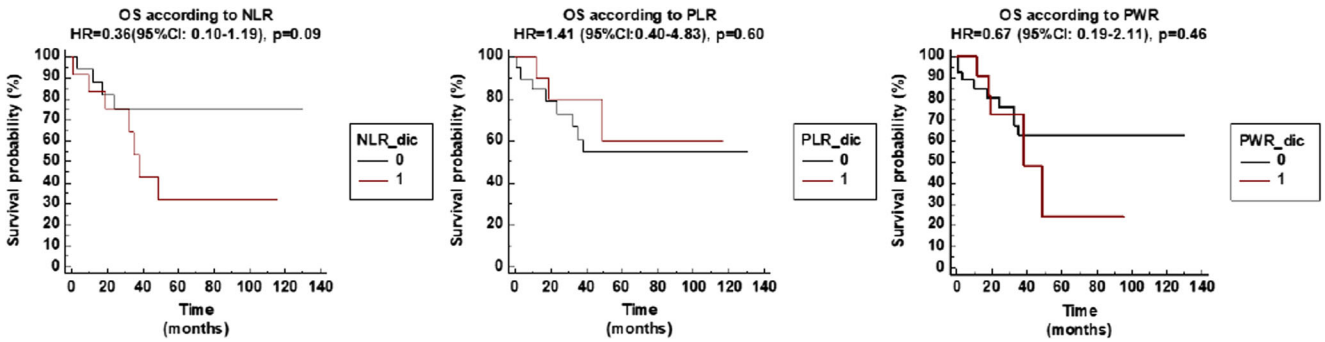

Fig. 3 Survival analysis of NLR, PLR, and PWR as predictors of overall survival

be used as a single parameter for choosing a type of operation, but a high NLR can suggest the need of a more detailed examination before the surgery and during the operation. Moreover, this association might be useful for planning future studies on the effectiveness of chemotherapy or on follow-up protocols.

Author contributions Anna Pozza: study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript

Bruno Pauletti: acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript

Marco Scarpa: study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript

Cesare Ruffolo: acquisition of data, drafting of manuscript, critical revision of manuscript

Nicolò Bassi: drafting of manuscript, critical revision of manuscript

Marco Massani: study conception and design, drafting of manuscript, critical revision of manuscript

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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