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Prognostic value of pre-operative systemic immune-inflammation index and platelet to lymphocyte ratio in peritoneal carcinomatosis of ovarian origin

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ABSTRACT

Background and objectives: The aim of this study was to investigate the impact of systemic immune-inflammation index (SII), platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) on the survival outcomes of patients who underwent to cytoreductive surgery (CRS) and HIPEC for ovarian peritoneal carcinomatosis.

Methods: A retrospective analysis of 68 cases following surgery at our department between 2015 and 2020 was performed. Receiver Operating Characteristic (ROC) curve was used with Youden index to calculate the optimal cutoff values for SII, PLR and NLR.

Results: Univariate analysis revealed that high preoperative values of SII, PLR and NLR were correlated with worse overall survival (OS) and disease-free survival (DFS) in these patients. In the multivariable analysis, high SII was recognized as an independent prognostic factor for OS (CI 95%: 0.002- 3.835, p = 0.097) and high PLR was recognized as an independent prognostic factor for DFS (CI 95%: 0.253–2.248, p = 0.007).

Conclusion: SII and PLR could be useful prognostic tools to predict outcomes of patients who underwent to CRS and HIPEC for ovarian peritoneal carcinomatosis.

1. Introduction

In its early stages, ovarian cancer presents with few symptoms, resulting in over half of all patients being diagnosed at an advanced stage, and causing around 125,000 deaths yearly worldwide [1].

Surgery is the main treatment approach to early-stage ovarian cancer, whereas the standard of care for advanced tumors has been cytoreductive surgery in combination with systemic chemotherapy. In recent years, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) has shown to improve survival rates in advanced stage ovarian cancer patients [2].

In recent times, as well, the scientific community has developed a better understanding of this disease's behavior, in which the body's inflammatory and immune response plays a crucial role. Blood cell counts of neutrophils (N), lymphocytes (L), and platelets (P) are a reflection of this response; and some have suggested their ratios (neutrophil-to-lymphocyte [N-L] and platelet-to-lymphocyte [P-L]), as well as the systemic immune-inflammatory index (SII) can be used as prognostic tools. Several studies have concluded that higher preoperative values of these ratios are associated with a poorer prognosis in patients with solid organ tumors, and in those with peritoneal carcinomatosis of colorectal origin [3–10].

In ovarian cancer, both N-L and P-L ratios have been shown to have an unfavorable impact on progression-free survival (PFS) and overall survival (OS) rates [11].

However, the role of these newer prognostic factors has yet to be studied in peritoneal carcinomatosis of ovarian cancer. The purpose of this study is to analyze the usefulness of these ratios as prognostic factors in patients diagnosed with peritoneal carcinomatosis of ovarian origin, who have undergone cytoreductive surgery and HIPEC.

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2. Materials and methods

2.1. Data collection

We performed a retrospective, single-center study of patients who underwent cytoreductive surgery and HIPEC for ovarian peritoneal carcinomatosis from January 2015 to December 2020 at our department.

The patients' clinical information were collected from their electronic medical record.

Inclusion criteria: Patients with radiological and/or pathological diagnosis of peritoneal carcinomatosis of ovarian cancer who underwent cytoreductive surgery and HIPEC, and whose medical history, laboratory parameters, and surgical sheet were complete. Exclusion criteria: Active anti-tumor treatment prior to inclusion in the study, such as chemotherapy, radiation therapy, immunotherapy, and corticosteroid therapy; patients with data of active infection; patients with hematological diseases and/or autoimmune diseases.

2.2. Ethics statement

The present study was approved by the Research Ethics Committee of our hospital. The requirement for informed consent was waived owing to the retrospective nature of this study.

2.3. Preoperative assessment

The blood test results used during the study were taken from the time of diagnosis of peritoneal carcinomatosis of ovarian cancer and before the administration of neoadjuvant chemotherapy if they received it. So, none of the patients had active anti-tumor treatment when we collected their serological tests.

2.4. Definitions

We divided the patients into two main profiles: those with a de-novo peritoneal carcinomatosis diagnosed by imaging techniques or exploratory laparoscopy, and those who had undergone surgery for ovarian cancer in the past and whose disease progressed into peritoneal carcinomatosis.

The age recorded was that of the patient at the time of cytoreductive surgery and HIPEC. Response to neoadjuvant chemotherapy was divided into two groups, according to results in radiological findings: if no disease was found, patients were considered to have had full radiological response; in cases where the tumor had shrunk or not progressed, the radiological response was considered partial-stable. Radiological response to neoadjuvant chemotherapy was defined following RECIST 1.1 criteria [12].

N-L and P-L were calculated as the ratio of absolute neutrophil count and platelet count, respectively, divided by absolute lymphocyte count. SII was calculated using the following formula: SII=(P*N)/L. where P, N, and L refer to the peripheral platelet, neutrophils, and lymphocyte counts, respectively.

Ninety-day postoperative complications were recorded and classified using the Clavien-Dindo score [13].

Local relapse was defined as the recurrence of the tumor within the surgical field, whereas systemic relapse was defined as the recurrence of the tumor outside the surgical field.

2.5. Surgical technique

A complete abdominal cavity exploration was performed to evaluate the extent of peritoneal seeding, which was recorded as Peritoneal Cancer Index (PCI) score [14]. Following this, cytoreductive surgery was carried out using the Sugarbaker technique [15]. After the surgery, completeness of cytoreduction score (CCR) was calculated to assess the volume of residual disease. Findings were classified into four categories: CCR0 indicated no macroscopic residual cancer remained; CCR1 indicated no residual nodule larger than 5 mm in diameter remained; CCR2 indicated a residual nodule from 5 mm to 2.5 cm in diameter remained; CCR3 indicated a residual nodule larger than 2.5 cm remained [14].

The chemotherapy agent used for the HIPEC was paclitaxel 120mg/m2, over 60 min. Patients with allergies to paclitaxel were given cisplatin 75mg/m2.

2.6. Variables

The following variables were studied: epidemiological—age, sex, past medical history; serological tests— neutrophils, platelets, and lymphocytes at the time of diagnosis of peritoneal carcinomatosis.

Additional values collected for this study were: prior surgical history of primary ovarian tumor, grade (if patient had already undergone surgery, tumor pathology of the first procedure was considered), neoadjuvant chemotherapy and patient's response, PCI calculated during surgery, degree of tumor cytoreduction, and type of treatment used in HIPEC. Long-term follow-up variables considered were: disease-free survival (DFS) measured in months after the carcinomatosis surgery, and overall survival (OS) rates.

2.7. Follow-up

Patients were followed up with an outpatient consultation every 3 months during the first 2 years for follow-up testing, including tumor markers and CT or MRI; then, every 6 months until the 5-year mark.

2.8. Statistical analysis

Continuous variables are represented by the means (standard deviation) if the distribution was normal or medians (inter-quartile range) if it was non-normal. Categorical variables are represented by the frequencies of their categories. The Chi-square and Student's t-tests were used to compare categorical and continuous variables, respectively.

Receiver Operating Characteristic (ROC) curve was used with Youden index [maximum (sensitivity + specificity-1)] to calculate the optimal cutoff values for N-L, P-L, and SII.

For the univariate analysis of prognostic factors, survival rates were estimated using the Kaplan-Meier survival curve, and compared using the Log-rank test. Factors that showed statistical significance in univariate analysis of $p \leq 0.2$ were entered into the Cox proportional hazard model for multivariate analysis. For the purpose of this study, independent variables where $p \leq 0.05$ were considered significant.

All statistical calculations were performed with the IBM SPSS Statistics 21.0 software.

3. Results

A total of 68 patients underwent cytoreductive surgery and HIPEC during the study period.

The mean age of patients at the time of surgery was 55.93 ± 9.036 years. Forty-five (45) patients (66.2%) were 60 or younger, whereas 23 (33.8%) were over 60 when they had surgery.

Forty-one (41) patients (60.3%) were diagnosed with peritoneal carcinomatosis during evaluation, while the remaining 27 (39.7%) received this diagnosis after undergoing surgery for the ovarian tumor, whether for relapse or as a finding in pathology results of the primary intervention. None of these patients had active chemotherapy treatment at the diagnosis of peritoneal carcinomatosis. 4 of the 7 women who showed tumor relapse in the CT during their following had received and finished their adjuvant chemotherapy several years ago.

Sixty-three (63) patients (92.6%) received neoadjuvant chemotherapy, of which one was given doxorubicin, another one carboplatin plus gemcitabine, and all others a treatment plan with carboplatin and

paclitaxel. Eleven (11) patients (17.5%) showed full radiological response, and 52 (82.5%) had partial/stable radiological response for the disease.

During the surgical procedures, we observed that 48 patients (70.6%) had a PCI ≤15, while 20 (29.4%) had a PCI >15. CC-0 cytoreduction was achieved in all but one case, with a CC-1 score. Histopathological characteristics of the ovarian tumors are included on Table 1.

Postoperative complications were classified per the Clavien-Dindo score and included on Table 2.

For the analysis of prognostic ratios, we used ROC curves to identify the optimal cutoff point, with the highest sensitivity and specificity, for each ratio with the final variable being *exitus* caused by cancer (Fig. 1). Cutoff points for N-L with a 95% confidence interval (CI) were: 1.83 (sensitivity: 85.7% specificity: 16.7%), P-L: 189.73 (sensitivity: 78.6% specificity: 44.4%), and SII: 564.80 (sensitivity: 85.7% specificity: 29.6%).

Based on these cutoff points we divided patients into two groups for analysis: N-L ≤ 1.83 (low); >1.83 (high); P-L ≤ 189.73 (low) > 189.73 (high); and SII ≤564.80 (low) > 564.80 (high) (Table 3).

Classification of patients as described above is shown on Table 4.

We did not find a correlation between higher values of N-L, P-L, and SII with poorly differentiated tumors or with patients who had a PCI >15, which are considered unfavorable prognosis factors in cases of ovarian peritoneal carcinomatosis.

As for survival rates, with a median follow-up time of 25 months (IQR: 38–11.25 months), OS at 12, 24, 36, and 48 months was 95%, 89%, 77%, and 68%, respectively, with a median OS of 60 months.

We carried out an analysis of the cutoff parameters of prognostic ratios with the OS of patients, and found that patients with lower N-L, P-L, and SII generally had better OS rates (Fig. 2).

We also performed a univariate analysis of prognostic factors impacting OS (Table 5), which showed the patient's age, whether they had undergone surgery for the ovarian primary tumor, PCI, response to neoadjuvant chemotherapy and P-L and SII values as the prognosis-affecting variables. A multivariate analysis was then performed considering these variables; PCI (CI 95%: 0.126–2.386), response to chemotherapy (CI 95%: 4.092 to −0.357), and SII values (CI 95%: 0.002- 3.835) were shown to be independent prognostic factors.

DFS at 12, 24, 36, and 60 months was 76%, 56%, 46%, and 46%, respectively, with a median of 26 months.

Patients with higher N-L, P-L, and SII usually had lower DFS rates than those with lower values (Fig. 3).

In terms of prognostic factors impacting DFS (Table 6), the univariate analysis highlighted the role of the patient's age, surgical history of the primary tumor, high PCI, response to neoadjuvant chemotherapy, and high N-L, P-L, and SII values as contributing variables. Upon multivariate analysis, it was determined that independent predictors of DFS were age (CI 95%: 0.288–1.962), PCI (CI 95%: 0.371–2.272), and the P-L ratio (CI 95%: 0.253–2.248).

4. Discussion

To the best of our knowledge, our study is the first to evaluate the influence of N-L, P-L, and SII ratios in the outcomes of patients who have undergone surgery for peritoneal carcinomatosis of ovarian cancer.

In recent years, there has been a growing interest in the role played by prognostic ratios based on inflammatory markers such as neutrophils, platelets, and lymphocytes. Although their prognostic usefulness has been well established for different types of tumors, their potential use in the decision-making process for patients with ovarian peritoneal carcinomatosis has yet to be assessed.

Currently, the standard of care for ovarian cancer with peritoneal carcinomatosis is chemotherapy combined with cytoreductive surgery. One of the main prognostic factors associated with this type of tumors is the initial response to chemotherapy, with most ovarian tumors being responsive to platinum-based therapy [16].

In the past decade, studies have emerged assessing the potential benefits of intraperitoneal chemotherapy during the cytoreductive surgery. A randomized study by Driel et al., in 2018, showed that adding HIPEC to the interval cytoreductive surgery rendered better OS and DFS rates than cytoreduction alone, while not having increased side effects [17].

At our unit, we recommend the use of neoadjuvant chemotherapy to the majority of patients, in order to reduce the tumor load and achieve

Table 1
Histopathological characteristics of the ovarian tumors.

HISTOLOGICAL CLASSIFICATION	Cases n (%)
Serous adenocarcinoma	42 (82.3)
Mucinous adenocarcinoma	4 (7.9)
Clear cell carcinoma	4 (7.9)
Granulosa cell tumor	1 (1.9)
HISTOLOGICAL TYPE	**Cases**
Poor- differentiated	46 (86.8)
Well- differentiated	7 (13.2)

Table 2
Postoperative complications classified per the Clavien-Dindo score.

CLAVIEN-DINDO	Cases n (%)
I	12 (17.6)
II	1 (1.5)
IIIa	1 (1.5)
IIIb	13 (19.1)
V	1 (1.5)

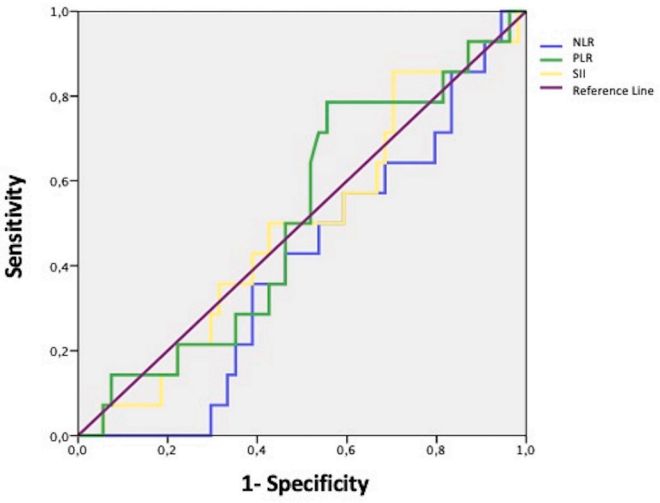

Fig. 1. Receiver operating characteristics curve analysis of systemic immune-inflammation index (SII), platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR).

Table 3
Distribution of patients based on the cutoff points of systemic immune-inflammation index (SSI), platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR).

	SSI		PLR		NLR	
	≤564.80	>564.80	≤189.73	>189.73	≤1.83	>1.83
Cases n (%)	18 (26.5)	50 (73.5)	27 (39.7)	41 (60.3)	11 (16.2)	57 (83.8)

Table 4
Baseline characteristics of study patients. NC: neoadjuvant chemotherapy. PCI: Peritoneal Cancer Index.

	Cases n	SSI n (%)		p value	PLR n (%)		p value	NLR n (%)		p value
		≤564.80	>564.80		≤189.73	>189.73		≤1.83	>1.83	
Age (years)										
≤60	45	20 (44.4)	25 (55.6)	0.264	20 (44.4)	25 (55.6)	0.264	8 (17.8)	37 (82.2)	0.616
>60	23	7 (30.4)	16 (69.6)		7 (30.4)	16 (69.6)		3 (13)	20 (87)	
Primary tumor surgery										
NO	41	9 (22)	32 (78)	<0.001	9 (22)	32 (78)	<0.001	3 (7.3)	38 (92.7)	0,014
YES	27	18 (66.7)	9 (33.3)		18 (66.7)	9 (33.3)		8 (29.6)	19 (70.4)	
Response to NC										
Partial-stable	52	14 (26.9)	38 (73.1)	0.545	20 (38.5)	32 (61.5)	0.896	8 (15.4)	44 (84.6)	0.818
Full	11	2 (18.2)	9 (81.8)		4 (36.4)	7 (63.6)		2 (18.2)	9 (81.8)	
Histological type										
Poor-differentiated	46	17 (37)	29 (63)	0.309	17 (37)	29 (63)	0.309	6 (13)	40 (87)	0.050
Well- differentiated	7	4 (57.1)	3 (42.9)		4 (57.1)	3 (42.9)		3 (42.9)	5 (57.1)	
PCI										
≤15	48	21 (43.8)	27 (56.3)	0.291	21 (43.8)	27 (56.3)	0.291	8 (16.7)	40 (83.3)	0.865
>15	20	6 (30)	14 (70)		6 (30)	14 (70)		3 (15)	17 (85)	

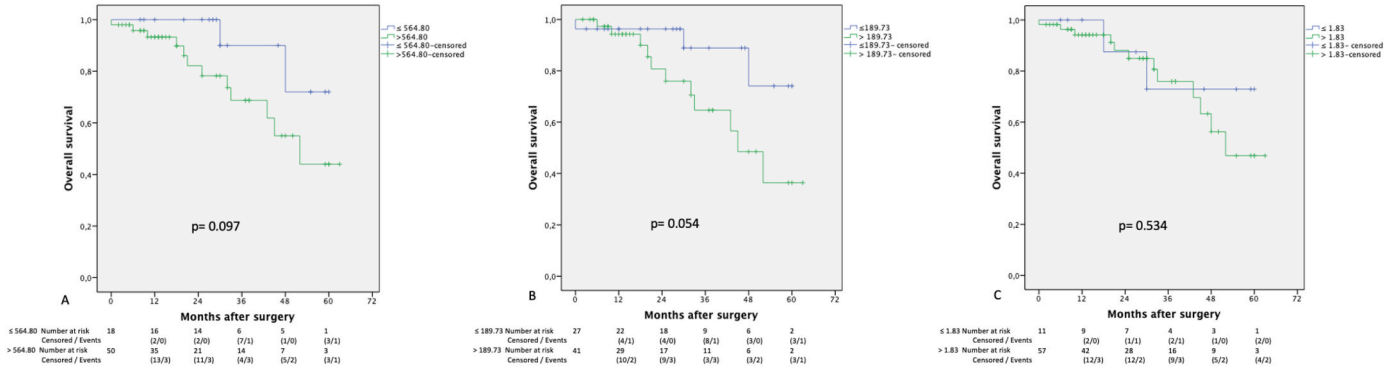

Fig. 2. Kaplan-Meier curves of overall survival based on systemic immune-inflammation index (A), platelet-lymphocyte ratio (B) and neutrophil-lymphocyte ratio (C).

Table 5
Univariate and multivariate analyses of factors affecting OS of patients with peritoneal carcinomatosis of ovarian origin (p < 0.2).

	Univariate analysis		Multivariate analysis	
	p value	HR	p value	HR
Age (≤60y vs > 60y)	0.142*	2.268		
Primary tumor surgery (No vs Yes)	0.184*	0.463		
Histological type (Poor vs well-differentiated)	0.442	1.350		
Response to NC (Partial-stable vs Full)	0.061*	0.249	0.061	0.249
PCI (≤15 vs > 15)	0.021*	3.246	0.021	3.246
SII (low vs high)	0.097*	3.325	0.097	3.325
PLR (low vs high)	0.054*	3.289		
NLR (low vs high)	0.534	1.605		

CC-0 cytoreduction, as well as the use of HIPEC to improve OS and DFS rates.

In recent times we have witnessed advances in chemotherapy and surgical approaches but the study of tumor pathogenesis has not fallen behind. The key role played by the immune response and systemic inflammatory processes in the development and progression of different tumors has become evident. Although its precise mechanisms are not completely understood yet, the systemic inflammation is thought to play an important role in progression of different neoplasms. The inflammatory response produced by the tumor is a factor in different stages of the tumor pathogenesis, acting as the trigger of the initial genetic mutations and promoting tumor spread. Different types of cells and cytokines in the host are responsible for this response, which can be measured by the blood levels of several inflammatory markers, including neutrophils, lymphocytes, and platelets [9].

Neutrophils, as a reaction to the presence of tumor cells, produce and secret cytokines which promote cancer cells adhesion and seeding in the peritoneum. As well, platelet activation releases growth and pro-angiogenic factors, such as interleukin-6 and TGF-β, which promote growth, migration and angiogenesis of tumor cells. Lymphocytes are responsible of the immune defense against tumor cells so, when their levels are low, cytotoxic cell death is blocked which may produce a favorable tumor microenvironment in the peritoneum for the proliferation, progression and spread of cancer cells. All of these changes predispose to tumor proliferation and development of metastases through inhibition of apoptosis, promotion of angiogenesis, and DNA damage [9,10].

Hence, elevated serum levels of neutrophils and platelets may reflect systematic immune-inflammation response to the tumor and lymphopenia may show a worse tumor immune defense. These findings provide us a new insight in relation to the influence of inflammatory parameters on tumor pathogenesis and progression.

Lately, values obtained from the combination of inflammatory markers, such as the N-L and P-L ratios, have been used as prognostic factors in different solid malignancies. Several studies have found that higher N-L and P-L preoperative ratios are associated with a poorer prognosis in the case of ovarian [18], breast [3], lung [19], esophageal [5], stomach [6], hepatocarcinoma [7], and colorectal [8] cancers.

Similarly, the systemic immune-inflammatory index (SII), which takes into account peripheral blood counts of platelets, neutrophils, and lymphocytes [SII = (P*N)/L], has been found to be another prognostic marker with an even greater predicting power than the two other ratios,

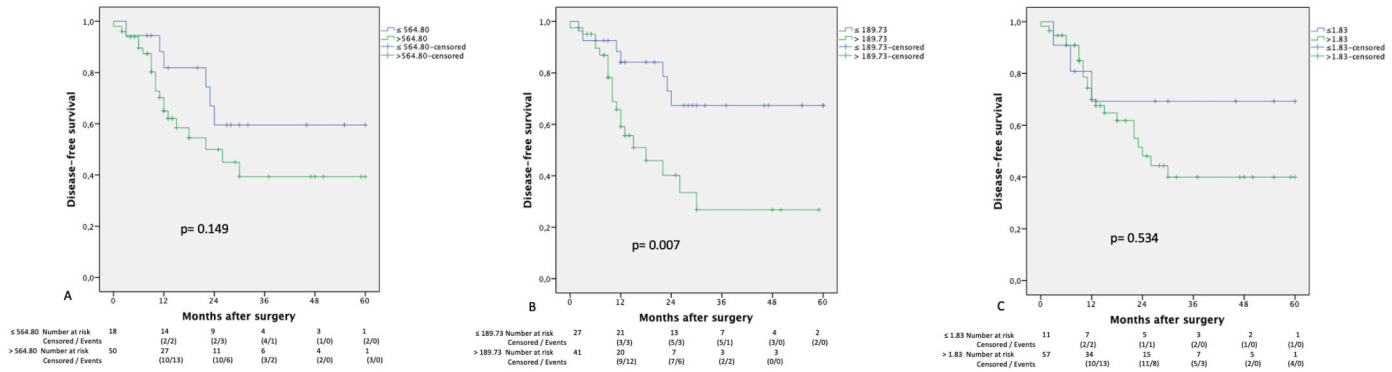

Fig. 3. Kaplan-Meier curves of disease-free survival based on systemic immune-inflammation index (A), platelet-lymphocyte ratio (B and neutrophil-lymphocyte ratio (C).

Table 6
Univariate and multivariate analyses of factors affecting DFS of patients with peritoneal carcinomatosis of ovarian origin ($p < 0.2$).

	Univariate analysis		Multivariate analysis	
	p value	HR	p value	HR
Age (≤60y vs > 60y)	0.005*	2.881	0.005	2.881
Primary tumor surgery (No vs Yes)	0.063*	0.461		
Histological type (Poor vs well-differentiated)	0.593	0.821		
Response to NC (Partial-stable vs Full)	0.969	0.982		
PCI (≤15 vs > 15)	0.002*	3.276	0.002	3.276
SII (low vs high)	0.153*	1.927		
PLR (low vs high)	0.008*	3.088	0.008	3.088
NLR (low vs high)	0.352	1.759		

and higher levels of this marker have been associated with more unfavorable OS and DFS rates in patients with colon cancer or hepatocarcinoma [20,21]. The meta-analysis by Yang et al. showed that patients in the elevated SII groups had shorter OS rates in cases of hepatocarcinoma, stomach cancer, squamous cell carcinoma of the esophagus, urinary tract cancer, lung carcinoma, and acral melanoma [9].

The role of SII as a prognostic factor in cases of tumor spread to the abdominal cavity has also been studied in the case of carcinomatosis of colorectal origin. In a recent study by Yan et al. published in 2020, a correlation was found between high preoperative values of N-L, P-L, and SII and a poorer OS, but the only variable found to be a favorable prognostic factor was a low SII [10].

The N-L, P-L and SII may reflect more reliably the balance between host inflammation and immune response in cancer patients, than neutrophil, lymphocyte and platelet count alone, which may be easily influenced by other factors.

In our analysis, we observed that high preoperative N-L, P-L, and SII values were associated with a poorer OS in women who underwent surgery for peritoneal carcinomatosis of ovarian origin in our cohort. Patients with N-L > 1.83, P-L > 189.73, and/or IIS >564.80 had a poorer prognosis.

Independent prognostic variables of OS were the response to neo-adjuvant chemotherapy ($p = 0.061$, HR = 0.249), PCI at time of surgery ($p = 0.021$, HR = 3.246), and the preoperative SII value ($p = 0.097$, HR = 3.325).

Of the three prognostic ratios assessed, studies have found a stronger prognostic factor in SII. In our analysis, SII was the only independent prognostic factor that worked as a predictor of OS in these patients, similar to what was found by Yan et at. in patients with peritoneal carcinomatosis of colorectal origin [10].

Our study also showed that higher levels of N-L, P-L, and SII were linked to a poorer DFS, with the P-L ratio having statistical significance ($p = 0.007$). Independent variables with an impact on the DFS in our cohort were age ($p = 0.005$, HR = 2.881), PCI ($p = 0.002$, HR = 3.276) and the P-L ratio ($p = 0.008$, HR = 3.088).

Therefore, although all three ratios of systemic inflammatory response impacted both the OS and the DFS, the SII and P-L were stronger prognostic predictors for women in our cohort.

The main limitation in our study is that it is a retrospective analysis with a small sample of patients from a single center and from the same region. Thus, a broader multi-center study to validate results and attain higher statistical power would be interesting.

Furthermore, in the multivariate analysis, only high PLR was recognized as an independent prognostic factor for DFS (95% CI: 0.253–2.248, $p = 0.007$). The rest of parameters showed a trend towards a worse prognosis. Therefore the results should be interpreted with caution.

Additionally, we only analyzed patients who underwent surgery for ovarian carcinomatosis; however, our unit performs cytoreduction combined with HIPEC for other tumors, which leaves an open door for studying the role of these ratios as prognosis predictors in the future.

5. Conclusions

Per our findings we can draw three main conclusions: patients with ovarian carcinomatosis with high preoperative values in the N-L, P-L, and SII ratios trend to have poorer OS and DFS rates; high SII values are an independent prognostic factor of OS; and high P-L values are an independent prognostic factor of DFS. Therefore, these preoperative prognostic ratios could be a useful and simple tool in predicting survival for patients with peritoneal carcinomatosis of ovarian origin, thus improving patient preoperative screening for a surgery with high morbidity and mortality rates.

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Data statement

The data that support the findings of this study are available on request from the corresponding author.

Ethical approval

The study was approved by the Ethical Committee of our institution.

Author contribution

Gerardo Blanco-Fernández: Design of the work, data collection and analysis, drafting the work and revising it critically for important intellectual content, final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Julen Ramón-Rodríguez: Data collection and analysis, Revising the work critically for important intellectual content, final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of competing interest

None.

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