International Surgery Journal
Borges E et al. Int Surg J. 2025 Dec;12(12):2077-2083
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20253829

Original Research Article

The predictive value of preoperative neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio and systemic immune-inflammation index for organ failure following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a retrospective analysis

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Received: 26 August 2025
Revised: 07 October 2025
Accepted: 25 October 2025

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ABSTRACT

Background: Several inflammation-based scores such as neutrophil-to-lymphocyte ratio (NLR) monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been identified as new prognosticators in several tumors. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is a complex procedure with the potential for high morbidity. Our aim is to analyze if biomarkers can be predictor of organ failure after CRS-HIPEC.
Methods: A retrospective analysis of all patients admitted to our intensive care unit (ICU) following CRS-HIPEC. The primary endpoint was the need for organ support. Variables considered statistically significant in the univariable analysis were included in a logistic regression.
Results: Among 107 patients admitted to the ICU after CRS-HIPEC, 44.8% had organ failure. Patients with postoperative organ failure had higher preoperative NRL and SII. However, these ratios did not independently predict organ failure. Peritoneal cancer index (PCI) was the only significant predictor of organ failure (OR 1.077, p=0.005).
Conclusions: This study highlights the complex interplay between systemic inflammation and organ failure following CRS-HIPEC. Although NLR and SII reflected an inflammatory response in patients who developed organ failure, they did not emerge as independent predictors after adjustment for other variables. In contrast, the PCI effectively stratified risk, underscoring the importance of preoperative assessment of disease burden. These findings emphasize the critical role of ICU admission for postoperative monitoring in this high-risk population, as most patients with organ failure experienced multiple organ dysfunction and higher mortality during ICU stay. Overall, inflammatory biomarkers were not found to be significant predictors of organ failure after CRS-HIPEC.

Keywords: Organ failure, Post-operative, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy, Intensive care

INTRODUCTION

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC), is a complex well-establish treatment modality for peritoneal surface malignancies, both primary cancers and metastasis secondary to another solid tumor, generally gastrointestinal or ovarian.[1] It was first described in 1998 by Sugarbaker, and consist firstly

in the surgical removal of visible tumor from peritoneal surfaces and abdomin-pelvic organs, followed by heated highly concentrated chemotherapy delivered intraoperatively to the peritoneum.[2,3] Hyperthermia has direct cytotoxic effects and improve chemotherapy penetration leading to apoptosis of tumor cells and inhibition of angiogenesis.[4]

CRS-HIPEC induces a complex systemic and inflammatory response, with notable post-surgery systemic dysregulation.[5] The immediate post-operative period is characterized by an exaggerated metabolic and inflammatory response and is associated with some life-threatening complications. Due to the postoperative systemic inflammatory response, it is difficult to accurately interpret inflammatory biomarkers as either a normal reaction or not, and no single test has proven to be foolproof.[6] Although some studies have highlighted the prognostic value of serological biomarkers in solid tumors, very few have investigated their clinical utility in patients with peritoneal metastases particularly submitted to CRS-HIPEC.

Several studies have been shown that some blood count indices like NLR, MLR and PLR are inflammatory markers and good predictors of prognosis and survival in patients with cancer.[7-10] Similarly, the SII has been increasingly investigated as a prognostic marker in various malignancies.[11] The aim of our study is to analyze if a preoperative blood count ratio can predict immediate postoperative organ failure.

METHODS

Retrospective analyses of all consecutive patients admitted at the ICU of Instituto Português de Oncologia Francisco Gentil, Lisbon-Portugal, after CRS-HIPEC between January 2017 and September 2023. Demographic and clinical data, as sex, age, comorbidities, laboratory data from preoperative blood count parameters, length of hospitalization, prognostic scoring systems and surgical data, as primary organ neoplasia, drug, peritoneal carcinomatosis index (PCI) and completeness of cytoreduction score (CC) were obtained from patient records.

Cell count-derived ratios were calculated from the preoperative analyses, including the NLR, MLR, PLR, and the SII. The SII was determined as the product of neutrophil and platelet counts, divided by the lymphocyte count.

The primary endpoint was stablished as the need of organ support during ICU stay, specifically vasopressor therapy, invasive mechanical ventilation or renal replacement therapy. Patients who were extubated upon ICU admission or within one hour were not considered to need organ support. At our institution, routine postoperative admission to the ICU is standard following CRS-HIPEC.

Inclusion criteria

All adult patients (≥18 years) CRS-HIPEC at Instituto Português de Oncologia Francisco Gentil, between January 2017 and September 2023, and were electively admitted to the ICU in the immediate postoperative period, were included.

Exclusion criteria

Exclusion criteria comprised patients with incomplete clinical, surgical, or laboratory data; absence of preoperative complete blood count necessary for calculating inflammatory ratios (NLR, MLR, PLR, and SII); ICU admission for reasons other than postoperative monitoring after CRS-HIPEC; or emergency or palliative procedures not involving standardized CRS-HIPEC protocols.

Statistical analysis

Data were analyzed using the statistical package for the social sciences, version 29.0 (IBM SPSS statistics; SPSS Inc., Chicago, IL). Variables were reported as means with standard deviations, medians with interquartile ranges or the frequencies and percentages, as appropriated.

Univariable analysis was performed using student t-test, Mann-Whitney U test or Chi-square test. A two-tailed $p<0.05$ was considered statistically significant (Table 1). Variables found to be statistically significant were included in a univariate analysis, followed by a multivariate logistic regression (Table 4). All parameters were available for more than 90% of patients and were analyzed according to per-protocol principle.

RESULTS

A total of 107 patients were admitted electively in our ICU which representing about 14.5% of all surgical patients. There were 58 women and 49 men, with a mean age of 55 years (range 18-74). The most common comorbidities were arterial hypertension (35.5%) and hyperlipidemia (27.1%) and the majority had systemic chemotherapy previously (66.4%).

Almost every patient underwent a first time CRS-HIPEC (90.7%). Most clinical indication was due to pseudomyxoma peritonei from the appendix (40.2%) or peritoneal carcinomatosis from a tumor from colon (33.6%). In our hospital, there is a standardized protocol for the choice of chemotherapeutic agent used that considers the primary tumor and the morphological characteristics of the patient. The procedure is performed using an open technique, with a chemotherapeutic agent heated to 42ºC, administered over a 60-minute duration. In this series mitomycin C was the most prevalent drug (78.5%).

Intraoperatively, the PCI and CC score were assigned, and both were significantly higher in the organ failure group (23 vs 10, p<0.0001; and 1 vs 0, p=0.014).

At ICU admission, acute physiology and chronic health evaluation II (APACHE II), simplified acute physiology score II (SAPS II) and simplified acute physiology score III (SAPS III) were calculated, and all were higher in the organ support group (11.3 vs 9.6, p=0.034; 30.8 vs 21.2, p<0.001; 47.7 vs 36.9, p<0.001). In-UCI death occurred in 1.9% (n=2) and death in 28 days after CRS-HIPEC in 2.8% (n=3). Both ICU and hospital stay were longer when the patient needed organ support. The median UCI stay increased 3 days (4 vs 1, p<0.001) and the total hospital stay in 10 days (19 vs 9, p<0.001).

Table 1: Baseline characteristics of the study population.

Demographics		Total, (n=107)	Organ failure, (n=48)	Non-organ failure, (n=59)	P value
Sex					
Male		45.8% (n=49)	45.8 % (n=22)	45.8% (n=27)	0.994
Female		54.2% (n=58)	54.2% (n=26)	54.2% (n=32)	
Age (in years)		55.2±11.6	54.9±12.4	55.3±11.1	0.873
Comorbidities					
Arterial hypertension		35.5% (n=38)	41.7% (n=20)	30.5% (n=18)	0.230
Diabetes mellitus type 2		13.1% (n=14)	18.8% (n=9)	8.5% (n=5)	0.117
Obesity		13.1% (n=14)	14.6% (n=7)	11.9% (n=7)	0.678
Hyperlipidemia		27.1% (n=29)	25.5% (n=12)	28.8% (n=17)	0.659
Previous systemic chemotherapy		66.4% (n=71)	60.4% (n=29)	71.2% (n=42)	0.241
Hospital stay					
ICU, days		2 (1-4)	4 (2-6)	1 (1-2)	<0.001
Total, days		14 (8-22)	19 (13-21)	9 (7-18)	<0.001
Preoperative laboratory tests					
Leukocytes, 10^9/L		7.38 (5.87-8.73)	7.93 (6.63-9.36)	6.71 (5.52-8.49)	0.021
Neutrophile, 10^9/L		4.28 (3.35-5.52)	4.67 (3.87-5.73)	3.94 (2.87-5.02)	0.027
Lymphocytes, 10^9/L		1.89 (1.49-2.42)	1.86 (1.36-2.61)	1.98 (1.58-2.40)	0.754
Monocytes, 10^9/L		0.55 (0.42-0.72)	0.55 (0.43-0.69)	0.54 (0.41-0.72)	0.819
Plaquets, 10^9/L		235 (196-320)	262 (199-391)	229 (192-312)	0.247
NLR		2.24 (1.54-2.98)	2.55 (1.88-3.57)	2.09 (1.37-2.66)	0.038
MLR		0.29 (0.21-0.40)	0.29 (0.18-0.40)	0.3 (0.22-0.38)	0.883
PLR		122.5 (100.9-183.3)	125.5 (107.8-263.9)	119.9 (97.1-167.8)	0.144
SII		588.5 (367.8-880.4)	673.2 (403.2-985.1)	517.5 (292.8-725.4)	0.008
CRS-HIPEC					
Many times					
	1	90.7% (n=97)	91.4% (n=44)	89.8% (n=53)	1.000
	>1	9.4% (n=10)	8.3% (n=4)	10.2% (n=6)	
Clinical indication					
	Pseudomyxoma peritonei	40.2% (n=43)	45.8% (n=22)	35.6% (n=1)	0.355
	Colorectal cancer	33.6% (n=36)	29.2% (n=14)	37.3% (n=22)	
	Ovary cancer	11.2% (n=12)	12.5% (n=6)	10.2% (n=6)	
	Malignant mesothelioma	8.4% (n=9)	10.4% (n=5)	6.8% (n=4)	
	Other	6.6% (n=7)	2.1% (n=1)	10.1% (n=6)	
Drug					
	Mitomycin C	78.5% (n=84)	79.2% (n=38)	78% (n=46)	0.998
	Cisplatin+ Adriamycin	15% (n=16)	14.6% (n=7)	15.3% (n=9)	
	Cisplatin+ doxorubicin	6.5% (n=7)	6.3% (n=3)	6,8% (n=4)	
PCI		16 (8-28)	23 (11-36)	10 (6-20)	<0.001
CC		0 (0-1)	1 (0-1)	0 (0-1)	0.014
Scores					
APACHE		10.0±4.0	11.3±4.7	9.6±3.3	0.034
SAPS II		25.5±9.9	30.8±9.5	21.2±7.6	<0.001
SAPS III		41.8±11.2	47.7±10.4	36.9±7.4	<0.001
Death at UCI		1.9% (n=2)	4.2% (n=2)	0%	-
Death 28 days after the CRS-HIPEC		2.8% (n=3)	4.2% (n=2)	1.7% (n=1)	-

Patients with postoperatively organ failure had a higher preoperative median leukocyte count (7.93 vs 6.71×10^9/l, p=0.021) and median neutrophile count (4.67 vs 3.94×10^9/l, p=0.027). Pos-operatively organ failure was simultaneously related with a higher pre-operative NLR (2.55 vs 2.09, p=0.038) and SII (673.2 vs 517.5, p=0.008). The remaining pre-operative laboratory test and cell-related ratios were similar.

During ICU stay, 70% (n=34) of patients required vasopressor support, with a median duration of 0 days (IQR 0-4.5). Additionally, 83.3% (n=40) received invasive mechanical ventilation, with a median duration of 21.5 hours (IQR 4.75-75.5) (Table 2). No patients required renal replacement therapy in this group. A combination of vasopressor support and invasive mechanical ventilation was required in 54.2% (n=26) of patients (Table 3).

Table 2: Organ support requirements.

Organ support	Total, (n=107)	Organ failure, (n=48)
Vasopressor	31.8% (n=34)	70% (n=34)
Duration, days	0 (0-4.5)	
Invasive mechanical ventilation	37.4% (n=40)	83.3% (n=40)
Duration, hours	21.5 (4.75-75.5)	
Renal replacement therapy	0%	0%

Table 3: Simultaneous organ support requirements in patients with organ failure.

Organ support	Organ failure, (n=48)
Vasopressor	29.2% (n=14)
Invasive mechanical ventilation	1.7% (n=8)
Vasopressor and invasive mechanical ventilation	54.2% (n=26)

Variables found to be statistically significant in univariate analysis were analyzed in multivariable logistic regression and none of preoperative NLR (p=0.572) or preoperative SII (p=0.619) were significant as predictors of organ failure. PCI was the only predictor of organ failure (OD 1.077, p=0.005) (Table 4).

Table 4: Logistic regression.

Parameters	Multivariable analysis	
	OR (95% CI)	P value
NLR	1.062 (0.863-1.306)	0.572
SII	1.000 (0.999-1.001)	0.619
PIC	1.077 (1.023-1.134)	0.005
CC	0.856 (0.525-1.396)	0.533

DISCUTION

To the best of our knowledge, our study is the first that aim to evaluate whether preoperative inflammatory biomarkers can predict organ failure following CRS-HIPEC. Hematological blood counts are readily accessible as they are routinely used in clinical practice. However, CRS-HIPEC is a complex procedure that requires an experienced team of surgeons, anesthesiologists, and nursing staff, and is only performed at specialized centers. Therefore, several studies have emphasized the importance of centralizing the procedure in specialized institutions to achieve better outcomes.[12]

Primary peritoneal malignancies are rare, but the peritoneum is a common site of metastases and has been considered a terminal condition.[13] Recent treatments, such as CRS-HIPEC, have significantly improved patient survival and are increasingly being considered as therapeutic options. Although the average patient is typically younger, generally in their mid-50s to early 60s, our cohort had a substantial proportion of patients with comorbidities, particularly cardiovascular diseases or diabetes.[14] Although not statistically significant, patients who experienced post-operative organ failure tended to be slightly younger but had a higher burden of comorbidities, supporting articles that argue age alone is not a contraindication for high-morbidity operations. Furthermore, CRS-HIPEC can achieve comparable perioperative and survival outcomes in well selected elderly patients.[15]

Initially, CRS-HIPEC was used for peritoneal surface malignancies arising from appendiceal neoplasms. In recent decades, however, its application has been extended to many other primary tumors.[16] Our study highlights this new approach, noting that while appendiceal tumors are the most common origin, they account for less than half of the cases. In our series, colorectal cancer was the primary tumor in approximately one-third of patients, supporting advances in the treatment of peritoneal metastases and consistent with many studies supporting this as a standard treatment option.[14]

Over the past two decades, significant advances have been made and cytoreductive surgery has become more aggressive and highly complex. The procedure can vary from the excision of a single peritoneal nodule to a complete peritonectomy, often involving multivisceral resections and the creation of up to 5 anastomoses.[17] Intraoperatively, the tumor burden of the peritoneum is estimated by the PCI, with higher scores representing more advanced disease, and has been used to predict surgical outcomes and prognosis.[18] Similarly, the CC score is estimated after cytoreductive surgery and is classified as 0 when there is no residual peritoneal disease and 1 when there is less than 2.5 mm of residual disease. Both CC-0 and CC-1 are considered complete

resection and are associated with improved prognosis and survival.[19] Patients requiring organ support had higher PCI and CC scores, consistent with the poor prognosis typically associated with these indices.

CRS-HIPEC is characterized by systemic dysregulation after surgery due to a complex systemic and systemic inflammatory response.[5] Studies show that HIPEC triggers both local and systemic inflammatory responses, in part due to the high temperatures used in the procedure.[20] This may activate ion channels and inflammatory pathways, leading to increased release of cytokines such as IL-1β, IL-6, and TNF-α.[21] These inflammatory mediators contribute to systemic dysregulation, including oxidative stress and neuroinflammation, which can affect immune function and lead to postoperative complications.[22] Hyperthermia further exacerbates this challenge by increasing vascular permeability. As a result, the interpretation of inflammatory parameters in the postoperative period of CRS-HIPEC becomes even more complex. The difficulty in accurately interpreting laboratory assessments is particularly important because infection is one of the most common and serious complications. The postoperative period is characterized by significant complications with morbidity ranging from 12 to 52% and mortality ranging from 0.9 to 5.8%.[23]

Tumor-associated inflammation is a significant area of research and discussion due to its role in tumor progression and its impact on patient outcomes.[24] However, in some tumor as colorectal, the relation between inflammation and tumorigenesis is well-established and affects the development of tumor and might also affect the efficacy of cancer therapies.[25] In recent years, many studies have analyzed the utility of inflammatory markers to predict survival and postoperative course.[10] Ratios derived from different blood cell types (neutrophils, lymphocytes, platelets, monocytes) has been used to assess the immune response and prognosis in various medical conditions.[26] The most common ratios found in literature are neutrophil-to-lymphocyte and platelet-to-lymphocyte. The SII is a recent formula that has the goal of a more complex relation between blood count cells.[11] Regarding patients that had CRS-HIPEC, a study retrospectively analyzed 160 patients and concluded that there are higher values of preoperative NLR and mean platelet volume, and PLR on postoperative were associated with decreased 1-year survival.[27] Simultaneously, three studies concluded that elevated preoperative NLR and PLR are associated with increased postoperative complications and poorer prognosis.[28-30] The underlying mechanism of the NLR and PLR ratios is not fully understood.

This study reveals that while the univariable analysis suggests a positive trend for both NLR and SII, their statistical significance disappears when controlling for other factors, indicating that they are not significant predictors for postoperative organ failure. Initially, both NLR and SII were higher in the organ failure group which is consistent with previous literature suggesting that higher levels of systemic inflammation correlate with worse outcomes in postsurgical patients, including an increased risk of organ dysfunction.

However, in multivariable logistic regression models, neither NLR nor SII emerged as statistically significant independent predictors of organ failure. These findings suggest that although elevated inflammatory markers may reflect an overall increased inflammatory state, they alone are not sufficient to predict organ failure in this patient population. This discrepancy between the descriptive analysis and the regression models suggests that the relationship between systemic inflammation and postoperative organ failure is likely multifactorial. Other factors, such as extent of disease and surgical outcomes, may play a more direct role in driving organ failure. Therefore, PCI was considered a significant independent predictor of organ failure in the multivariable regression model. PCI demonstrated an OR of 1.077, suggesting that for every unit increase in PCI, there is a 7.7% increase in the odds of organ failure. These results are consistent with previous research showing that patients with extensive peritoneal disease are at higher risk for complications. The CC score, while clinically relevant, did not emerge as a statistically significant predictor of organ failure in our model. Despite the lack of statistical significance in this model, it is important to note that CC remains an important clinical endpoint, influencing both oncologic outcomes and postoperative morbidity. The role of CC in predicting organ failure may be more complex and warrants further investigation in larger, more diverse cohorts.

Our study highlights the importance of ICU admission following CRS-HIPEC for postoperative monitoring. Among patients requiring organ support, most experienced multiple organ failure, necessitating both vasopressor therapy and invasive mechanical ventilation. Despite, the median duration of both organ supports was less than one day, patients with organ failure had a longer length of stay in both the ICU and infirmary. Mortality rates were within the range reported in the literature, and two from the three deaths that occurred within 28 days post-surgery, were in the ICU. The APACHE, SAPS II, and SAPS III scores, which assess physiological status of the patient and mortality risk, provided valuable insight in our series. Patients who underwent CRS-HIPEC and had organ failure had higher scores on these prognostic indices, as expected.

This study is not without its limitations. Selection bias is inherent due to the retrospective design. Sample size may limit the ability to detect small but clinically meaningful effects. In addition, inflammatory markers may be influenced by confounding factors such as infection or other pre-existing conditions, which were not fully explored in this analysis. Future studies should aim to validate these findings in larger, more heterogeneous

patient populations and explore whether more dynamic measures of inflammation, such as perioperative changes in inflammatory markers, could better predict organ failure. Moreover, the inclusion of other clinical variables may improve the predictive power of future models.

CONCLUSION

The results of this study highlight the complexity of predicting organ failure after CRS-HIPEC. While markers of systemic inflammation such as NLR and SII are elevated in patients who develop organ failure, they do not independently predict this outcome when adjusted for other variables. In contrast, PCI stands out as a predictor of organ failure, highlighting the importance of preoperative assessment of disease burden in risk stratification.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Borges E, Sousa M, Marum S, Castro M, Bouw MJ. The predictive value of preoperative neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio and systemic immune-inflammation index for organ failure following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a retrospective analysis. Int Surg J 2025;12:2077-83.