

Post-operative inflammatory marker surveillance in colorectal peritoneal carcinomatosis

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Statement of Translational Relevance:

Low post-op LMR (days 4-7) at cut-off of 0.93, high postop NLR (days 8-21) at a cut-off of 13.26 and high post-op PLR (days 22-56) at a cut-off of 369.65 were optimal for post-op surveillance and prognostication in colorectal peritoneal. The proposed cut-offs should be validated in a larger population of CPC patients. We have also characterised and reported the changes in inflammatory marker levels and the constituent inflammatory cells over 90 days post-op, after which they returned to pre-op levels and this general trend appears to be consistent across tumour sub-types. Future studies on post-op inflammatory markers should account for the inflammatory response profile when selecting surveillance periods so that studies are comparable and results can be interpreted with greater certainty.

Abstract

The prognostic significance of inflammatory markers in solid cancers is well established, albeit with considerable heterogeneity in the cut-offs used, periods surveyed and reports of prognostic significance. We sought to investigate the trend of post-op inflammatory markers in peritoneal carcinomatosis (PC) and to propose optimal surveillance periods and cut-offs that can be validated in a larger population. Data was collected from a prospectively maintained database of PC patients treated at our institution from April 2001 to March 2019. Platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR) and lymphocyte-monocyte ratio (LMR) were collected preoperatively and on post-op day 0, 1-3, 4-7, 8-21, 22-56 and 57-90 as averages. Cut-offs for each marker at each time point was determined by maximally selected rank statistics and the optimal surveillance periods were selected by maximising hazard ratios. Kaplan-Meier method and cox proportional hazard regression models were used to investigate the association between inflammatory markers and 1-year overall survival (OS) and recurrence-free survival (RFS) with clinicopathological parameters. Low post-op LMR (days 4-7) (cut-off: 0.93), high postop NLR (days 8-21) (cut-off: 13.26) and high post-op PLR (days 22-56) (cut-off: 369.65) were optimal for post-op surveillance and prognostication in colorectal PC in univariate and multivariate analyses. A composite score of these 3 markers was also prognostic for survival, however, these cut-offs are not generalisable to other tumour sub-types in PC. The proposed cut-offs should be validated in a larger population of CPC patients and future studies should account for the inflammatory response profile when selecting appropriate surveillance periods.

1 Introduction

2
3 Inflammation is a hallmark of cancer (1), and its role in oncogenesis and cancer progression is
4 well established (2-5). Expectedly, there has been considerable interest in using inflammatory
5 blood biomarkers and prognostic tools such as the Glasgow score (6-8) to predict survival and
6 disease progression in cancer patients. Inflammatory marker ratios such as the platelet-
7 lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR) and lymphocyte-monocyte ratio
8 (LMR) have also been widely studied for this purpose in solid tumours (9-11).

9
10 However, there is substantial heterogeneity between these studies as highlighted in several
11 meta-analysis reports (11,12) and this heterogeneity limits translatability to clinical practice.
12 Firstly, there is no consensus on a cut-off for each marker, either pre-operatively or post-
13 operatively. Secondly, the studies differ significantly in the method by which appropriate cut-
14 offs are determined while other studies report the significance of these markers as continuous
15 variables without using a cut-off or use methods to derive cut-offs specific to the study cohort
16 that may not be generalisable. Next, each inflammatory marker may or may not be prognostic
17 for each primary tumour type and has different cut-offs.

18
19 Even when comparing studies with similar methodology and cut-offs on the same primary
20 tumour type, there is considerable variation in the prognostic significance of biomarkers. For
21 example, some studies report that elevated pre-operative NLR is associated with poor outcomes
22 in colon cancer but not rectal cancer (13-17). Additionally, there is conflicting data on reported
23 outcomes for the same cancer types. For instance, there is ambiguity on whether elevated pre-
24 operative NLR is associated with both poor overall survival (OS) and disease-free survival
25 (DFS)/ progression-free survival (PFS) (10) or only poor OS but not DFS/PFS in colorectal
26 cancer (16,18). Furthermore, our group had previously found that pre-operative NLR is not a
27 prognostic factor for colorectal peritoneal carcinomatosis (CPC) and pseudomyxoma peritonei
28 (PMP) (19), while other groups have reported that pre-operative NLR and post-operative PLR
29 were good prognostic factors (20-22) suggesting that these markers may have different
30 prognostic potential in peritoneal and metastatic cancers compared to primary solid tumours as
31 has been previously suggested (23).

32
33 While there are fewer studies on post-operative inflammatory markers, these studies differ
34 greatly in the specific post-operative time period when the inflammatory markers are surveyed.
35 Studies on the post-operative trends of these inflammatory markers also suggest that there
36 should be different cut-offs for different post-operative time points (20,24). Hence, most of the
37 post-operative studies cannot be directly compared, and at times report contradictory findings
38 in the same cancer type. For example, some studies report post-operative NLR as a useful
39 prognostic factor in colorectal cancer (25) while others report it as a poor prognostic factor
40 (26,27).

41
42 Hence, although there has been a large volume of studies published on this topic, it's
43 translatability to clinical practice has been limited. With this in mind, we sought to investigate
44 the prognostic utility of postoperative inflammatory marker surveillance in patients with
45 peritoneal carcinomatosis in a large tertiary institution in Asia. In doing so, we aim to determine
46 the optimal period for surveillance and to propose a cut-off for these markers that can be
47 validated in a larger multi-centre patient population.

48 Materials and Methods

This study was approved by the SingHealth Centralised Institutional Review Board (IRB Ref: 2018/2638) and was conducted in compliance with all applicable SingHealth institutional policies and regulations. Demographic and clinicopathological data for this study was collected from a prospectively maintained database and electronic medical records of all patients with peritoneal carcinomatosis treated at the National Cancer Centre Singapore (NCCS) from April 2001 to March 2019. PLR, NLR and LMR were constructed by taking the ratios of the absolute counts of the respective components of the full blood count panel, where available, for each patient pre- (up to 1 week prior to date of procedure) and post-operatively over 90 days. To determine the ideal post-operative period for surveillance, averages of these ratios were taken pre-operatively and on post-operative day 0, 1-3, 4-7, 8-21, 22-56 and 57-90. These surveillance periods were determined based on a previous study on colorectal cancer patients (24) and supported by our observation of the general trend of the host immune response during the post-operative period (Supplementary Figure S1). OS and recurrence-free survival (RFS) are defined as date of surgery to date of death from any cause or last follow-up and date of surgery to date of disease recurrence at any site, respectively. Cancer staging is based on routine post-operative histopathological analysis and clinical assessment according to the American Joint Committee on Cancer (AJCC) staging manual.

Statistical analyses

Kruskal-Wallis test was used to compare the distribution of inflammatory marker ratios across different tumour subtypes and paired samples T-test was used to compare post-operative inflammatory marker levels to pre-operative levels to determine when they returned to pre-operative levels. Cut-offs for PLR, NLR and LMR at each surveillance period was determined using the maximally selected rank statistics (28,29) on the R package Maxstat with the Horton and Lausen (HL) p -value approximation method (30). Patients were subsequently dichotomised into a 'high' and 'low' group based on the cut-offs at each time-point. 1-year OS and RFS were analysed using the Kaplan-Meier method for each inflammatory marker at each time period and the log-rank test was used to determine the hazard ratio.

Cox proportional hazard regression models were used to investigate if there was an association between the inflammatory markers at the chosen time points and 1-year OS and RFS in both univariate and multivariate analyses with clinicopathological parameters described in Table 1. Variables with $p \leq 0.1$ in the univariate analysis were progressed to a multivariate analysis using backward logistic regression. A composite score of the different markers across time was constructed and the prognostic significance was determined by the Kaplan-Meier method.

All analyses were performed using SPSS software version 25 (SPSS Inc., Chicago, IL) and R (Version 3.6.2, open source) and a 2-sided $p < 0.05$ was considered to be statistically significant.

Results

Patient characteristics

436 patients with peritoneal carcinomatosis who underwent surgery at our centre between April 2001 and March 2019 were recruited with informed consent. 161 patients (36.9%) had primary tumour of colorectal origin, 121 (22.8%) had an ovarian origin, 111 (25.5%) had appendiceal origin, 26 (6.0%) had primary peritoneal cancer and 17 (3.9%) had mesothelioma origin (Figure 1).

In a subpopulation of patients with colorectal primary tumour of colorectal origin (n = 161) (Table 1), 84.5% (n = 136) had cytoreductive surgery (CRS) while 80.7% (n = 130) had hyperthermic intraperitoneal chemotherapy (HIPEC) at our centre with a median age of 57 at the time of treatment. Majority of the patients (70.2%, n = 113) were more than 50 years old. The patients were predominantly female (59.0%, n = 95) and Chinese (82.0%, n = 132) with an ECOG score of either 0 (80.7%, n = 130) or 1 (9.3%, n = 15). Median PCI score was 6 (range 3-12.5) and the completeness of cytoreduction (CC) score was mostly 0 (81.4%, n = 131). Median hospital stay duration was 12 days (range 9-15.5) while median OS was 18 months (range 10-33) and RFS was 11 months (range 6-19). The distribution of TNM stages and histological subtypes are reported in Table 1.

PLR, NLR and LMR Trends

Although the general profiles of PLR, NLR and LMR for each primary tumour types were similar for all 436 patients in the study (Supplementary Figure 2), there were significant differences in the distribution of ratio levels during different time points as evidenced by the Kruskal-Wallis test ($p < 0.001$, $p = 0.040$ and $p = 0.001$ for PLR, NLR and LMR respectively). Notably, primary tumour subtypes differed in the duration of post-op inflammatory response as evidenced by a longer duration for elevated NLR in mesothelioma and appendiceal origin patients (up to 8-21 days post-op) compared to other primary tumour types (up to days 1-3 post-op) (Supplementary Figure 2).

Hence, given the variation in inflammatory marker trends between primary tumour sub-types and the differences observed in literature with regards to cut-offs for different primary solid tumour types, we decided to focus on the subset of patients with colorectal peritoneal carcinomatosis (CPC) since it was the most common primary tumour type. The trends of PLR, NLR and LMR and the corresponding profiles of the constituent inflammatory cells over the pre-op and post-op periods surveyed are presented in Figure 2. These trends were similar to the profile of inflammatory response observed in the data pooled for all 436 patients across primary tumour sub-types (Supplementary Figures 1 and 2).

The comparison of ratios surveyed at different time points compared to pre-op levels is presented in Table 3. PLR and NLR returned to pre-op levels between 57-90 days post-op while LMR returned to pre-op levels between 22-56 days.

Optimal cut-off and post-operative surveillance period for 1-year OS

Subjecting our sub-population of 161 CPC patients to maximally selected rank statistics analyses, we determined the optimal cut-offs for each surveillance period as presented in Table 2.

Elevated PLR was associated with poor survival at all time-points surveyed and the best hazard ratio for 1-year OS was obtained during post-op days 22-56 (HR 5.629, 95% CI 3.087-10.264, $p < 0.001$) with a cut-off of 369.65. While pre-op NLR was not prognostic for 1-year OS, low post-op NLR within 24 hours at a cut-off of 6.33 (HR 0.304, 95% CI 0.175-0.526, $p < 0.001$) and high post-op NLR beyond 24 hours to 90 days were associated with poor 1-year OS. The best hazard ratio for poor 1-year OS associated high postop NLR was during post-op days 8-21 (HR 3.638, 95% CI 1.894-6.988, $p < 0.001$) with a cut-off of 13.26. For LMR, high early post-op LMR within 24 hours (HR 2.403, 95% CI 1.419-4.070, $p = 0.001$) at a cut-off of 2.32, low pre-op LMR (HR 0.502, 95% CI 0.312-0.807, $p = 0.004$) and low post-op LMR beyond 4 days were associated with poor 1-year OS. The best hazard ratio for poor 1-year OS associated

low post-op LMR was during post-op days 4-7 (HR 0.172, 95% CI 0.091-0.325, $p < 0.001$) at a cut-off of 0.93. LMR surveyed between post-op days 1-3 was not prognostic for 1-year OS.

Optimal cut-off and post-operative surveillance period for 1-year RFS

Pre-op PLR was not prognostic for 1-year RFS. Elevated post-op PLR was associated with poor survival at 4-7 days and 22-90 days whereby the best hazard ratio for 1-year RFS was obtained during post-op days 57-90 (HR 7.127, 95% CI 2.525-20.116, $p < 0.001$) with a cut-off of 101.80. While pre-op NLR and post-op NLR from days 1-3 were not prognostic for 1 year RFS, low post-op NLR within 24 hours at a cut-off of 7.20 (HR 0.453, 95% CI 0.282-0.728, $p = 0.01$) and high post-op NLR beyond 4 to 90 days were associated with poor 1-year RFS. The best hazard ratio for poor 1-year RFS associated high post-op NLR was during post-op days 57-90 (HR 2.416, 95% CI 1.360-4.289, $p = 0.003$) with a cut-off of 1.57. Pre-op LMR and LMR surveyed within 24 hours post-op were not prognostic for 1-year RFS. Low post-op LMR beyond 24 hours was associated with poor 1-year RFS. The best hazard ratio for poor 1-year RFS associated low post-op LMR was during days 8-21 (HR 0.264, 95% CI 0.105-0.663, $p = 0.005$) at a cut-off of 2.88.

Univariate and Multivariate Analyses

The cut-offs for post-op surveillance periods identified previously were subjected to univariate and multivariate analyses with other clinicopathological and demographic patient characteristics described in Table 1.

In univariate analysis, race, cytoreductive surgery (CRS), duration of peritonectomy, completeness of cytoreduction (CC) score, intra-op complications, post-op PLR days 22-56, post-op NLR days 8-21 and post-op LMR days 4-7 were prognostic for 1-year OS at $p < 0.1$ (Table 4). In multivariate models presented in Table 5, post-op PLR days 22-56, post-op NLR days 8-21 and post-op LMR days 4-7 were prognostic for 1-year OS at $p < 0.05$. In univariate analysis for 1-year RFS, cytoreductive surgery, PCI score, duration of HIPEC, CC score, intra-op and post-op complications were significant prognostic factors while no inflammatory markers were prognostic.

Composite score for OS

A composite score was computed whereby low post-op LMR days 4-7, high post-op NLR days 8-21, high post-op PLR days 22-56 based on the cut-offs reported above were assigned values of 1 and subjected to Kaplan-Meier survival analyses (Figure 3). Scores of 0, 1 and a combination of 2 and 3 showed a significant difference in OS ($p < 0.001$).

Discussion

Our results show that inflammatory markers measured at specific time points during post-operative follow up may allow us to identify patients requiring closer monitoring for disease recurrence or poor survival. Specifically, low post-op LMR (days 4-7) at cut-off of 0.93, high post-op NLR (days 8-21) at a cut-off of 13.26 and high post-op PLR (days 22-56) at a cut-off of 369.65 were determined to provide the best prognostic information for poor 1-year OS. A composite score of these 3 markers was also prognostic for survival.

Although the time periods and cut-offs identified (with the exception of post-op PLR days 22-56) do not agree with a previous study on primary colorectal cancer (24), this difference may be explained by the fact that inflammatory markers in peritoneal carcinomatosis may have different prognostic significance compared to primary tumours as previously suggested (23).

Hence, further research into the prognostic role of inflammatory markers in peritoneal metastatic cancers is warranted, as up to 60, 50 and 32% of ovarian, pancreatic and colon cancers respectively, will develop peritoneal carcinomatosis with significant impact on patients' quality of life (abdominal distension, intestinal obstruction etc.) (31-33). Despite advances in aggressive treatment strategies, including a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), long-term survival remains low with meta-analyses citing median OS of 35.3 months, median RFS of 2 years and a 5-year average OS rate of 40% in patients with CPC (34,35). Given the poor patient outcomes, further research in this area could potentially lead to enhanced surveillance and early intervention for patients at higher risk of mortality and disease recurrence.

In our report, we have also characterised the trends of the inflammatory marker ratios and the constituent blood cell levels over 90 days post-op for all 436 patients and 161 patients with CPC specifically. Given that we found differences between primary tumour subtypes in peritoneal carcinomatosis, our proposed cut-offs and surveillance periods are only perhaps generalisable to patients with CPC. However, the general trend of changes in the post-op inflammatory cell and ratio levels appear consistent across primary tumour subtypes, with the exception of NLR as described in the results. Hence, it will be interesting to study if the trends are similar across other cancer types including non-metastatic cancers, and if any variation in the trend could be prognostic of adverse outcome.

Prior studies have reported that high post-op monocyte counts are associated with poor survival in lung and oesophageal cancer patients (36,37) within 4 days and 1 week post-op respectively. Although we similarly found that high LMR measured within 24 hrs post-op is associated with a poorer prognosis, we also found that high post-op LMR beyond 1-day post-op is associated with better prognosis. While this difference may be attributable to differences in primary tumour biology and surveillance periods, it will be interesting to study if the change from poor to good prognosis associated with high monocyte count could be explained by temporal differences in the proportion of M1 pro-inflammatory and anti-tumour macrophages to M2 pro-tumorigenic macrophages (38-40). Hence, early post-operative changes in the host immune macroenvironment may be important in determining recurrence or survival and studying the mechanisms underlying differences between patients may provide insights into potential immunotherapeutic strategies. Furthermore, given the temporal changes in the levels of post-op inflammatory marker levels and differences in prognostic significance at different time points that we have reported, future studies on the prognostic value of such markers should account for this variation when selecting surveillance periods so that studies are comparable and results can be interpreted with more certainty.

There are several limitations in this study. Firstly, although we sought to investigate the prognostic potential of inflammatory markers in peritoneal cancers using a cohort of 436 patients, we had to limit our study to a smaller sub-population of 161 CPC patients after learning that the primary tumour types had an influence on the post-operative longitudinal profile of inflammatory markers as well as the cut-offs. Secondly, we did not validate our findings in an appropriate validation cohort. Next, there could be sampling bias as patients with data available over all 90 days or on later days of the surveillance period could have a relatively more adverse post-operative course requiring hospitalisation or more frequent follow up.

While these blood biomarkers provide a simple, cost-effective and readily reproducible prognostic tool for patient management, their clinical translatability has been limited by the heterogeneity in previous studies, the lack of consensus on optimal time periods for

surveillance and ideal cut-offs that are validated in large multi-centre cohorts . Hence, future studies should aim to validate our proposed cut-offs and surveillance periods for CPC patients and a similar approach should be taken with other cancer types with cancer-specific cut-offs.

Conclusions

Post-operative surveillance of inflammatory markers serially may allow for prognostication of poor disease outcome and allow for identification of patients requiring more frequent follow-up or early intervention. Future studies should focus on validating the proposed cut-offs and surveillance period in large multi-centre studies on the same cancer type.

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Figure Legends

397 **Figure 1.** Flowchart illustrating study population.

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399 **Figure 2.** Trend of PLR and NLR and LMR and constituent inflammatory cell levels over
400 pre-op and post-op periods surveyed, Mean +/- 2 standard deviations

401

402 **Figure 3.** Kaplan-Meier survival analysis for 1-year OS composite score of LMR (4-7 days),
403 NLR (8-21 days) and PLR (22-56 days) ($p < 0.001$).

Table 1: Demographic and clinicopathological characteristics of patients with colorectal peritoneal carcinomatosis (CPC), n = 161

Variable		Frequency (%) or Mean (SD) or Median (IQR)
Number of CRS		136 (84.5%)
Number of HIPEC		130 (80.7%)
Age at CRS/ CRS-HIPEC		57 (47-65)
	≤ 50	48 (29.8%)
	>50	113 (70.2%)
Gender	Male	66 (41.0%)
	Female	95 (59.0%)
Race	Chinese	132 (82.0%)
	Malay	6 (3.7%)
	Indian	3 (1.9%)
	Others	20 (12.4%)
ECOG Status	0	130 (80.7%)
	1	15 (9.3%)
Total hospital stay (days)		12.00 (9.00-15.50)
Histology	Adenocarcinoma	109 (67.7%)
	Mucinous Adenocarcinoma	35 (21.7%)
	Mucinous Adenocarcinoma with Signet-Ring cell	3 (1.9%)
	Signet-Ring cell	6 (3.7%)
	Tubulovillous Adenoma	2 (1.2%)
	Unknown	6 (3.7%)
Tumour Grade	Grade 1	1 (0.6%)
	Grade 2	60 (37.3%)
	Grade 3	7 (4.3%)
	Unknown	75 (46.6%)
T Stage	X	4 (2.5%)
	1	1 (0.6%)
	2	3 (1.9%)
	3	42 (26.1%)
	3B	1 (0.6%)
	4	31 (19.3%)
	4A	36 (22.4%)
	4B	22 (13.7%)
	Unknown	12 (7.5%)
N Stage	0	45 (28.0%)
	1	20 (12.4%)
	1A	8 (5.0%)
	1B	11 (6.8%)
	1C	3 (1.9%)
	2	16 (9.9%)
	2A	16 (9.9%)
	2B	16 (9.9%)
	X	5 (3.1%)
	Unknown	12 (7.5%)

M Stage	0	77 (47.8%)
	1	59 (36.6%)
	X	1 (0.6%)
	Unknown	14 (8.7%)
Complications (Clavien-Dindo)	Grade 1	15 (9.3%)
	Grade 2	31 (19.3%)
	Grade 3	17 (10.6%)
	Grade 4	1 (0.6%)
	Grade 5	0 (0.0%)
Comorbidities	Hypertension	47 (29.2%)
	Diabetes	21 (13.0%)
	Hyperlipidaemia	32 (19.9%)
	Ischemic Heart Disease	3 (1.9%)
	COPD	1 (0.6%)
	Asthma	4 (2.5%)
	Other Malignancy	6 (3.7%)
	Others	64 (39.8%)
	None	47 (29.2%)
PCI Score		6.00 (3.00-12.50)
Completeness of Cytoreduction (CC) Score	0	131 (81.4%)
	1	3 (1.9%)
	2	1 (0.6%)
	3	7 (4.3%)
	Unknown	19 (11.8%)
Overall Survival (OS) (months)		18 (10-33)
Recurrence Free Survival (RFS) (months)		11 (6-19)

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Table 2: Cut-off determination for PLR, NLR and LMR using maximally selected rank statistics

Marker		1-year Overall Survival					1-year Recurrence Free Survival				
		Cut-Off		Hazard Ratio	95% Confidence Interval	p-value	Cut-Off		Hazard Ratio	95% Confidence Interval	p-value
PLR	Pre-op	245.93	Below: 131 Above: 30	2.896	1.697-4.943	0.000	111.73	Below: 36 Above: 125	1.447	0.932-2.245	0.100
	Post-op <24h	512.90	Below: 128 Above: 26	2.702	1.523-4.792	0.001	155.56	Below: 21 Above: 133	0.637	0.388-1.047	0.075
	Post-op Day 1-3	255.40	Below: 103 Above: 53	2.250	1.412-3.586	0.001	389.17	Below: 137 Above: 19	1.436	0.816-2.527	0.209
	Post-op Day 4-7	288.15	Below: 92 Above: 49	3.081	1.891-5.021	0.000	285.37	Below: 90 Above: 51	1.576	1.051-2.363	0.028
	Post-op Day 8-21	546.36	Below: 77 Above: 33	2.341	1.374-3.990	0.002	251.83	Below: 19 Above: 91	1.568	0.879-2.798	0.128
	Post-op Day 22-56	369.65	Below: 92 Above: 20	5.629	3.087-10.264	0.000	200.44	Below: 57 Above: 55	1.751	1.131-2.711	0.012
	Post-op Day 57-90	141.79	Below: 31 Above: 67	4.788	2.021-11.341	0.000	101.80	Below: 16 Above: 82	7.127	2.525-20.116	0.000
NLR	Pre-op	2.99	Below: 108 Above: 53	1.553	0.973-2.480	0.065	1.41	Below: 15 Above: 146	1.449	0.750-2.797	0.270
	Post-op <24h	6.33	Below: 22 Above: 132	0.304	0.175-0.526	0.000	7.20	Below: 27 Above: 127	0.453	0.282-0.728	0.001
	Post-op Day 1-3	18.71	Below: 135 Above: 21	2.401	1.405-4.104	0.001	14.83	Below: 118 Above: 38	0.711	0.461-1.096	0.122
	Post-op Day 4-7	7.99	Below: 89 Above: 52	3.298	2.022-5.379	0.000	7.73	Below: 84 Above: 57	1.785	1.202-2.652	0.004
	Post-op Day 8-21	13.26	Below: 96 Above: 14	3.638	1.894-6.988	0.000	5.83	Below: 50 Above: 60	1.601	1.030-2.490	0.037
	Post-op Day 22-56	2.76	Below: 53 Above: 59	2.732	1.489-5.015	0.001	2.76	Below: 53 Above: 59	1.864	1.188-2.925	0.007
	Post-op Day 57-90	3.48	Below: 74 Above: 24	2.618	1.465-4.679	0.001	1.57	Below: 28 Above: 70	2.416	1.360-4.289	0.003
LMR	Pre-op	2.86	Below: 63 Above: 98	0.502	0.312-0.807	0.004	4.59	Below: 130 Above: 31	0.794	0.506-1.245	0.315
	Post-op <24h	2.32	Below: 130 Above: 24	2.403	1.419-4.070	0.001	2.87	Below: 137 Above: 17	1.419	0.806-2.498	0.226
	Post-op Day 1-3	3.03	Below: 138 Above: 18	0.485	0.217-1.080	0.076	2.68	Below: 133 Above: 23	0.514	0.290-0.909	0.022
	Post-op Day 4-7	0.93	Below: 14 Above: 127	0.172	0.091-0.325	0.000	3.09	Below: 126 Above: 15	0.312	0.143-0.680	0.003
	Post-op Day 8-21	0.91	Below: 14 Above: 96	0.327	0.162-0.659	0.002	2.88	Below: 97 Above: 13	0.264	0.105-0.663	0.005
	Post-op Day 22-56	1.93	Below: 30 Above: 82	0.348	0.201-0.602	0.000	2.37	Below: 43 Above: 69	0.544	0.347-0.851	0.008
	Post-op Day 57-90	1.78	Below: 19 Above: 79	0.503	0.266-0.950	0.034	1.56	Below: 11 Above: 87	0.349	0.162-0.751	0.007

413 **Table 3:** Comparison of post-operative levels of PLR, NLR and LMR to pre-operative levels
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		n	Mean	Std. Deviation	p-value
PLR	Pre_PLR	154	187.3459	121.67427	<0.001
	Post_PLR	154	349.5737	214.15793	
	Pre_PLR	156	185.3791	119.88244	<0.001
	PLR_1_3	156	257.6505	156.90973	
	Pre_PLR	141	182.8699	122.31300	<0.001
	PLR_4_7	141	278.0572	132.87895	
	Pre_PLR	110	194.5539	131.99190	<0.001
	PLR_8_21	110	470.0503	254.30959	
	Pre_PLR	112	199.1694	132.94043	0.003
	PLR_22_56	112	254.8966	174.83580	
	Pre_PLR	98	197.8894	126.40405	0.487
	PLR_57_90	98	209.4319	132.18706	
NLR	Pre_NLR	154	2.8635	1.84132	<0.001
	Post_NLR	154	15.9165	12.43156	
	Pre_NLR	156	2.8909	1.91296	<0.001
	NLR_1_3	156	12.3954	6.75174	
	Pre_NLR	141	2.7911	1.75874	<0.001
	NLR_4_7	141	8.1585	5.27138	
	Pre_NLR	110	2.9726	2.02266	<0.001
	NLR_8_21	110	7.9589	5.69414	
	Pre_NLR	112	3.0846	2.11733	0.019
	NLR_22_56	112	3.8631	3.07263	
	Pre_NLR	98	2.9493	2.03312	0.428
	NLR_57_90	98	3.2726	3.47582	
LMR	Pre_LMR	154	3.4443	1.69638	<0.001
	Post_LMR	154	1.8307	2.98153	
	Pre_LMR	156	3.4373	1.69966	<0.001
	LMR_1_3	156	1.9390	1.18861	
	Pre_LMR	141	3.4517	1.55537	<0.001
	LMR_4_7	141	2.0770	1.06396	
	Pre_LMR	110	3.2620	1.72841	<0.001
	LMR_8_21	110	1.8956	.94330	
	Pre_LMR	112	3.2875	1.78397	0.147
	LMR_22_56	112	3.0477	1.45893	
	Pre_LMR	98	3.2831	1.68392	0.330
	LMR_57_90	98	3.1221	1.63617	

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416 **Table 4:** Univariate overall and recurrence-free survival analyses
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1-year Overall Survival				
Marker/ Variable		Hazard Ratio	95% Confidence Interval	p-value
Race	Chinese	<i>Ref</i>		0.049
	Malay	1.133	0.273-4.700	0.864
	Indian	0.000	0.000-0.000	0.976
	Others	2.540	1.323-4.875	0.005
CRS Performed		0.232	0.130-0.415	<0.001
Duration of Peritonectomy		1.003	1.001-1.005	0.007
CC Score	0	<i>Ref</i>		<0.001
	1	3.900	0.929-16.734	0.063
	2	0.000	0.000	0.981
	3	10.919	4.671-25.525	<0.001
Intraop Complications		4.626	1.754-12.202	0.002
PLR	Post-op Day 22-56	4.241	2.088-8.614	<0.001
NLR	Post-op <24h	0.578	0.287-1.162	0.124
	Post-op Day 8-21	3.460	1.623-7.376	0.001
LMR	Pre-op	0.583	0.337-1.010	0.054
	Post-op <24h	1.862	0.947-3.658	0.071
	Post-op Day 4-7	0.274	0.131-0.576	0.001
1-year Recurrence Free Survival				
Marker/ Variable		Hazard Ratio	95% Confidence Interval	p-value
CRS Performed		0.577	0.347-0.959	0.034
PCI Score		1.053	1.015-1.092	0.006
Duration of Hipec		1.037	1.008-1.068	0.014
CC Score	0	<i>Ref</i>		0.001
	1	3.706	1.148-11.969	0.029
	2	0.000	0	0.975
	3	4.075	1.855-8.953	<0.001
Intraop Complications		5.507	2.560-11.847	<0.001
Postop Complications		1.612	1.049-2.479	0.030
PLR	Post-op Day 57-90	1.702	0.930-3.113	0.084
NLR	Post-op <24h	0.581	0.337-1.001	0.051
	Post-op Day 57-90	1.383	0.775-2.468	0.273
LMR	Post-op Day 8-21	0.576	0.301-1.101	0.095

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Table 5: Multivariate overall survival analysis

Variable		1-year Overall Survival		
		Hazard Ratio	95% Confidence Interval	p-value
PLR	Post-op Day 22-56	10.702	3.788-30.235	<0.001
NLR	Race	<i>Ref</i>		
	Chinese	3.964	0.483-32.555	0.018
	Malay	4.477	1.530-13.103	0.200
	Others			0.006
	Intra-op complication	3.103	1.023-9.409	0.045
	Post-op Day 8-21	9.575	3.496-26.221	<0.001
LMR	Intra-op complications	4.081	1.509-11.034	0.006
	Post-op Day 4-7	0.183	0.078-0.429	<0.001