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Original Article

Role of Pretreatment Pan-Immune Inflammation Value as Predictive Marker of Response to Neoadjuvant Therapy in Locally Advanced Rectal Cancer: A Prospective Observational Study in a Tertiary Cancer Center

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Abstract

Introduction Neoadjuvant treatment in locally advanced rectal cancer (LARC) led to downstaging in nearly 50 to 60% of patients and pathological complete response (pCR) rates in 9 to 30% cases. However, cases not responding to neoadjuvant treatment encounter either a delay in definitive treatment or progression.

Objective To evaluate the role of pan-immune inflammation value (PIV) as a predictive marker of response to neoadjuvant therapy in LARC.

Materials and Methods A prospective observational study was conducted to validate the predictive value of response to pretreatment PIV in patients with LARC.

Results One hundred twenty patients were enrolled in the study. Patients with higher PIV values were found to have poorer radiological response as compared with patients with lower values (55.1 vs. 75.8%, $p = 0.045$). Also, patients with high micro-satellite instability status had poor responses. pCR was seen in 21 patients (19.6%). Patients with high PIV value had a pCR rate of 11.6% as compared with 34.0% in the low PIV group.

Conclusion Pretreatment PIV value appears to be a predictive marker of response to neoadjuvant treatment in LARC.

Keywords
- pan-immune inflammation value
- rectal neoplasm
- pathologic complete response
- neoadjuvant therapy

Introduction

Colorectal carcinoma (CRC) is the third most frequent cancer among all cancers globally, irrespective of gender status and accounts for 1.9 million cases per year worldwide. Rectal cancer makes up 30 to 35% of CRC globally, with the rest being colon cancer.[1]

The standard management of locally advanced rectal cancer (LARC; cT3–4/N+) is neoadjuvant treatment followed by surgery.[2] This approach resulted in downsizing, downstaging, and residual-free resection, which led to improved local control and sphincter preservation.[3] Different neoadjuvant approaches like total neoadjuvant therapy (TNT), neoadjuvant concurrent chemoradiotherapy

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(NACTRT), and neoadjuvant chemotherapy (NACT) can be considered for LARC. However, the response to neoadjuvant therapy varies among patients. Fifty to sixty percent of patients are down-staged following neoadjuvant therapy, with ~9 to 30% of patients having a pathologic complete response (PCR).[4] Cases that did not respond to neoadjuvant treatment encountered either a delay in definitive treatment or progression.

Numerous studies have been done among solid cancers to develop a predictive marker for neoadjuvant treatment. Tumor markers like serum carcinoembryonic antigen (CEA) and CA19.9 not only help in diagnosis but also have prognostic value. A serial decrease in absolute value during neoadjuvant treatment predicts pathological complete response (pCR).[5] However, the role of the pretreatment value of these tumor markers as a predictive marker for neoadjuvant treatment is controversial.

Inflammation has become a part of carcinogenesis and cancer growth. Inflammatory markers have been studied in a variety of solid cancers as prognostic values in both definitive and metastatic settings.[6–8] Markers, such as the neutrophil-to-lymphocyte ratio,[9] and systemic inflammatory index[10] were studied to assess their predictive value in various cancers. In recent times, a novel marker, the pan-immune-inflammation value (PIV),[11–13] which incorporates neutrophil, platelet, monocyte, and lymphocyte (neutrophil x platelet x monocyte/lymphocyte), has been studied in metastatic and neoadjuvant settings in various solid cancers. Taking into consideration the value of pretreatment markers to predict the response of neoadjuvant treatment, we conducted a prospective study to validate the predictive value of pretreatment PIV value in LARC.

Materials and Methods

Study Design and Setting

This prospective observational study was conducted at a tertiary cancer center between January 2023 and September 2024. The minimum sample size was calculated for diagnostic test evaluation assuming a specificity of 70.6%,[9] absolute precision of 10%, and 90% confidence and disease prevalence of 11.6% of all cancers (GLOBOCON 2020 worldwide), yielding a required minimum sample size of 64 patients. The study included 120 patients with LARC who underwent neoadjuvant treatment (NACT/NACTRT/TNT) during this period.

Objectives

The study objective is to evaluate the role of pretreatment PIV value as a predictive marker of response to neoadjuvant treatment in patients with LARC.

Expected Outcomes

The primary outcome is to correlate the baseline PIV value with radiological response after neoadjuvant treatment.

The secondary outcome is to correlate the baseline PIV value with pathological response, including pCR.

Inclusion Criteria

- Adults $\geq$18 years.
- Patients with nonmetastatic LARC (cT3/4 or N+).
- Patients with no synchronous or metachronous CRC.

Exclusion Criteria

- Patients with unknown prior treatment history.
- Eastern Cooperative Oncology Group (ECOG) Performance score of 2 and above.
- Presence of autoimmune disease.

Treatment Protocols

- TNT APPROACH: Short course radiation therapy (SCRT) 25 Gy/5 fractions followed by NACT (CAPOX q3 weekly or mFOLFOX q2 weekly) to complete 6 months (at least 6 weeks as NACT) of perioperative therapy, further followed by definitive surgery.

This approach is preferred in patients with cT4, cN2, or positive mesorectal fascia.

- NACTRT APPROACH: NACTRT (45 Gy/25 fractions with concurrent capecitabine 625 mg/m^2 BD on the radiation day followed by definitive surgery, followed by adjuvant chemotherapy (CAPOX q3weekly or FOLFOX q2 weekly) to complete 6 months of perioperative therapy.

Patients with LARC were enrolled in the study after biopsy and metastatic workup. Baseline characteristics and pretreatment blood parameters were recorded. Immune markers were calculated. Planned neoadjuvant treatment was given as per the standard schedule, followed by either abdominoperineal resection (APR) or low anterior resection (LAR) with transmesorectal resection. Postoperative histopathological evaluation was done according to the College of American Pathologists (CAP) guidelines.

Statistical Analysis

SPSS program version 23.0 for Windows was used for data analysis. The PIV cutoff used the value (454) from an earlier study.[14] The pre-chemotherapy PIV values were divided into two groups: low PIV ($<$454) and high PIV ($>$454). To examine the relationship between the ordinal variable, the chi-square test and the logistic regression test were applied.

Ethics

The study was approved by the Institutional Review Board of Kidwai Memorial Institute of Oncology, dated April 13, 2023, approval number KMIO/MEC/2023/04/PG/M0/19A. This study was conducted in accordance with the principles of Helsinki's declaration (1960).

Results

A total of 120 patients were enrolled in the study. The age of the patients ranged from 18 to 78 years, with a median age of

Table 1 Patient characteristics

Patient characteristics	No. of patients (total = 120)	Percentage
Age	Median: 50 y Range: 18–78 y	
Sex		
Male	71	59.16%
Female	49	40.84%
Comorbidity		
Diabetes mellitus	25	20.83%
Hypertension	29	24.16%
Hypothyroidism	7	5.83%
Habits		
Alcohol	35	29.16%
Smoking	39	32.5%
Presentation		
Bleeding per rectum	68	56.66%
Altered bowel habits	49	40.83%
Abdominal pain	39	32.5%
Tenesmus	29	24.16%
Weight loss	18	18.33%
Intestinal obstruction	7	5.83%

Table 2 Tumor characteristics

	Number of patients	Percentage
Grade		
Grade 1	18	15%
Grade 2	76	63.3%
Grade 3	26	21.6%
Histology		
Adenocarcinoma	109	90.8%
Mucinous	11	9.2%
Primary tumor staging		
T2	11	9.2%
T3	58	48.3%
T4a	38	31.7%
T4b	13	10.8%
Nodal staging		
N0	13	10.8%
N1	69	57.5%
N2a	29	24.2%
N2b	9	7.5%
Overall staging		
II	13	10.8%
IIIA	47	39.2%
IIIB	44	36.7%
IIC	16	13.3%
Mesorectal fascia positivity		
Yes	26	21.7%
No	94	78.3%
Micro-satellite stability		
Low/Stable	105	87.5%
High	15	12.5%
Total	120	100%

50 years. Male patients (59.16%) were found to be more as compared with female patients (40.84%). The most common presentations were per rectal bleeding (56.6%), altered bowel habits (40.8%), abdominal pain (32.5%), tenesmus, and weight loss. Seven patients had intestinal obstruction at presentation (►**Table 1**).

More than one-third of the patients had stage IIIA (39.2%), followed by IIIB (36.7%), IIIC (13.3%), and stage II (10.8%). The majority of the patients had either T3 or T4a, whereas approximately only 10% of patients had T2 and T4a. Nodal positivity was seen in 89.2% patients, in which the majority of the patients had N1 disease. The most common histology was adenocarcinoma, whereas mucinous type, comprised 9.2% of patients. Most of the patients had grade II followed by grade III. Twenty-six (21.7%) patients were found to have mesorectal fascia (►**Table 2**).

Serum CEA levels in patients ranged from 0.31 to 1,195.72 ng/mL, with a mean value of 48.48 ± 173.61 ng/mL. Blood parameters have been summarized in ►**Table 3**. Out of 120 patients, 62 (51.66%) patients had low PIV values (i.e., <454) and 58 patients (48.33%) had high PIV values (i.e., >454). Apart from the CEA value, the rest of the parameters were found to be equally distributed among both cohorts. Serum CEA values were found to be higher in the high PIV group patients as compared to the low PIV group ($p = 0.001$).

More number of patients have received TNT as compared with NACTRT. The majority of patients had a partial response (57.5%), whereas a complete response was seen in 8.3% patients only. Fifteen percent of patients had disease progression at the end of neoadjuvant therapy. Neither grade, stage, nor type of neoadjuvant treatment resulted in a significant difference in radiological response. Patients with higher PIV values were found to have poorer radiological response as compared with patients with lower values (response rate: 55.2 vs. 75.7%, $p = 0.045$). Also, patients with high micro-satellite instability (MSI) status had poor responses (►**Table 4**).

All the patients were evaluated for definitive surgery, 99 patients (82.5%) were found to be operable, while others were deemed inoperable due to metastatic disease, surgically inoperable, or medical reasons (►**Table 5**). Among the operated patients, tumor regression score grades (TRGs) 0, 1, 2, and 3 were seen in 10, 23, 41, and 12 patients, respectively, while TRG was not available for 13 patients.

Table 3 Hematological parameters in patients

Hematological parameters	Mean	Range	Unit
Serum carcinoembryonic antigen	48.83	0.31–1195.72	ng/mL
Hemoglobin	11.51	5.6–15.0	g%
Platelet count	340.1	121–912	10^3/μL
Total leukocyte count	8.21	2.44–18.70	10^3/μL
Absolute neutrophil count	5.34	1.70–15.50	10^3/μL
Lymphocyte count	1.86	0.35–4.31	10^3/μL
Monocyte count	0.613	0.15–1.61	10^3/μL
Basophil count	0.051	0.00–0.480	10^3/μL

Table 4 Radiological responses from patients

	Patients	Poor response	PR	CR	*p*-Value
Overall	120	41 (34.2%)	69 (57.5%)	10 (8.3%)	
Gender					0.822
Male	71	26 (36.7%)	39 (54.9%)	6 (8.4%)	
Female	49	15 (30.6%)	29 (59.2%)	4 (8.2%)	
Age					0.83
< 60 y	66	24 (36.4%)	37 (56.0%)	5 (7.6%)	
> 60 y	54	17 (31.5%)	32 (59.2%)	5 (9.3%)	
Grade					0.32
1	18	3 (16.7%)	13 (72.2%)	2 (11.1%)	
2	76	30 (39.5%)	39 (51.3%)	7 (9.2%)	
3	26	8 (30.8%)	17 (65.4%)	1 (3.8%)	
Histology					
Adenocarcinoma	109	36 (33.0%)	64 (58.7%)	9 (8.3%)	0.68
Mucinous Adenocarcinoma	11	5 (45.5%)	5 (45.5%)	1 (9.0%)	
CEA level					0.95
Normal	55	19 (34.5%)	31 (56.4%)	5 (9.1%)	
Elevated	65	22 (33.8%)	38 (58.5%)	5 (7.7%)	
PIV value					0.045
Low	62	15 (24.2%)	40 (64.5%)	7 (11.3%)	
High	58	26 (44.8%)	29 (50.0%)	3 (5.2%)	
Treatment					0.59
TNT	69	26 (37.7%)	37 (53.6%)	6 (8.7%)	
NACTRT	51	15 (29.4%)	32 (62.7%)	4 (7.9%)	
MSI status					0.011
Low/Stable	105	31 (29.6%)	64 (60.9%)	10 (9.5%)	
High	15	10 (66.7%)	5 (33.3%)	0 (0%)	

Abbreviations: CEA, carcinoembryonic antigen; MSI, micro-satellite instability; NACTRT, neoadjuvant concurrent chemo-radiotherapy; PIV, pan-immune inflammation value; TNT, total neoadjuvant therapy.

Patients who underwent surgery but without a TRG score were excluded from the pathological response evaluation; so, out of 120 patients, 107 patients were included for the pathological evaluation (86 were operated and 21 were inoperable). pCR (TRG1) was seen in 21 patients (19.6%). Among various factors assessed, only the PIV value was associated with pathological response. Patients with high PIV value had a pCR rate of 11.6% as compared with 34.0% in

Table 5 Surgical outcomes of patients

Operability	Overall
Operable	99 (82.5%)
Inoperable	21 (17.5%)
Metastatic	11 (9.17%)
Localized (surgically inoperable)	7 (5.83)
Medical inoperable	3 (2.5%)

the low PIV group. High MSI patients have numerically lower pCR as compared with low or stable MSI; however, it was nonsignificant (►**Table 6**).

On subgroup analysis, in patients with low or stable MSI, high PIV was associated with lower radiological response and pCR (►**Table 5**). On univariate and multivariate logistic regression, only the PIV value appeared to be a predictor of pCR.

Discussion

Inflammation has been attributed to tumor development and progression. A tumor micro-environment enriched with neutrophils and monocytes increases oncogenic growth by stimulating the development of myeloid-derived suppressor cells.[15] Also, monocyte transforms into tumor-associated macrophage that likely has an important role in invasion and metastasis.[16] Platelet plays an important role in angiogenesis. Lymphocyte, an anticancer immunity cell, inhibits tumor growth and metastasis.[17] Thus, in recent years, a novel marker considering the role of immune cells was developed, namely, PIV value. PIV value has gained attention in recent years as a prognostic and predictive marker in various solid cancers. A meta-analysis assessing six trials in the metastatic and nonmetastatic setting concluded worse overall survival in patients with high PIV value and thus its prognostic value.[18] However, its role as predictive value was still questionable. In this study,

Table 6 Diverse pathological responses from patients

Parameter	Patients	TRG1	TRG2	TRG3	TRG0	*p*-Value
Overall	86	10 (27.8%)	41 (47.6%)	12 (13.6%)	10 (13.2%)	
Gender						
Male	50	13 (26%)	25 (50%)	6 (12%)	6 (12%)	0.50
Female	36	10 (27.8%)	16 (44.4%)	6 (16.7%)	4 (11.1%)	
Age						
< 60 y	49	12 (24.5%)	23 (51.1%)	6 (12.2%)	8 (16.6%)	0.452
> 60 y	37	11 (29.7%)	18 (48.6%)	6 (16.2%)	2 (5.4%)	
Grade						
1	17	6 (35.3%)	7 (41.2%)	1 (5.9%)	3 (17.6%)	0.342
2	45	13 (28.9%)	21 (46.7%)	5 (11.1%)	6 (13.3%)	
3	24	4 (16.6%)	13 (54.2)	6 (25%)	1 (4.2%)	
Histology						
Adenocarcinoma	76	21 (27.6%)	36 (47.4%)	10 (13.2%)	9 (11.8%)	0.912
Mucinous adenocarcinoma	10	2 (20%)	5 (50%)	2 (10%)	1 (10%)	
CEA level						
Normal	45	9 (20%)	26 (57.8%)	5 (11.1%	5 (11.1%)	0.241
Elevated	41	14 (34.1%)	15 (36.6%)	7 (17.1%)	5 (12.2%)	
PIV value						
Low	41	16 (39.0%)	14 (34.1%)	3 (7.4%)	8 (19.5%)	0.027
High	45	7 (15.6%)	27 (60%)	9 (20%)	2 (4.4%)	
Treatment						
TNT	48	14 (29.2%)	26 (54.2%)	5 (10.4%)	3 (6.2%)	0.181
NACTRT	38	9 (23.7%)	15 (39.5%)	7 (18.4%)	7 (18.4%)	
MSI status						
Low/Stable	76	22 (28.9%)	37 (48.7%)	7 (9.2%)	10 (13.2%)	0.0035
High	10	1 (10%)	4 (40%)	5 (50)%	0 (0%)	

Abbreviations: CEA, carcinoembryonic antigen; MSI, micro-satellite instability; NACTRT, neoadjuvant concurrent chemo-radiotherapy; PIV, pan-immune inflammation value; TNT, total neoadjuvant therapy.

the significance of PIV value in predicting response to neoadjuvant therapy in LARC was assessed.

Nonmetastatic LARC was treated with neoadjuvant therapy (NACTRT, TNT). Radiological and pathological responses were evaluated and their relation with different markers was assessed. Patients with low PIV values had better radiological and pathological responses as compared with high PIV. Patients with high PIV values had a radiological complete response (CR) rate of 5.2% and downsizing of 55.2% as compared with 11.3 and 75.8% with low PIV values, respectively. Patients with high PIV value had a pCR rate of 11.6 versus 34.0% in high PIV value. High MSI status was associated with a poor radiological response but not with a pathological response. However, a number of patients for this to be proven were found to be negligible.

Finally, pathological and radiological responses were assessed in low/stable MSI patients. PIV value was also found to be a significant predictive marker in this subgroup. Shen et al demonstrated the role of preoperative PIV value in LARC. Low PIV value resulted in higher PCR rates as compared with high PIV ($p = 0.029$), with ypT0 rates of 21.6 versus 8.1%, respectively.

The study also found significant disease-free survival (hazard ratio = 2.53; 95% CI, 1.58–4.06; $p = 0.002$) and overall survival (hazard ratio = 3.08; 95% CI, 1.77–5.35; $p = 0.001$) differences in low and high PIV value groups. Thus, the mentioned study concluded that PIV value is a predictive marker of response to neoadjuvant treatment and also a prognostic marker for survival.[14]

Strengths

PIV has not been extensively studied in LARC, and to our knowledge, this study is the only study besides the above-mentioned study in this setting. This study is a prospective study conducted in a tertiary cancer center with inclusion of all forms of neoadjuvant treatment, which reflects outcomes in a practical clinical environment. Both radiological and pathological responses were analyzed in this study, thus giving comprehensive insight. Also, the sample size included was larger than the minimum calculated, which improves statistical power.

Future Prospects

Though this study is still in the investigational phase, the question arises whether it can be used with baseline workup to better risk-stratify patients and to identify the cohort of patients who are going to respond poorly to the standard treatment and thus consider treatment intensification. Also, MRI-based pCR prediction is the cornerstone for the "wait-and-watch" approach; the question of "Can PIV value be used along with MRI as an extra factor for patient selection?" needs exploration.

Generalizability of Research

PIV is simple, cost-effective, and based on routine blood counts; thus, it can easily be incorporated into baseline workup even in low-resource settings.

Limitations

There are a few limitations of the study, one being a nonrandomized single-center prospective study. The correlation of PIV value with survival was also not addressed in this study. Also, this study leaves many gray areas like PIV dynamics during treatment and its comparison with other inflammatory markers. This study used a predetermined cut-off value to evaluate its role; as such, no universally validated or standardized cut-off value is available. Also, its interpretation in patients with active infection, autoimmune disease, or steroid use is still a question.

Conclusion

To summarize, PIV value appeared to be a predictive marker of radiological and pathological response in LARC patients treated with neoadjuvant treatment. It can be helpful in identifying the subgroup of patients who might not do well with neoadjuvant treatment. Though this study answers many questions and opens an area of research, randomized studies are needed to strengthen its role in a clinical setting.

Patient's Consent

Informed consent was taken from each patient.

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None.

Conflict of Interest

None declared.

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