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Original Article

Utility of Neutrophil–Lymphocyte Ratio, Platelet–Lymphocyte Ratio, Mean Platelet Volume–Platelet Count Ratios: Diagnostic and Prognostic Markers in Patients with Hepatocellular Carcinoma, Prostate Carcinoma, Stomach Carcinoma, and Aplastic Anemia

V S Srikanth, M Gopala Krishna Pillai, Cinzia Keechilot, Ashwin Rajkumar, Tushar Tatineni[1]

Departments of General Medicine and [1]Radiation Oncology, Amrita Institute of Medical Sciences and Research Centre AIMS, Affiliated to Amrita Vishwa Vidyapeetham, Ponekkara, Kochi, Kerala, India

Abstract

Introduction: The purpose of the study is to study the potential role of neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and mean platelet volume (MPV)–platelet ratio as diagnostic and prognostic markers in patients with hepatocellular carcinoma (HCC), prostate cancer, stomach cancer, and aplastic anemia. **Materials and Methods:** We have conducted the present study by screening 208,486 patients who have got admitted during January 2013–June 2017 as in patients in our hospital. The data collected were analyzed for NLR, PLR, and MPV–platelet ratio. **Inclusion Criteria:** Patients admitted with a diagnosis of HCC, prostate cancer, stomach cancer, and aplastic anemia irrespective of the age and gender. **Exclusion Criteria:** Patients with multiple malignancies, the presence of secondary infection, and any source of sepsis. SPSS tool was used for statistical analysis. **Results:** Cost-effective predictive and prognostic biomarkers identified in the study are – NLR for liver cancer, prostate cancer, and stomach cancer; PLR for prostate and stomach cancer; MPV/plate ratio can be used in addition to NLR for liver cancer. These ratios were not significant in aplastic anemia. **Conclusion:** From our study, we conclude that NLR and PLR are better cost-effective predictor and prognostic markers of HCC, prostate cancer, and stomach cancer. These ratios can be used at the primary health-care level as it can be derived from a simple complete blood count/peripheral smear. Early identification of carcinoma is possible using these potential markers along with the respective clinical presentations and symptoms. These ratios will reduce the financial burden on the patients from rural and low socioeconomic background and will aid in better management of the disease process.

Keywords: *Carcinoma, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, and mean platelet volume/platelet ratio*

Introduction

As per statistical reports of 2015, it is estimated that about 14 million new cancer cases were diagnosed, and >8 million cancer deaths occurred worldwide. Out of this, 1 million new cases were reported from India and nearly 700,000 of the deaths occurred only in India.[1] The number of new cancer cases reported will rise to 22 million within the next two decades. When seen globally, nearly 1 in 6 deaths occur due to cancer, of which liver cancer (788,000 deaths) and stomach cancer (754,000 deaths) stand to be the major carcinoma mortality cause.[1,2]

More than 60% of the world's new cancer cases occur in Africa, Asia, and Central and South America. About 70% of the world's cancer deaths also occur in these regions as these subcontinents are in developing phase when compared to rest of the world and have minimal access to advanced diagnostic modality at the primary health-care centers. Late-stage presentation and poor diagnosis and treatment are a common cause of majority of the death. The total annual economic cost of cancer is estimated to be approximately US$ 1.16 trillion.[2]

In recent years, accumulating evidence demonstrated that increased systemic inflammation is associated with poor cancer-specific survival in a variety of cancers.[3-7] These studies revealed that the host's inflammatory response to cancer and/or the systemic effects exerted by the

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Address for correspondence:
Dr. M Gopala Krishna Pillai, Amrita Institute of Medical Sciences and Research Centre, Ponekkara, Kochi - 682 014, Kerala, India.
E-mail: dr.mgkpillai61@gmail.com

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cancer cells lead to upregulation of the inflammatory process, inducing the proliferation and metastasis of cancer cells by inhibiting apoptosis, promoting angiogenesis, and repairing DNA damage.[8,9] The presence of a systemic inflammatory response can be detected by neutrophil–lymphocyte ratio (NLR).[10] Studies have shown that an elevation in NLR correlated with tumor progression, metastasis, and clinical outcome in a variety of cancers.[11-16] In this study, we are focusing on analyzing the utility of these ratios as predictive and prognostic markers in various cancers.

The prediction is with reference to early identification and timely referral to right oncology center. This will improve the cure rate and survival probability of the carcinoma patients. In the study, the predictive potential of the biomarkers is evaluated. These markers will prove to be useful in predicting the malignancy as a differential diagnosis at primary health-care centers and timely referral to malignancy management.

Although advancements happens across the world in oncology management, there is an increasing trend in Cancer incidence and Cancer mortality. This is mainly due to economic burden of the treatment cost and lack of cost-effective diagnostic modality at primary health-care centers. In this study, we are focusing on using NLR, platelet–lymphocyte ratio (PLR), and mean platelet volume (MPV)/platelet ratio as cost-effective biomarkers for screening and differentiating the common cancers in rural and primary health-care setups.

Materials and Methods

The present study is a retrospective, hospital-based observational study. We conducted the present study by screening 208,486 patients who have got admitted during January 2013–June 2017 as in patients in our hospital. Out of the total population, 100 cases in each of hepatocellular carcinoma (HCC), stomach cancer, prostate cancer, and aplastic anemia were selected as the study group. Maximum number of aplastic anemia cases reported in the study period was 102 cases, and hence, the sample size was chosen as 100 in each of the carcinoma study group. The control group was formed with an equal number of patients without any carcinoma presentation and other comorbidities. Irrespective of the stage of the disease process in each of the carcinoma test group, the predictive and prognostic potential of the biomarkers was evaluated.

Table 1: *t*-test analysis for Hepatocellular Carcinoma

Statistical Test	MPV	NLR	PLR	MPV/platelet ratio
Mann-Whitney U	4392	2288	4648	2995
Wilcoxon W	9442	7338	9698	8045
Z	-1.486	-6.627	-0.86	-4.9
Asymptotic significance (2-tailed)	0.137	0.0001	0.39	0.0001

P=0.0001 shows NLR and MPV/platelet ratio have very high statistical significance for Hepatocellular Carcinoma

The data collected were analyzed for NLR, PLR, and MPV–platelet count ratio.

Laboratory investigations

Laboratory investigation reports of the study groups and control groups were recorded in predesigned pro forma for statistical analysis. CRP, neutrophil count, lymphocyte count, and platelet volume were analyzed and compared

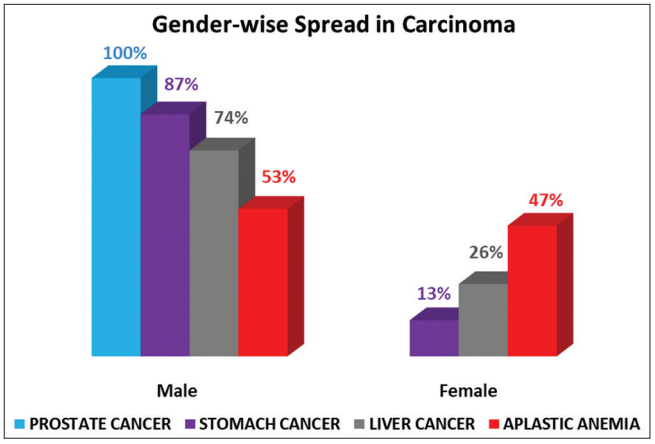


Figure 1: Carcinoma presentation – Spectrum across gender and Age

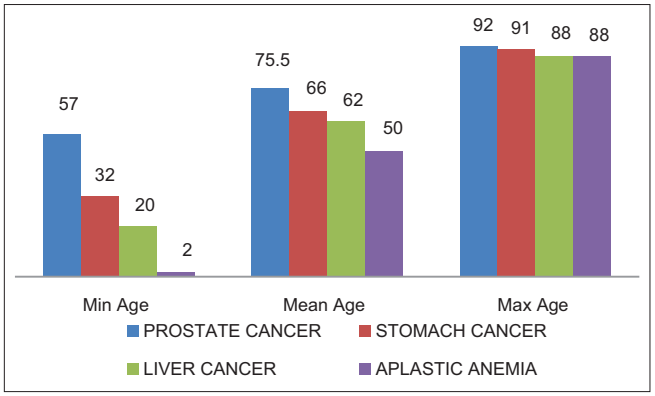


Figure 2: Presenting age in various carcinoma under study

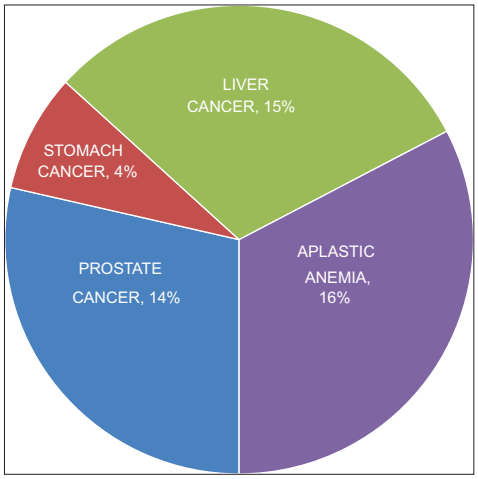
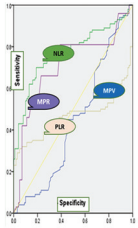


Figure 3: In-hospital mortality represented in carcinoma study groups

Table 2: Analysis of Bio-Markers for Hepatocellular Carcinoma

Area Under Curve (ROC) Analysis for Sensitivity & Specificity					
Test result variable (s)	Area	Std. error	Asymptotic Sig.	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
MPV	0.439	0.041	0.137	0.359	0.52
NLR	0.771	0.034	0	0.704	0.839
PLR	0.465	0.045	0.393	0.377	0.553
MPV/platelet ratio	0.708	0.038	0	0.633	0.783



NLR and MPV/platelet ratios show very high statistical significance for Hepatocellular Carcinoma

Table 3: *t*-test analysis for prostate Carcinoma

Statistical test	MPV	NLR	PLR	MPV/ Platelet ratio
Mann-Whitney U	4845	2025	3274.5	4003
Wilcoxon W	9895	7075	8324.5	9053
Z	-0.38	-7.278	-4.217	-2.437
Asymptotic significance (2-tailed)	0.704	0.0001	0.0001	0.015

P=0.0001 shows NLR and PLR have very high statistical significance for Prostate Carcinoma

with the standard laboratory reference value as mentioned below for understanding the deviations in the study group marker values. NLR, PLR, and MPV–platelet count were calculated and compared to the control group results.

- Neutrophil count (60%–80%)
- Lymphocyte count (20%–40%)
- MPV (6.8–10 f).

Inclusion criteria

The patients admitted with a diagnosis of HCC, prostate cancer, stomach cancer, and aplastic anemia irrespective of the age group.

Exclusion criteria

Patients with >1 malignancy reported the presence of secondary infection, any source of sepsis, and other comorbidities.

Data collection and statistical analysis

For each member of the study groups, demographic information, details of various symptoms and reported clinical presentations, and laboratory investigations as mentioned above were recorded onto a standard data collection sheet as per the study pro forma and later transferred to a Microsoft Excel spreadsheet for further statistical analysis.

In this study, we analyzed complete blood count (CBC)/peripheral smear reports of the patients. All these tests were done in the same machine, and the results were analyzed and stored as computerized database. There is no scope for observer variability. It is an NABH- and ISO-certified laboratory where all the tests conducted are standardized and documented according to certification standards.

Data were organized and compiled into Microsoft Excel Version 2010. (Microsoft Corporation, One Microsoft Way Redmond, WA 98052-6399 USA) and data were systematically analyzed by SPSS 20.0 version. The assumption of $P < 0.05$ was considered as statistically significant in the "*t*-tests" studied.

Predictive and prognostic significance of laboratory tests has been arrived at by following the below steps:

1. The results of each of the test variables were statically analyzed using "*t*-test" with the assumption of $P < 0.05$ as hypothesis significance
2. When the tests proved to be significant, ROC curve analysis is done to confirm the specificity and sensitivity over the range of mean values
3. Test variables were confirmed to have significance if the area under curve showed >50% of coverage in area under curve analysis
4. Finally, the predictive significance of the test parameters is substantiated by comparing the mean values of each of the parameters with their respective control group values and symptomatic evaluation of the test groups. This showed the indicative potential of the biomarkers.

The prognostic potential is evaluated similar to the predictive capability of the biomarkers. The indicative cutoff values of the biomarkers are arrived at using data from very high sample size. These cutoff values along with the symptoms and presenting conditions are used for evaluating the disease prognosis during every visit after the start of the treatment course.

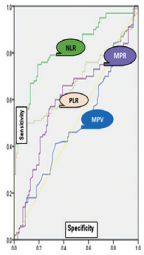
Results

Observations and analysis of data in this study are presented in tables and figures listed here. Various carcinoma presentations in the study population are shown in Figure 1, and Figure 2 shows the spread spectrum across gender and age. Figure 3 shows in-hospital mortality observed in various carcinoma study groups.

Statistical analysis for HCC is shown in Table 1. The *t*-test observation showed that NLR and MPV/platelet ratio was highly significant markers as indicated in Table 1. ROC analysis for sensitivity and specificity showed NLR had

Table 4: Analysis of Bio-Markers for Prostate Carcinoma

Area Under Curve (ROC) Analysis for Sensitivity & Specificity					
Test result variable (s)	Area	Std. error	Asymptotic Sig.	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
MPV	0.493	0.041	0.867	0.412	0.574
NLR	0.816	0.03	0	0.757	0.876
PLR	0.673	0.039	0	0.596	0.75
MPV/platelet ratio	0.6	0.041	0.015	0.519	0.68



NLR and PLR Ratios show very high statistical significance for Prostate Carcinoma

Table 5: *t*-test analysis for stomach carcinoma

Statistical test	MPV	NLR	PLR	MPV/platelet ratio
Mann-Whitney U	3588.5	2135.5	2751	0
Wilcoxon W	8638.5	7185.5	7801	5050
Z	-3.469	-7.005	-5.496	-13.063
Asymptotic Significance (2-tailed)	0.001	0.0001	0.0001	0.0001

P=0.001 and less show MPV, NLR, PLR and MPV/platelet ratio have very high statistical significance for Stomach Carcinoma

covered 77% and MVP/platelet ratio 70% which were observed to be the most sensitive and specific markers out of the four markers analyzed as indicated in Table 2 for HCC.

The outcome of *t*-test for prostate carcinoma showed that NLR, PLR, and MPV/platelet ratio were highly significant as indicated in Table 3. ROC analysis showed NLR had occupied 81% of area in the area under curve analysis, PLR 67%, and MVP/platelet ratio 60% [Table 4].

Statistical analysis for stomach carcinoma is shown in Table 5. The *t*-test results indicate that NLR and PLR were highly significant markers in stomach cancer.

ROC analysis shows NLR and PLR are highly significant compared to other markers. Area under curve indicates the coverage for each marker as NLR 80%, PLR72%, MVP/platelet ratio 44%, and MPV 35% [Table 6].

Post identification of the significance of the NLR, PLR, and MPV/platelet ratios for each of the carcinoma under study as mentioned above, the cutoff range for each of these markers in various carcinoma conditions was arrived by comparing the weighted average of mean values of the biomarkers in every specific carcinoma studied and healthy control group mean values for these biomarkers. The indicative cutoff values are presented in Table 7. High correlation was observed between the indicative cutoff values of the biomarkers in a specific carcinoma condition and the presenting clinical conditions and symptoms recorded for the respective carcinoma under study. This significance observed provides a decision pointer for early screening of the carcinoma condition and further reference for effective disease management.

Discussion

Hepatocellular carcinoma

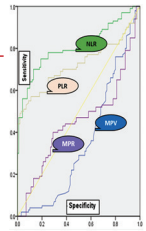
The incidence of HCC was more common in male population with a mean age group of 62 years which was in line with a study conducted by Sahil Mittal that showed an age predominance 45–65 years.[17] HCC was associated more with lower socioeconomic group, in population where alcoholism was more common. The major presenting complaints were right hypochondrial pain with weight loss, jaundice, and ascites in >60% of the patients. Out of these patients, in-hospital mortality was 15%. Our study showed that in HCC the most significant markers were NLR and MPV/platelet ratio, which were highly significant to be used as predictor and prognostic marker with a $P = 0.0001$, respectively. We also found NLR had occupied 77% in ROC. Furthermore, a cut value of NLR >4.25 and MPV/platelet ratio >0.07 was arrived. A similar study was done by Xiao *et al*. where they proved NLR to be a useful prognostic marker in China.[18] To further support the results, NLR was associated with tumor size and clinical tumor node metastasis stage from a study conducted by Liao *et al*.[19] MPV/platelet ratio occupied 70% area under the curve. A similar study conducted by Cho *et al*. showed a similar result where MPV/platelet ratio was identified as an important biomarker in prognostic and predictive utility.[20] Whereas MPV and PLR were not statistically significant to be used as a biomarker in HCC. Contrary to our result, Mona *et al*. conducted a study in which MPV was found to be a good prognostic and predictive marker (N4). Wencong Ma and Ping Zhang showed PLR was a significant marker to be used a prognostic marker which is a variant from our finding.

Prostate cancer

In prostatic carcinoma, the mean age group of the presentation was 75 years. Prostate cancer prevalence was observed irrespective of socioeconomic condition. The major presenting complaints were urinary retention 26%, urinary frequency 22%, and decreased urinary stream in 31%. Prostatic cancer analysis showed that NLR and PLR were significant markers with a $P = 0.0001$. When further analysis done using ROC, it showed NLR and PLR occupied 81% and 67% of the area under the curve

Table 6: Analysis of Bio-Markers for Stomach carcinoma

Area under Curve (ROC) Analysis for Sensitivity & Specificity					
Test result variable (s)	Area	Std. error	Asymptotic Sig.	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
MPV	0.351	0.039	0	0.274	0.428
NLR	0.808	0.032	0	0.746	0.871
PLR	0.721	0.038	0	0.646	0.796
MPV/platelet ratio	0.447	0.042	0.193	0.365	0.528



NLR and PLR Ratios show very high statistical significance for stomach carcinoma

Table 7: Potential biomarkers and their cutoff values for different carcinoma studied

Biomarker cutoff values			
Carcinoma	NLR	PLR	MPV/platelet ratio
Hepatocellular carcinoma	>4	Insignificant	>0.07
Prostate carcinoma	>5	>16	Insignificant
Stomach carcinoma	>4	>15	Insignificant

PLR – Platelet-to-lymphocyte ratio; NLR – Neutrophil-to-lymphocyte ratio; MPV – Mean platelet volume

respectively. They are found to be effective as predictive and prognostic marker. Minimum Cut-Off value for NLR and PLR were calculated as 5 and 16 respectively. In line with our findings, similar results were inferred from a study by Yin *et al*.,[21] Xiaobin Gu, and Xianshu Gao (N11) which showed NLR to be an effective prognostic marker. A study by Wang Y, Xu F, Pan J, and Zhu Y showed similar results, wherein PLR and NLR are showed as effective bio-markers. In contrary to out result, a study done in China showed MPV/platelet ratio was equally significant.[22]

Stomach cancer

The mean age group was 66 years. Stomach cancer prevalence was observed irrespective of socioeconomic condition. The major presenting complaints were loss of appetite 26%, hematemesis 34%, weight loss 30%, and difficulty in swallowing 22%. NLR, PLR, MPV, and MPV/platelet ratio were statistically significant with a $P = 0.0001$ for all markers except MPV which was 0.001. Further analysis with ROC curve showed NLR and PLR occupied 80% and 72% area under the curve, respectively. A cut value of NLR >4 and PLR >15 was arrived. Similarly, a study conducted by Hu ZD and Huang YL showed that, NLR was an effective prognostic marker to be used in gastric carcinoma.[23] Another study by Jingxu Sun, Xiaowan Chen, and Peng Gao also showed a similar result supporting this[24,25] Mutlu Dogan, Tulay Eren, and Nuriye Ozdemir showed in their study that NLR (≥2.5) seems to be poor prognostic factors in Metastatic Gastric Cancer (MGC). A study conducted by Mutlu Dogan, Tulay Eren, and Nuriye Ozdemir showed PLR to be significant in assessing the utility of PLR as a prognostic marker. In our study, we also showed MPV and MPV/platelet ratio to be very significant biomarkers with a $P < 0.0001$, which is mirroring the results of the study conducted by Matowicka-Karna *et al*.[26]

Aplastic anemia

NLR, PLR, and MPV ratio were not statistically significant to be used a biomarker as there was gross deviation from the normal value. Aplastic anemia is a rare disorder characterized by suppression of bone marrow function, resulting in progressive pancytopenia. A trigger-related abnormal T-cell response facilitated by some genetic predisposition has been postulated as the pathogenetic mechanism, leading to the overproduction of bone marrow-inhibiting cytokines.

Although Aplastic anemia is a pancytopenia condition, MPV is a size-dependent variable where we wanted to assess its significance in these conditions. NLR and PLR were assessed to prove that these ratios cannot be used in determining the aplastic anemia conditions.

Conclusion

HCC, prostate cancer, and stomach cancer are conditions which can be easily missed out from focus at the early stages of presentation, and if not promptly diagnosed and monitored, it will lead to poor clinical outcome and chances of spread of the diseases. In a rural setup and primary health-care level, high-end diagnostic facilities are not accessible because the devices and testing reagents are expensive and require high maintenance. The patient must be referred to a higher health-care center where such testing facility is available.

In an attempt to identify the early diagnostic methods, we analyzed and concluded that NLR, PLR, and MPV/platelet ratios are potential biomarkers having a high diagnosis and prognosis utility. NLR is highly predictive for liver cancer, prostate cancer, and stomach cancer. Similarly, PLR is for prostate cancer and stomach cancer. MPV/platelet ratio can be used in addition to NLR in liver cancer. NLR and PLR can be derived from a peripheral smear and CBC at the primary health-care centers even in rural parts of the country where high-end testing facilities are not available.

Contribution of our study to the field of oncology would be, when a patient is presenting at the primary health-care level

with the above-mentioned symptoms, his/her corresponding biomarker value should be calculated. If the test values of the bio-markers for a patient found to be above the cutoff value, then differential diagnosis of carcinoma should be considered. Instead of delaying by symptomatic treatment at the primary health care level, the patient should be referred to an oncology center for further management.

This simple and cost-effective test will reduce the financial burden of the disease on the patients from rural and low socioeconomic background and will aid in better patient care by early identification and better management of the disease process. For further evaluation, we call for a prospective multicenter study with larger sample sizes to rigorously assess the prognostic value of these ratios.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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