Prognostic and Diagnostic Significance of Platelet Indices in Patients with Urothelial Carcinoma

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Abstract: Some prognostic markers have been shown to determine the course and survival of Urothelial Cancer. A cross-sectional retrospective study, specifically looking at the role that various indices related to platelets—namely Mean Platelet Volume (MPV), platelet count and MPV/Platelet ratio—play in the diagnosis and prognosis of urinary bladder cancer, was conducted at the Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan (India) between January 2016 and August 2021 and included 76 patients who underwent multicore TURBT biopsy. Complete Blood Count (CBC) was used to determine platelet count, MPV and MPV/Platelet ratio. Platelet count was found to be more elevated in patients with high grade urothelial carcinoma and muscle invasive urothelial carcinoma as compared to patients with low grade urothelial carcinoma and non-muscle invasive urothelial carcinoma (p < 0.05). The median MPV and MPV/PLT ratio was found to be significantly lower in patients with high grade urothelial carcinoma and muscle invasive urothelial carcinoma as compared to patients with low grade urothelial carcinoma and non-muscle invasive urothelial carcinoma (p < 0.05). Thus, platelet indices can be useful supportive prognostic and diagnostic indicators in the determination of the clinical outcome of urothelial carcinoma.

Keywords: urothelial carcinoma; thrombocytosis; inflammation; Mean Platelet Volume

1. Introduction

Urothelial Carcinoma (Urinary Bladder Cancer) has been reported as being responsible for approximately 200,000 deaths and 549,000 cases in 2018 worldwide, and therefore is the 10th most common cancer but when both genders are considered, UC is the 7th most common cancer in the male population. Men account for about three-quarters of cases of all bladder cancer but these rates may vary with region [1]. Classical classification of bladder cancer divides them into two: Non-muscle invasive urothelial cancer or NMIUC (CIS, Ta and T1) and muscle-invasive urothelial cancer or MIUC (T2-T4). The former accounts for 75% of all cases, whereas 25% patients have MIUC or metastatic disease [2]. Even with advances in anti-cancer drug therapies and surgical procedures, survival rates are still not satisfactory [3]. Prognostication is important for making decisions regarding the treatment [4]. Hence, it becomes important to seek a novel and effective diagnostic and prognostic biomarker to improve the survivability.

There is evidence to suggest that inflammation plays an important role in the development of a tumor and its progression [5,6]. Systemic inflammation in patients with cancer is very likely to affect the micro-environment around the tumor and therefore promote tumor growth, resulting in poor prognosis [7]. New studies have shown that the Systemic Inflammatory Response (SIR) can greatly influence the progression of urological cancer [8–10]. Observations have been made regarding platelets supporting the growth of primary tumors via angiogenesis as well as contributing to providing physical and mechanical assistance to tumor cells, therefore giving them the opportunity to escape the immune system and extravasate to secondary organs [11]. The connection between the
pre-operative thrombocytosis and the aggressiveness of the tumor has been seen in cases of both non-urological and urological cancers [12–17].

There has been association of platelet indices, including platelet count and MPV, with the prognosis of various cancers such as upper gastrointestinal tumors [18,19], colorectal cancer [20,21], lung cancer [22], breast cancer [23] and urothelial carcinomas [24,25].

One prominent hallmark of platelet activation is MPV, which is the important measure of the platelet size [26]. A reduction in MPV has been associated with an incidence of high grade neoplasm and is explained by the fact that the inflammatory condition that arises in the case of carcinomas is hypothesized to cause excessive platelet consumption and therefore results in a reduction in MPV [27,28].

Hence, this study has been aimed at understanding the role of MPV, MPV/PLT ratio and platelet counts in cases of urothelial cancers.

The aim is to evaluate the prognostic and diagnostic significance of platelet indices in patients with Urothelial Carcinoma and to analyze the findings and data of various other studies that try to find a connection between the platelet indices and various forms of cancer.

2. Material and Methods

A cross-sectional study was conducted at the Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan (India) between January 2016 and August 2021 and included 76 patients who underwent multicore TURBT biopsy. The present study was in accordance with the Helsinki Declaration and it did not require ethics committee permission as it involved retrospective data.

Biopsy specimens were evaluated in the histopathology section of the Pathology Department. In patients with established diagnosis of urothelial carcinoma pre-biopsy demographic features, whole blood cell counts, including MPV, PLT count and MPV/PLT ratio and biopsy results, were evaluated. In all cases, pertinent hematoxylin and eosin-stained slides were reviewed by an expert pathologist. Criteria for diagnosing high grade UC included high nuclear:cytoplasmic ratio, nuclear pleomorphism with variably sized and shaped hyperchromatic nuclei, prominent nucleoli, the presence of mitotic figures and stromal reaction and that of low grade UC included low-grade cytology (low nuclear:cytoplasmic ratio and lack of pleomorphism/hyperchromasia/mitotic figures) with the usual morphologic features of invasion including single cells, cords, small nests, retraction artifact and stromal reaction.

Inclusion criteria—All biopsy samples received in the Pathology Department were included during the study period.

Exclusion criteria—Patients with any history of an autoimmune or inflammatory disease, hematological diseases like myeloproliferative disorder or infection were excluded.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 22 software (IBM Corp., Armonk, NY, USA). For descriptive analysis, number and percentage were used for categorical variables and mean, standard deviation and median for continuous variables. The Chi square test was used for comparison analysis of categorical variables between independent groups. The Mann Whitney U test was used for comparison between two independent groups and independent student t test for data that are normally distributed. Diagnostic and prognostic values of PLT count, MPV and MPV/PLT ratio were assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and positive likelihood ratio (PLR). $p$ Value < 0.05 was considered statistically significant.

3. Results

Out of a total of 76 patients of urothelial carcinoma, high grade was observed in 57 (75%) patients and low grade in 19 (25%) patients. Among these, 66 (86.84%) were male and 10 (13.16%) were female. Statistical insignificant difference in mean age was
observed between patients with high grade urothelial carcinoma and low grade urothelial carcinoma ($p > 0.05$). A statistically insignificant association was observed among patients with high and low grade carcinoma according to their gender ($p > 0.05$). Thus, the age and sex distribution of patients with HGUC and LGUC were similar (Tables 1 and 2).

Table 1. Demographic data.

| Characteristics | Invasive HGUC | Invasive LGUC | Non-Invasive HGUC | Non-Invasive LGUC |
|-----------------|--------------|---------------|-------------------|-------------------|
| Number of Patients | 50 | 8 | 7 | 11 |
| Age | 62.7 ± 11.73 | 64.38 ± 11.66 | 62.14 ± 4.63 | 66.09 ± 6.76 |
| Hemoglobin | 11.73 ± 2.22 | 11.28 ± 2.23 | 11.03 ± 3.24 | 13.28 ± 2.16 |
| TLC | 9887.6 ± 5185.79 | 9750 ± 4583.82 | 8528.57 ± 2139.87 | 8751.82 ± 4532.83 |
| Neutrophil % | 65.42 ± 10.99 | 69.93 ± 10.72 | 67.58 ± 11.39 | 62.45 ± 13.71 |
| ANC | 6790.95 ± 4721.61 | 7192.9 ± 4551.23 | 5896.7 ± 2265.35 | 5807.89 ± 4397.35 |
| LYMP % | 26.07 ± 10.89 | 23.53 ± 10.18 | 23.47 ± 9.70 | 29.6 ± 13.22 |
| ALC | 2246.39 ± 7638.31 | 1953.25 ± 606.84 | 1868.3 ± 682.95 | 2230.22 ± 858.29 |
| Platelets | 312.78 ± 159.75 | 273.63 ± 97.42 | 268 ± 71.76 | 204.64 ± 85.61 |
| NLR | 3.33 ± 2.41 | 4.25 ± 3.73 | 3.97 ± 3.11 | 3.27 ± 3.09 |
| PLR | 147.18 ± 69.43 | 152.07 ± 64.96 | 171.77 ± 112.52 | 106.05 ± 59.68 |
| MPV/PLT (Median) | 0.029 | 0.035 | 0.031 | 0.054 |
| MPV (Median) | 8.45 | 9.25 | 8.8 | 9.9 |

Table 2. Basal demography of patients ($n = 76$).

| Characteristics | Total ($n = 76$) | HGUC ($n = 57$) | LGUC ($n = 19$) | $p$ Value |
|-----------------|-----------------|-----------------|-----------------|----------|
| Age Mean ± SD | 63.83 ± 8.69 | 62.63 ± 11.07 | 65.37 ± 8.89 | 0.331 (NS) |
| Gender Male | 66 (86.84%) | 49 (85.96%) | 17 (89.47%) | 1.000 (NS) |
| Female | 10 (13.16%) | 8 (14.04%) | 2 (10.53%) | |
| Type of Urothelial Carcinoma Invasive | 58 (76.32%) | 50 (87.72%) | 8 (42.11%) | <0.001 (S) |
| Non-Invasive | 18 (23.68%) | 7 (12.28%) | 11 (57.19%) | |

Out of the 76 patients, 58 (76.32%) were found to have invasive carcinoma and 18 (23.68%) non-invasive carcinoma. Among the 58 patients with invasive urothelial carcinoma, 50 (86.21%) had high grade and 8 (13.79%) had low grade, whereas among 18 patients with non-invasive urothelial carcinoma, 7 (38.89%) had high grade and 11 (61.11%) had a low grade of urothelial carcinoma. Hence, a statistically significant association was observed between type of urothelial carcinoma and its grading ($p < 0.05$) (Table 2).

The cut off value was determined to be less than equal to 9.25 for MPV (sensitivity = 72%, specificity = 58%, PPV = 84%, NPV = 41% and PLR = 1.71). Similarly, cut off values for all the three parameters were obtained and the sensitivity, specificity, PPV, NPV and PLR values were analyzed with these cut off values. It was found that values of diagnostic approaches were better in MPV as compared to PLT count and MPV/PLT ratio (Table 3).

Table 3. Diagnostic parameters for plt, mpv and mpv/plt between HGUC and LGUC.

| Cut Off | Sensitivity (%) | Specificity (%) | PLR | PPV (%) | NPV (%) |
|---------|----------------|----------------|-----|---------|---------|
| PLT $\geq 257.5$ | 63.16 | 57.89 | 1.50 | 81.82 | 34.38 |
| MPV $\leq 9.25$ | 71.73 | 57.89 | 1.71 | 83.67 | 40.74 |
| MPV/PLT $\leq 0.033$ | 61.40 | 68.42 | 1.94 | 85.37 | 37.14 |
Platelet count was found to be more elevated in patients with high grade urothelial carcinoma as compared to patients with low grade urothelial carcinoma \( (p < 0.05) \).

The median MPV and MPV/PLT ratio was found to be significantly lower in patients with high grade urothelial carcinoma as compared to patients with low grade urothelial carcinoma \( (p < 0.05) \) (Table 4).

### Table 4. Comparison of mean platelet count, mpv and mpv/plt among patients with HGUC and LGUC.

|                | HGUC \((n = 57)\) | LGUC \((n = 19)\) | \( p \) Value |
|----------------|-------------------|------------------|--------------|
| PLT count      | Mean \( \pm \) SD | Median | Min–Max | Mean \( \pm \) SD | Median | Min–Max |
|                | 307.28 \( \pm \) 151.99 | 233.68 \( \pm \) 94.8 | <0.001 *    |
| MPV            | 8.6               | 6.8–12.5        | 9.6         | 8.1–13        | 0.006 ** |
| MPV/PLT        | 0.03              | 0.01–0.13       | 0.05        | 0.02–0.13     | 0.018 ** |

* T test, ** Mann Whitney U test.

Platelet count was found to be more elevated in patients with muscle invasive urothelial carcinoma as compared to patients with non-muscle invasive urothelial carcinoma \( (p < 0.05) \).

The median MPV and MPV/PLT ratio was found to be significantly lower in patients with muscle invasive urothelial carcinoma as compared to patients with non-muscle invasive urothelial carcinoma \( (p < 0.05) \) (Table 5).

### Table 5. Comparison of mean platelet count, MPV and MPV/PLT among muscle invasive urothelial carcinoma and non-muscle invasive urothelial carcinoma.

|                | Muscle Invasive UC \((n = 42)\) | Non Muscle Invasive UC \((n = 16)\) | \( p \) Value |
|----------------|---------------------------------|-----------------------------------|--------------|
| PLT count      | Mean \( \pm \) SD | Median | Min–Max | Mean \( \pm \) SD | Median | Min–Max |
|                | 317.79 \( \pm \) 162.17 | 280.06 \( \pm \) 124.54 | <0.001 *    |
| MPV            | 8.25                           | 6.8–12.5 | 9.15       | 7.6–13       | 0.05 ** |
| MPV/PLT        | 0.02                           | 0.007–0.131 | 0.03        | 0.012–0.102 | <0.001 ** |

* T test, ** Mann Whitney U test.

Platelet count was found to be more elevated in patients with non-invasive high grade urothelial carcinoma as compared to patients with non-invasive low grade urothelial carcinoma \( (p < 0.05) \).

The median MPV and MPV/PLT ratio was found to be significantly lower in patients with non-invasive high grade urothelial carcinoma as compared to patients with non-invasive low grade urothelial carcinoma \( (p < 0.05) \) (Table 6).

### Table 6. Comparison of mean platelet count, MPV and MPV/PLT among non-invasive HGUC and non-invasive LGUC.

|                | Non-Invasive HGUC \((n = 7)\) | Non-Invasive LGUC \((n = 11)\) | \( p \) Value |
|----------------|-------------------------------|-------------------------------|--------------|
| PLT count      | Mean \( \pm \) SD | Median | Min–Max | Mean \( \pm \) SD | Median | Min–Max |
|                | 268 \( \pm \) 71.76 | 204.64 \( \pm \) 85.61 | <0.001 *    |
| MPV            | 8.8                           | 6.8–12.5 | 9.9        | 8.1–13       | 0.03 ** |
| MPV/PLT        | 0.031                         | 0.01–0.13 | 0.054       | 0.02–0.13   | <0.001 ** |

* T test, ** Mann Whitney U test.

### 4. Discussion

In the prognosis of Muscle Invasive urothelial Cancer (MIUC), inflammatory changes and hematological markers play an important role [29]. The lowering of survival rates in many cancers has been associated with thrombocytosis. A rise in platelet count aid in the progression of the cancer, as well as its metastasis by facilitating angiogenesis and the lodging of tumor cells at remote sites [30]. In cases of bladder cancer, raised levels of endothelial derived growth factor have been linked with tumor progression and that
of PDGF-β with a recurrence of bladder cancer [31]. The transcription factor GATA-2 plays a role in platelet production and when it is overexpressed it causes anemia and also promotes differentiation of megakaryocytes [32]. However, the assessment of these indices is not extensively used in clinical practice because of the high costs. This study aligned its findings indirectly using a simpler platelet activation marker.

Thrombocytosis in patients with bladder cancer as compared to controls has also been observed by Madkour B S [33]. He also observed that patients with tumors having distant metastasis showed even higher levels of platelets when compared with patients who have local non-invasive tumors and invasive tumors with only regional lymph node involvement [33]. These observations are aligned with the studies of Sierko and Wójtkiewicz, who also suggested the presence of thrombocytosis in cancer patients [34].

In contrast to this, the study done by Mori K et al. could not find a significant association between platelet count and cancer specific survival in UC [35]. Unsatisfactory prognosis in patients with thrombocytosis has also been shown in other kinds of tumors [36–38]. Lowered survival rates in patients with thrombocytosis before Radical cystectomy have also been shown in Todenhöfer’s study [17]. High-risk patients for cancer specific deaths can be screened by using thrombocytosis as a criterion.

Therefore, the above mentioned prognostic model may aid urologists to assess the requirement of preoperative chemotherapy in patients undergoing radical cystectomy. Preoperative thrombocytosis helps alert surgeons in the identification of the patients who are at the highest risk of recurrence and cancer-specific death.

MPV is a precise estimation of the dimension of platelets calculated by hematological analyzers. Measuring the MPV is economical, non-invasive and saves time and hence is a very useful predictor. MPV is an early parametric feature of activated platelets. The healthy range for MPV is 7.5 to 12 fL [39]. Physiologically, MPV shows an inverse relationship with the amount of PLTs linked with the process of maintaining homeostasis and preserving the fixed platelet mass [40–44]. The relation between MPV and the survival of a patient may be because of inflammation [6]. Large platelets release a variety of pro-inflammatory cytokines and are more likely to aggregate as they are more reactive than their smaller counterparts. Intensive infiltration of large platelets into vascular and intestinal walls is the follow up of aggregation at inflammation sites [45]. On the other hand, due to the excessive increase in the release of pro-inflammatory cytokines, the rate of release of small-sized platelets from the bone marrow is increased as these cytokines impede with megakaryopoiesis [46].

Decreased MPV values are an indication of the enhanced consumption of larger platelets in the inflammatory state. High-grade inflammatory diseases are hence associated with low levels of MPV and the opposite is the course of anti-inflammatory therapy, as suggested by recent reports [45]. A significant reduction in MPV and the MPV/PLT ratio in cases of non-small cell lung cancers was revealed by Inagaki et al. [46]. The reduction in MPV in renal cell cancer patients in contrast to healthy individuals has been presented by Yun et al. [24]. Kumagai’s study also confirmed decreased MPV levels in individuals with lung cancer as compared to their healthy control counterparts [22]. Aksoy et al. [40] added to these findings by reporting decreased MPV in solid tumors that metastasize to bone marrow. In contrast to this, several publications show a link between malignancies and increased MPV. Kurt et al. [42] showed significantly raised levels of MPV in individuals with hepatocellular carcinoma when compared to individuals suffering from chronic hepatitis and healthy individuals. Li JY et al. [43] also observed increased MPV in patients with colon cancer when contrasted with normal individuals.

In a large study conducted by Toll AD et al. [47], it was found that only 41 patients out of 225 [18%] had invasive low grade urothelial carcinoma; in contrast to this, our study found that eight out of 58 [13.79%] patients had low grade urothelial carcinoma; this disparity may be due to referral bias or small study size. In our study, out of a total of 76 patients, 58 [76.32%] patients found with invasive carcinoma and 18 [23.68%] with non-invasive carcinoma, in developing countries such as India, a population with low
economic status, have inaccessibility/late accessibility to health facilities which may be the reason for a larger number of invasive carcinomas. The findings of this study show thrombocytosis, reduced MPV and MPV/PLT ratio in patients with high grade urothelial cancer when contrasted with low grade urothelial cancer. Hence, based on this study’s findings, it is highly suggestive that high platelet count MPV and MPV/PLT ratio can be of diagnostic value in urothelial tumors. Thus, further studies looking into the relationship and link between platelet counts, MPV and cancer are required to properly establish these findings.

Limitations

This study was limited by the possibility of referral bias and population migration. The size was low, thus the choice for statistical test was limited. This study was a single-center retrospective study and results from more large validation studies are required to confirm the findings. Cut-off values varied, which could lead to heterogeneity between studies.

5. Conclusions

Through this study we have demonstrated that platelet indices, such as thrombocytosis, decreased MPV, and decreased MPV/Platelet ratio, can be useful supportive prognostic and diagnostic features for the determination of the clinical outcome of urothelial carcinoma. MPV and MPV/Platelet ratio are cheap, non-invasive and time efficient markers that can prove to be important factors in the prognosis of Urothelial cancer while treating cases of bladder cancer, although more specific research is needed to establish the role of these markers in clinical practice.

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