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Preoperative monocyte-to-lymphocyte ratio as a potential predictor of bladder cancer

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Abstract

Objectives: The aim of this study was to investigate the role of preoperative Monocyte-to-Lymphocyte ratio (MLR) as a potential predictor of bladder cancer (BC).

Methods: Clinical data of patients who underwent TURBT at our institution between 2017 and 2021 were collected and retrospectively analysed. MLR was obtained from preoperative blood analyses performed within 1 month from hospital admission. The association of MLR with different clinic-pathological features obtained from histological reports was further analysed. Statistical analysis was performed using the Kruskal Wallis test for non-parametric variables, assuming $p<0.05$ as statistically significant.

Results: 510 patients were included in the study (81% males, 19% females), with a mean age of 71.66 ± 11.64 years. Mean MLR was higher in patients with any-type bladder cancer, reporting an MLR of 0.41 ± 0.11 compared to 0.38 ± 0.43 in patients without bladder cancer ($p=0.043$). In the subsequent comparison among low-grade and high-grade bladder cancer, MLR did not report statistically significant differences, with 0.29 ± 0.12 for low-grade BC and 0.51 ± 0.81 for high-grade BC ($p=0.085$)

Conclusions: Our findings reported elevated preoperative MLR should be considered a potential biomarker predicting malignancy for bladder tumours. Furthermore, research are necessary to assess its role in discerning low-grade from high-grade patients.

Keywords: inflammation biomarkers; monocyte; monocyte-to-lymphocyte ratio; non muscle invasive bladder cancer.

Introduction

Bladder cancer (BC) is the 10th most common cancer worldwide, with a higher incidence in developed countries and approximately 80% of tumors being diagnosed in elderly patients (age 70 years or older) [1, 2]. BC occurs mainly in man, with an estimated rate of 26.5/100,000 and 5.5/100,000 in men and women respectively [3]. BC can be divided into urothelial and non-urothelial carcinoma. The most common type is urothelial carcinoma, which occurs in 90% of all cases, while the non-urothelial carcinoma, which includes squamous cell carcinoma (SCC), adenocarcinoma, small-cell carcinoma sarcoma, carcinosarcoma, paraganglioma, melanoma and lymphoma accounts for the remaining 10%. Up to 70–85% of patients with BC are initially diagnosed as non-muscle invasive bladder cancer (NMIBC), while 15–30% is diagnosed as muscle invasive bladder cancer (MIBC) [4–6].

The initial treatment strategy of patients with NMIBC is the transurethral resection of bladder tumor (TURBT), followed by intravesical therapy of bacillus Calmette–Guerin or chemotherapy (according to grade and focality of the tumor), while, in MIBC, radical cystectomy (RC) with bilateral pelvic lymphadenectomy represents the best treatment [7]. Despite advances in diagnosis and management there is a lack of reliable biomarkers useful in diagnosis, prognosis, and follow-up.

In the last decades, several studies reported inflammation as a pivotal role in many tumorigeneses process such as proliferation, invasion, metastasis, and angiogenesis [8, 9]. Due to this, several inflammatory indexes as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR),

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monocyte to lymphocyte ratio (MLR), have been identified and proposed as prognostic biomarkers in different cancers including BC [10–15].

These biomarkers are characterized by different sensitivity and/or specificity, low-cost, powerful in stratifying patients [16–18]. Despite this, to the best of our knowledge, no previous studies reported MLR as predictor of BC.

The aim of this study is to investigate the role of preoperative MLR ratio as a potential predictor of bladder cancer (BC).

Materials and methods

Patients who underwent TURBT at University Hospital "Federico II" of Naples between January 2017 and January 2021 were retrospectively analyzed. According to the European Association of Urology (EAU) guidelines, all patients underwent TURBT after a cystoscopy suggesting a potential malignancy. The study was conducted according to the World Medical Association Declaration of Helsinki and written informed consent was provided by all patients. Due to the retrospective nature of the study no ethical committee was required. Patients >18 years with a previous cystoscopy performed within two months suggesting potential malignancy were included in the study. Patients with acute infection, acute systemic inflammatory conditions (as autoimmune diseases), coagulation-related diseases, hepatic dysfunction and any other potential tumor at the time of cystoscopy were excluded. Routine venous blood samples were obtained within 30 days before scheduled surgery while demographic information was retrieved by trained personnel from medical records. MLR was calculated as the ratio between monocyte-to-lymphocyte values. Patients were further divided in four categories: negative (i.e. those with no cancer identified at the histopathological analysis after TURBT), benign (i.e. patients who reported chronic cystitis, focal atrophies or similar lesions at the histopathological analysis), low-grade cancer and high grade cancer.

Statistical analysis

Means and standard deviations were reported for continuous variables while frequencies and percentages were reported for categorical variables. Kolmogorov-Smirnov test was used to assess normality of data before proceeding to further analysis. Kruskal Wallis Test was utilized to evaluate variables in relation to histopathological results (negative, benign, low-grade and high-grade BC) while Mann – Whitney U test was utilized for variables in relation to the presence of any BC. Statistical analysis was conducted using IBM SPSS software (version 25, IBM Corp, Armonk, NY, USA), considering $p<0.05$ as statistically significant.

Results

510 patients were retrospectively involved in the study. Descriptive characteristics and preoperative laboratory data are reported in Table 1. Mean age at time of surgery was 71.66 years, with a preponderance of male patients compared to female patients (81% vs. 19%). 15.3% of patients were diabetics while 11.4% of patients reported some grade of chronic kidney disease (eGFR <90 mL/min). At the histopathological analysis performed after TURBT, a total of 340 (66.6%) BC were reported, accounting 152 (29.8%) low-grade BC and 188 (36.9%) high-grade BC. 59 (17.36%) patients, among the 340 BC, reported a muscle-invasive BC (MIBC). When parameters were compared regarding the presence of any cancer or not, age was higher in the first group with 73.45 ± 10.80 vs. 68.30 ± 12.43 ($p<0.0001$). Conversely, hemoglobin was 13.57 ± 1.92 in patients with BC compared to 14.18 ± 1.56 of patients without BC. Similarly, red blood cells were 4.62 ± 0.81 vs. 4.90 ± 0.70 ($p=0.002$); creatinine was 1.08 ± 0.56 vs. 1.29 ± 0.37 ($p=0.004$); albumin was 4.22 ± 0.44 vs. 4.35 ± 0.40 ($p=0.047$); uric acid was 5.77 ± 1.56 vs. 5.33 ± 1.38 ($p=0.015$); ALT was 19.59 ± 12.53 vs. 20.06 ± 9.48 ($p=0.036$); fibrinogen was 345.79 ± 98.40 vs. 324.08 ± 90.96 ($p=0.019$); finally, MLR was 0.41 ± 0.11 vs. 0.38 ± 0.43 ($p=0.043$). Among categorical variables, gender was, also in this case, unbalanced toward male, with 83.7% BC patients being male ($p=0.030$) (Table 2). Regarding comparisons among low-grade and high-grade bladder cancer, differences in preoperative data are reported in Table 3. Age was increasingly higher from negative results to high-grade BC, reporting 69.86 ± 11.48 years for negative results, 66.38 ± 13.73 years for benign results, 71.38 ± 10.18 years for low-grade BC and 74.92 ± 10.96 years for high-grade BC ($p<0.0001$). Mean pre-operative hemoglobin reported, conversely, decreasing values from negative results to high-grade BC, with 14.15 ± 1.68 g/dL for negative results, 14.26 ± 1.47 g/dL for benign results, 13.87 ± 1.84 g/dL for low-grade BC and, finally, 13.34 ± 1.92 g/dL for high-grade BC ($p=0.001$). Red blood cells count were similarly different among negative, benign, low-grade and high-grade patients with, respectively, 7.09 ± 1.92 × 103/uL, 7.27 ± 2.14 × 103/uL, 7.73 ± 4.46 × 103/uL and 6.92 ± 2.35 × 103/uL ($p=0.001$). Although creatinine differences were statistically significant among negative (1.09 ± 0.87 mg/dL), benign (1.07 ± 0.75 mg/dL), low-grade (1.07 ± 0.68) and high-grade (1.08 ± 0.43) BC, we did not observe a clinically relevant value in those findings ($p=0.008$). Regarding albumin, patients with negative results reported a mean value of 4.31 ± 0.34 g/dL, patients with positive results reported 4.41 ± 0.47 g/dL, low-grade BC patients reported 4.25 ± 0.43 g/dL while high-grade BC patients reported 4.19 ± 0.44 mg/dL ($p=0.026$). ALT was similarly 19.60 ± 9.14 mg/dL in patients with negative results, 20.82 ± 9.94 mg/dL in patients with benign results

Table 1: Descriptive characteristics of patients involved.

	Mean	Standard deviation
Age, years	71.66	11.64
Haemoglobin, g/dL	13.78	1.82
White blood cells ($\times 10^3$/uL)	7.24	3.06
Red blood cells ($\times 10^6$/uL)	4.71	0.79
Lymphocytes (%)	25.62	8.53
Monocytes (%)	6.59	1.93
Neutrophils (%)	63.43	9.86
Eosinophils (%)	2.27	1.76
Basophils (%)	0.53	0.33
Creatinine, mg/dL	1.15	2.24
Albumin, g/dL	4.26	0.43
Uric acid, mg/dL	5.62	1.51
Total cholesterol, mg/dL	175.20	43.23
Triglycerides, mg/dL	120.56	71.05
LDL, mg/dL	111.49	39.25
HDL, mg/dL	46.15	12.89
AST, mU/mL	21.10	10.26
ALT, mU/mL	19.76	11.55
Fibrinogen, mg/dL	338.14	96.30
	Count	**Percentage**
Gender		
Male	413	81
Female	97	19
Diabetes		
Yes	78	15.3
No	432	84.7
Chronic kidney disease		
Yes	58	11.4
No	452	88.7
Cancer		
Yes	340	66.6
No	170	33.4
Grade		
Benign	77	15.1
Low-grade	152	29.8
High-grade	188	36.9
Muscle invasive bladder cancer		
Yes	59	17.36
No	281	82.64

and 20.37 ± 11.20 mg/dL and 18.99 ± 13.38 mg/dL in low-grade and high-grade BC patients, respectively (p=0.008). No statistically significant difference was reported instead for MLR values, as well as for other variables retrieved. Among categorical variables, gender was unbalanced towards male (p=0.047).

Discussion

In the last years, several data show as cancer-related inflammation and systemic inflammation response could be considered as new and important hallmark of cancer [19, 20]. Inflammation is one of the most important components of the tumor microenvironment, involved and related to survival and proliferation of malignant cells, cancer angiogenesis, metastasis, and invasion [21, 22].

To the best of our knowledge, this is the first clinical study to investigate the promising role of MLR as a diagnostic biomarker for bladder tumours. Among the innate and adaptive immune responses and tissue homeostasis monocytes and lymphocytes represent an essential component [23]. Monocytes have a double role in cancer pathway in fact they can induce the production of several inflammatory cytokines (VEGF, TNF-α and MCP-1) involved in many aspects as well as tumorigenesis, angiogenesis, and metastasis but they can also be attracted by tumor cells and stimulated to differentiate into tumor-associated macrophages, supporting the development and progression of tumor [24, 25]. Several previous studies investigated the role of MLR in BC [26–28]. Shi et al. showed MLR as an independently prognostic factor for overall survival (OS) and disease free survival (DFS) in patients who underwent radical cystectomy: high MLR (>0.54) was a predictor of shorter OS (HR: 2.30; 95% CI: 1.36–3.89; p=0.002) and DFS (HR: 2.13; 95% CI: 1.21–3.75; p=0.009) compared with low MLR (≤0.54) (27). Specifically in the setting of non-muscle invasive bladder cancer (NMIBC) Wang et al. [29] reported that MLR and its combination with NLR is a prognostic predictive biomarker after transurethral resection. The authors showed that elevated MLR and NLR levels were statistically related with adverse prognosis in patients with NMIBC in fact DFS (HR: 3.080; 95% CI: 1.870–5.074; p<0.001 for MLR-NLR 2 vs. MLR-NLR 0) and OS (HR: 2.815; 95% CI: 1.778–4.456; p<0.001 for MLR-NLR 2 vs. MLR-NLR 0). Elevated MLR is generally related to fewer lymphocytes [30, 31].

De Giorgi et al. reported in metastatic breast cancer lymphocytopenia as independent prognostic factor for OS (p=0.001) [32].

Joseph et al. [33] suggested that pretreatment lymphocytopenia was an adverse prognostic biomarker in MIBC and advanced BC [hazard ratio (HR) 1.6, 95% confidence interval (CI) 1.1–2.4; p=0.02]. Other interesting

Table 2: Preoperative data according to the presence of any cancer.

	No cancer		Cancer		p-Value
	Mean	**Standard deviation**	**Mean**	**Standard deviation**	
Age, years	68.30	12.43	73.45	10.80	**<0.0001**
Haemoglobin, g/dL	14.18	1.56	13.57	1.92	**0.002**
White blood cells ($\times 10^3$/uL)	7.16	2.05	7.29	3.49	0.926
Red blood cells ($\times 10^6$/uL)	4.90	0.70	4.62	0.81	**<0.0001**
Lymphocytes (%)	26.08	8.51	25.37	8.55	0.347
Monocytes (%)	6.40	1.95	6.69	1.92	0.090
Neutrophils (%)	62.70	10.29	63.82	9.61	0.207
Eosinophils (%)	2.42	2.04	2.20	1.59	0.501
Basophils (%)	0.58	0.41	0.51	0.27	0.101
Creatinine, mg/dL	1.29	0.37	1.08	0.56	**0.004**
Albumin, g/dL	4.35	0.40	4.22	0.44	**0.047**
Uric acid, mg/dL	5.33	1.38	5.77	1.56	**0.015**
Total cholesterol, mg/dL	178.73	43.60	173.29	42.99	0.124
Triglycerides, mg/dL	115.91	61.35	123.06	75.74	0.144
LDL, mg/dL	114.56	36.30	109.83	40.72	0.202
HDL, mg/dL	47.76	12.40	45.28	13.09	0.058
AST, mU/mL	20.43	6.87	21.46	11.66	0.817
ALT, mU/mL	20.06	9.48	19.59	12.53	**0.036**
Fibrinogen, mg/dL	324.08	90.96	345.79	98.40	**0.019**
Monocytes to lymphocytes ratio, MLR	0.38	0.43	0.41	0.11	**0.043**
	Count	**Percentage**	**Count**	**Percentage**	**p-Value**
Gender, male	135	75.8	273	83.7	**0.030**
Diabetes, yes	20	12.4	58	19.5	0.053
Chronic kidney disease, yes	15	18.5	43	26.1	0.190

Bold values are for p statistically significant, i.e < 0.05.

findings emerged by database analysis were in patients with BC, in which uric acid was higher than patients without BC; albumin was higher in patients without BC than in patients with BC [34, 35]. High uric acid is associated with different cancer as well as digestive cancer, urological cancers [36–39].

Chen et al. [40] reported high incidence of prostate, bladder, and renal cancers in gout patients. In fact, uric acid plays a double role as antioxidant and as pro-oxidant to generate inflammatory reactions and oxidative stress, that is involved in cancer development. Albumin is another interesting serum biomarker altered in different conditions including bladder cancer. We reported lower albumin level in patients with BC compared patients without BC. According to previous studies we hypothesized that the low levels could be related to inflammation status secondary to cancer. In fact, some products released by tumors as interleukin (IL)-6, and tumor necrosis factor-α inhibit the albumin production [41, 42].

To the best of our knowledge, this study represents one of the first to evaluate the role of preoperative MLR in the prediction of BC. We are however conscious of different limitations of our work, which comprehend: the retrospective nature of the study and the relatively small sample size of patients which might result in biases related to the patients selection and treatment; the absence of a defined follow-up which do not permit to obtain data regarding the prognosis of patients involved in the study as well as overall survival (OS), cancer specific survival (CSS), progression free survival (PFS) as well as recurrence free survival (RFS); the absence of data regarding the multifocality of the tumors at the time of cystoscopy and TURBT. In our study we reported that MLR was higher in patients with any-type BC compared to patients without BC and this corroborated the involvement of these white blood cells in cancer development. So, our results should be validated by external cohorts prior to considering MLR for clinical use.

Conclusions

Elevated preoperative MLR could be considered a potential predictor of bladder cancer albeit its role, as well as, the discernment between low-grade from high-grade tumors

Table 3: Preoperative data according to histopathological analysis.

	Negative		Benign		Low-grade		High-grade		p-Value
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	
Age, years	69.86	11.48	66.38	13.73	71.38	10.18	74.92	10.96	**<0.0001**
Haemoglobin, g/dL	14.15	1.68	14.26	1.47	13.87	1.84	13.34	1.92	**0.001**
White blood cells ($\times 10^3$/uL)	7.09	1.92	7.27	2.14	7.73	4.46	6.92	2.35	0.418
Red blood cells ($\times 10^6$/uL)	4.90	0.62	4.91	0.80	4.76	0.60	4.51	0.93	**<0.001**
Lymphocytes (%)	26.13	7.29	25.37	9.05	26.22	8.67	25.00	8.77	0.502
Monocytes (%)	6.66	1.55	5.96	1.63	6.59	1.89	6.82	2.19	0.23
Neutrophils (%)	62.02	8.68	64.34	9.98	62.99	10.26	64.07	9.99	0.284
Eosinophils (%)	2.61	2.05	2.23	2.12	2.08	1.48	2.29	1.66	0.117
Basophils (%)	0.61	0.49	0.54	0.33	0.55	0.30	0.48	0.25	0.115
Creatinine, mg/dL	1.09	0.87	1.07	0.75	1.07	0.68	1.08	0.43	**0.008**
Albumin, g/dL	4.31	0.34	4.41	0.47	4.25	0.43	4.19	0.44	**0.026**
Uric acid, mg/dL	5.51	1.46	5.22	1.28	5.60	1.45	5.87	1.64	0.069
Total cholesterol, mg/dL	172.22	38.90	184.83	47.92	176.71	46.01	171.38	40.47	0.180
Triglycerides, mg/dL	116.21	66.37	114.34	57.58	121.69	73.26	124.32	76.57	0.375
LDL, mg/dL	108.11	34.98	121.15	36.85	111.63	41.94	108.97	39.61	0.223
HDL, mg/dL	48.00	13.76	47.95	11.10	45.07	13.04	45.40	12.98	0.225
AST, mU/mL	19.98	5.86	20.79	7.35	22.25	14.46	20.83	8.72	0.936
ALT, mU/mL	19.60	9.14	20.82	9.94	20.37	11.20	18.88	13.38	**0.008**
Fibrinogen, mg/dL	316.34	73.75	334.33	109.10	338.11	88.79	349.93	104.02	0.166
Monocytes to lymphocytes ratio, MLR	0.27	0.12	0.50	0.15	0.29	0.12	0.51	0.81	0.085
	Count	**Percentage**	**Count**	**Percentage**	**Count**	**Percentage**	**Count**	**Percentage**	**p-Value**
Gender, male	70	75.3	57	74	124	81.6	162	86.2	**0.047**
Diabetes, yes	8	9.6	12	17.1	19	13.9	39	23.2	**0.033**
Chronic kidney disease, yes	9	23.7	6	15.4	15	19.7	28	30.1	0.233

Bold values are for p statistically significant, i.e < 0.05.

must be furthermore assessed. Further studies are required to confirm the promising role of MLR as a diagnostic and prognostic biomarker for bladder tumours.

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