Role of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio and platelets in prognosis of patients with prostate cancer

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Received February 3, 2022; Accepted May 11, 2022

DOI: 10.3892/ol.2022.13425

Abstract. The aim of the present analysis was to evaluate the platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelets (PLT) and neutrophil level for their prognostic values in patients with prostate cancer who had been treated with radiotherapy. A retrospective analysis of 152 patients who were treated in the Radiotherapy Department at Maria Sklodowska-Curie National Research Institute of Oncology (Gliwice, Poland) between January 2012 and December 2014 was performed. The prognostic value (overall survival; OS) of the pre-treatment PLR, NLR, LMR, PLT, neutrophil level and other laboratory factors such as: leukocyte, lymphocyte, monocyte, hemoglobin, RBC, prostate-specific antigen level (PSA), Gleason score, age, smoking and comorbid condition were assessed using univariate analysis. The cut-off point was determined for NLR as 'elevated' at >4.66, LMR >3.26 and the PLR was considered 'elevated' at >89.6. Median follow-up was 4.9 years. The 5 and 7-year OS rates were 81.5 and 72.2%, respectively. In univariate analysis higher NLR (P=0.007), higher level of PLT (P=0.004), higher level of neutrophils (P=0.013), elevated level of leukocyte (P=0.043) and lymphocyte (P=0.043) were factors significantly associated with decreased OS. No difference was found for PLR (P=0.308) and LMR (P=0.109). The other factor associated with decreased OS were: higher Gleason score (>7; P=0.005), higher PSA level (>20 ng/dl; P=0.0001), smoking (P=0.003) and older age (>70 years; P=0.018). In multivariate analysis, NLR, LMR, leukocyte and RBC were independently associated with prognosis in patients with prostate cancer. Elevated pre-treatment NLR [hazard ratio (HR)=10.83; P=0.001), LMR (HR=3.14; P=0.007) and higher leukocyte level (HR=3.14; P=0.007) were independently associated with increased mortality risk. Overall, pre-treatment NLR, PLR, leukocyte and RBC levels were revealed to be independent prognostic factors.

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Key words: prostate cancer, radiotherapy, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio, platelets, prognostic factors

Introduction

Prostate cancer accounts for 7.1% of all malignant diseases in adults in 2018 (3.8% of all deaths caused by cancer in men worldwide) (1). There is reported a strong link between prostate cancer and inflammation. Inflammation impacts every step of tumorigenesis, such as tumour initiation, promotion and metastatic progression (2). There are known several serum biomarkers and haematological indices of inflammation such as: C reactive protein (CRP), fibrinogen, lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) (3). The NLR is defined as neutrophil counts divided by lymphocyte counts. The prognostic value of NLR (worse OS in patients with high NLR) has been confirmed in metastatic castration-resistant prostate cancer (mCRPC). By contrast, the NLR was not significantly associated with prognosis of patients with localized PCa (4). Platelets are a source of active metabolites and proteins. They play an active role in numerous processes such as sepsis, inflammation, tissue regeneration and control of infection (5). Platelets can release growth factors (platelet-derived growth factor, platelet factor, transforming growth factor beta, vascular endothelial growth factor), which may stimulate tumor growth and angiogenesis (6). The PLR is calculated as the platelet count divided by the lymphocyte count. In urologic cancer a high PLR was significantly associated with worse overall survival. An elevated PLR was significantly associated with poor OS in renal cancer and with shorter OS or cancer-specific

survival in prostate cancer (7). The results of another study also indicated that an elevated PLR was significantly associated with poor OS in prostate cancer (8).

The objective of this study was to evaluate the blood platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelets (PLT), neutrophil and lymphocyte level for its prognostic value in patients with prostate cancer who were treated with radiotherapy.

Materials and methods

A retrospective analysis of 152 prostate cancer patients who were treated in Radiotherapy Department at Maria Sklodowska-Curie National Research Institute of Oncology (Gliwice, Poland) between January 2012 and December 2014 was performed. The median age of patients was 65.9 years (range from 47.6 to 83.0). 30.9% patients were at the age over 70 years and 17.1% were at the age ≤60 years. ZUBROD performance scale (9) was observed in 116 (76.3%) patients. Cancer in family history was reported in 44.7% of patients. All patients provided written informed consent regarding the use of their biological material for clinical research (all were routine laboratory analyses). The blood cell parameters including platelets, neutrophil and lymphocyte level, PLR, NLR and LMR were determined at the baseline, before first treatment (are pretreatment only). All blood parameter data were retrieved from patient record.

There are distinguished 3 general risk groups based on the PSA, DRE, and biopsy. Low risk group: tumor is confined to the prostate, the PSA is <10 and Gleason is ≤6. Intermediate risk: tumor confined to the prostate, the PSA between 10 and 20 or Gleason score 7. High risk group: tumor extends outside the prostate, the PSA>20, or Gleason score from 8 to 10 (10). In study group, 37.5% of prostate cancer patients belonged to high-risk group. Patient's characteristics is shown in Table I.

125 (82.2%) patients received initial androgen deprivation therapy or combined androgen blockade treatment. Surgery for prostate cancer (radical prostatectomy) was carried out in 21 (13.8%) patients. Radical radiotherapy was applied to 124 (81.6%) patients. Cyber knife treatment was used in 13 (8.6%) men. Overall survival (OS) was defined as a period of time from the date of radiotherapy treatment beginning to death or date of last follow up. Median follow-up was 4.9 years. The 5 and 7-year OS rates were 81.5 and 72.2%, respectively.

Fasting blood samples for analyses were collected in regular conditions between 7 and 9 AM using the BD TM Vacutainer TM system (Becton Dickinson), to EDTA (full blood count) tubes and tubes with serum clot activator. Blood samples were allowed to clot for 30 min, after which they were centrifuged at 3,800 x g for 10 min at 18-25˚C. The PSA levels were determined in the processed serum samples. The PSA concentrations were measured using automated chemiluminescent microparticle immunoassay (CMIA) in the Alinity analyser and commercial kit analyzer from Abbott Laboratories (Abbott Park). The full blood count was determined using the XN-2000 analyzer (Sysmex). PLR, NLR and LMR were computed for each participant based on the determined parameters.

Optimal cut-off values for NLR, PLR and MLR were determined using receiver operating characteristic curves analysis. The maximum value of Youden's index was used as a criterion for selecting the approximate cut-off value for laboratory parameters. Based on the cut-off values determined, the NLR was considered as 'elevated' at >4.66, the LMR value was 'elevated' at >3.26 and the PLR was considered 'elevated' at >89.6.

Statistical analysis was carried out using STATISTICA 13 software. Fisher test and Chi ^2 test with Yates correction were used to compare qualitative factors. A comparisons according to laboratory factors between two and three patient subgroups were performed by Mann-Whitney's U test and Kruskal-Wallis H test, respectively. Survival curves were obtained by Kaplan-Meier method, and compared using the log-rank test. The Cox proportional hazard model for the univariate and multivariate analyses of prognostic factors were applied. Differences were considered as significant if the P value was <0.05. Tendency of results was assessed if the P value was ≤0.10.

Results

Patient characteristics. In studied group, there were distinguished 3 general risk groups: low risk group (44 patients), intermediate risk (50 patients) and high risk group (57 patients). Higher lymphocyte level (P=0.043) and elevated PLT (P=0.038) were significantly associated with high risk group. There were also detected tendency to elevated red blood cells (RBC) level (P=0.196) and low risk group. There was no association between risk groups and NLR, PLR, LMR or other laboratory factors (Table II).

Patients who had radical prostatectomy were younger in comparison to group who was treated with radiotherapy (61.8 vs. 66.4; P=0.001). Similarly, group with surgery treatment had significantly more often elevated hemoglobin (Hgb) (14.60 g/dl vs. 13.90 g/dl; P=0.0053) and RBC (4.85 vs. 4.49; P=0.0004) level. There was observed tendency to higher PLR value in patients who had radical prostatectomy (136.5 vs. 115.8, P=0.062). Higher PSA level (>20 ng/ml) (35.9% vs. 4.8%; P=0.007) and higher Gleason score (>7) (19.1% vs. 0.0%; P=0.008) were detected in patients without surgery. There was no association between other factors such as: LMR (P=0.406), NLR (P=0.709), PLT (P=0.123), monocyte level (P=0.157), lymphocyte (P=0.353), leukocyte level (WBC) (P=0.869) and treatment strategy (radical prostatectomy vs. radiotherapy).

The prognostic value of elevated NLR. The 5-year OS was lower in NLR>4.66 in comparison to NLR≤4.66 (55.6% vs. 82.4%, P=0.009). There was no association between clinicopathological factors such as: age (P=0.319), Gleason score (P=1.00), PSA level (P=0.874) in both NLR subgroups. Significantly higher neutrophil level was observed in patients with high (>4.66) NLR compared to patients with low (≤4.66) NLR ($5.47x10^9$/l vs. $3.72x10^9$/l, P=0.009). Similarly, lower lymphocyte level ($1.09x10^9$/l vs. $1.83x10^9$/l, P=0.0045), lower LMR (1.38 vs. 3.3, P=0.0004) and higher PLR (240.7 vs. 115.5, P=0.001) was significantly detected in elevated NLR subgroup compared to low NLR subgroup. The other laboratory parameters (PLT (P=0.320), monocyte level (P=0.231), WBC level (0.224), Hgb (0.940), RBC (P=0.691)) were comparable in both NLR subgroups.

Table I. Patient's characteristics.

Clinical factors	Group	N (%)
Age	≤60 years	26 (17.1)
	>60 and ≤70 years	79 (52.0)
	>70 years	47 (30.9)
Gleason score	≤6	78 (51.3)
	7	49 (32.2)
	>7	25 (16.4)
PSA	<10 ng/ml	67 (44.1)
	10-20 ng/ml	36 (23.7)
	>20 ng/ml	48 (31.6)
	Missing	1 (0.7)
Smoking	No	76
	Yes	76
ZUBROD	0	116 (76.3)
	1	35 (23.0)
	2	1 (0.7)
Co morbid conditions	Yes	92 (60.5)
	Diabetes	8 (5.3)
	Hypertension	68 (44.7)
	Cardiological diseases	36 (23.7)
Cancer in family history		68 (44.7)
Treatment	Surgery	21 (13.8)
	Radical radiotherapy	124 (81.6)
	Cyberknife treatment	13 (8.6)
	Hormonotherapy	125 (82.2)

PSA, prostate-specific antigen; ZUBROD, performance scale.

The prognostic value of elevated PLR. There was also observed no association between 5-year OS and PLR (80.5% vs. 84.7%, P=0.288). We did not observe association between PLR level (PLR>89.6 vs. PLR≤89.6) and clinicopathological factors such as: age (P=0.414), Gleason score (P=0.280), PSA level (P=0.200), neutrophil level (P=0.223), monocyte level (P=0.086) and RBC (P=0.175). In contrary, there was observed significantly more frequently elevated NLR (2.08 vs. 1.66, P=0.002), higher PLT (230x10^9/l vs. 165x10^9/l, P=0. 0.0001), lower LMR (3.13 vs. 3.79, P=0.001) or lower Hgb level (13.9 g/dl vs. 14.3 g/dl, P=0. 0.020) in elevated PLR subgroup compared to patients with low PLR. Similarly, in high PLR subgroup was presented significantly lower WBC (6.16x10^9/l vs. 7.45x10^9/l, P=0.0009) and lower lymphocyte level (1.75x10^9/l vs. 2.44x10^9/l, P=0. 0.0001).

The prognostic value of elevated PLT. The worse OS rate was also observed in subgroup with higher PLT (>299x10^9/l) in comparison to lower PLT (58.0 vs. 83.7%, P=0.005), respectively. In the low PLT subgroup, patients with Gleason score ≤6 was observed significantly more often compared to the high PLT subgroup (54% vs. 23%, P=0.043). However, there was no significant differences in subgroup with high and low PLT according to factors such as: age (P=0.494), PSA (P=0.221), RBC (P=0.353), NLR (P=0.702), LMR (P=0.864) or Hgb level (P=0.059). In patients with higher PLT was observed more often elevated neutrophil level (5.38x10^9/l vs. 3.71x10^9/l, P=0.012), higher WBC (8.26x10^9/l vs. 6.31x10^9/l, P= 0.002), higher lymphocyte level (2.21x10^9/l vs. 1.78x10^9/l, P=0.045), higher monocyte level (0.77x10^9/l vs. 0.58x10^9/l, P=0.019) and elevated PLR (147.9 vs. 114.9, P=0.006).

The prognostic value of elevated LMR. The 'elevated' value of LMR (>3.26) (74.6% vs. 88.1%, P=0.103) were not associated with overall survival time in our group of patients. There was observed no association between LMR level and factors such as: age (P=0.398), Gleason score (P=0.779), PSA level (P=0.144), Hgb level (P=0.576), RBC (P=0.982) and PLT (P=0.944). In patients with elevated LMR (>3.26) was detected significantly lower neutrophil level (3.46x10^9/l vs. 3.91x10^9/l; P=0.026), lower monocyte level (0.47x10^9/l vs. 0.64x10^9/l, P=0.0001), lower NLR (1.61 vs. 2.37; P=0.0001), lower PLR (102.2 vs. 132.95; P=0.0001) and higher lymphocyte level (2.07x10^9/l vs. 1.58x10^9/l, P=0.0001).

The prognostic value of elevated neutrophil level. The 5-year OS was lower in subgroup with higher neutrophil level (>4.32x10^9/l) (76.8 vs. 83.9%, P=0.014). There was observed no differences between clinical factors such as: age (P=0.501), PSA level (P=0.595), PLR (P=0.530) or RBC (P=0.249) according to neutrophil level. Higher Gleason score (>7) significantly more frequent was observed in prostate cancer patients with higher neutrophil level (29 vs. 11%, P=0.008).

Similarly, in patients with higher neutrophils level (>4.32x10^9/l) were observed significantly higher WBC (8.07x10^9/l vs. 5.73x10^9/l; P=0.0001), higher monocyte level (0.69x10^9/l vs. 0.53x10^9/l; P=0.0001), higher Hgb level (14.3 g/dl vs. 13.9 g/dl; P=0.039), PLT (246.5x10^9/l vs. 201x10^9/l; P=0.0006), elevated NLR (2.49 vs. 1.71; P=0.0001), higher lymphocyte level (2.04x10^9/l vs. 1.78x10^9/l; P=0.050) and lower LMR (2.76 vs. 3.4; P=0.003) in comparison to patients with lower neutrophil level.

The prognostic value of elevated lymphocyte level. The worse OS rate was also observed in subgroup with higher lymphocyte level (>1.79x109/l) in comparison to lower lymphocyte level (71.7 vs. 92.2%, P=0.038).

In subgroups with higher and lower lymphocyte level there was observed no differences between clinical factors such as: age (P=0.548), RBC (P=0.102) or PLT (P=0.256). There was observed association between elevated lymphocyte level (>1.79x10^9/l) and higher Gleason score (≥7) (60.5 vs. 36.8%, P=0.004). In subgroup of patients with lymphocyte level <1.79 there was reported more frequently PSA 10 ng/ml (54%) in comparison to PSA 10-20 ng/ml (16%). The elevated laboratory parameters such as: neutrophil level (3.98x10^9/l vs. 3.51x10^9/l; P=0.016), WBC (7.35x10^9/l vs. 5.77x10^9/l; P=0.0001), monocyte (0.63x10^9/l vs. 0.54x10^9/l; P=0.0006), Hgb (14.25 g/dl vs. 13.8 g/dl; P=0.047) or LMR (3.77 vs. 2.75; P=0.0001) was detected more often in subgroup of patients with higher lymphocyte level (>1.79x10^9/l). In contrary, lower NLR (1.64 vs. 2.39; P=0.0001) and reduced PLR (97.7 vs. 154.1; P=0.0001) was also associated with elevated lymphocyte level.

Table II. Association between risk groups and NLR, PLR, LMR or other laboratory factors.

	Low-risk group		Intermediate-risk group		High-risk group		
Laboratory factors	Median	Min-max	Median	Min-max	Median	Min-max	P-value
Leukocyte ($x10^9$/l)	6.26	3.21-11.98	6.56	2.72-17.98	6.51	3.07-17.09	0.549
Neutrophil ($x10^9$/l)	3.75	1.50-7.83	3.68	1.43-14.99	3.87	1.43-13.27	0.849
Lymphocyte ($x10^9$/l)	1.69	1.02-5.83	1.85	0.69-4.01	1.94	0.57-3.30	0.043
Monocyte ($x10^9$/l)	0.59	0.25-1.39	0.58	0.24-1.42	0.58	0.28-1.40	0.777
RBC ($x10^{12}$/l)	4.62	3.82-5.78	4.53	3.60-5.52	4.47	3.33-5.34	0.196
Hgb (g/dl)	14.25	12.0-16.6	14.1	10.4-17.4	13.9	10.4-17.1	0.208
Platelets ($x10^9$/l)	197	144-339	216.5	127-393	239	122-445	0.038
NLR	2.19	0.59-4.62	1.79	1.04-11.62	1.86	0.85-7.74	0.216
PLR	117.3	26.2-265.4	116.5	39.2-280.7	118.0	58.8-433.3	0.854
LMR	2.93	1.19-13.25	3.19	1.20-5.92	3.40	1.14-5.89	0.375

PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLT, platelets; RBC, red blood cells; Hgb, hemoglobin.

Survival analysis. The 5 and 7-year OS rates were 81.5 and 72.2%, respectively. Median follow-up was 4.9 years. In univariate analysis, we detected factors significantly associated with poor OS. There were: higher NLR (P=0.007), higher level of PLT (P=0.004), higher level of neutrophils (P=0.013), higher level of leukocyte (P=0.043), higher level of lymphocyte (P=0.043). No difference was found for PLR (P=0.308) and LMR (P=0.109). The other factors associated with worse OS were: higher Gleason score (>7) (P=0.005), higher PSA level (>20 ng/dl) (P=0.0001), smoking (P=0.003) and older age (>70 years) (P=0.018) (Table III).

In multivariate analysis, NLR, LMR, leukocyte, RBC, PSA level, Gleason score, smoking and older age (>70 years) were independently associated with prognosis in prostate cancer patients. Elevated pre-treatment NLR (hazard ratio HR=10.83, P=0.001), LMR (HR=3.14, P=0.007) and higher leukocyte level (HR=3.14, P=0.007) were significantly associated with increased mortality risk. However higher RBC (HR=0.40, P=0.031) was significantly associated with decreased mortality risk in multivariate analysis (Table III).

There was observed tendency to worse OS in patients with higher pre-treatment PLR (HR=2.72, P=0.078) and cancer in family history (HR=0.47, P=0.087) in multivariate analysis, although were nonsignificant factors in univariate analysis.

Discussion

In this study we have evaluated the role of PLR, NLR, LMR, PLT and neutrophil level as prognostic factors in patients with prostate cancer who were treated with radiotherapy.

The role of NLR, PLR and LMR as a prognostic factors has been discussed in several studies. Meta-analysis conducted by Peng and Luo has shown that pretreatment elevated blood-based NLR, PLR, neutrophil or monocyte counts and lower LMR are associated with worse OS in prostate cancer patients. However, the higher NLR and monocyte counts, but lower LMR predicted worse PFS. The worse recurrence free survival (RFS) was only associated with higher level of NLR. In subgroup analysis the higher NLR may be a predictive factor for OS but only in patients with mCRPC who have received chemotherapy (11). The other meta-analysis presented that an elevated NLR is significantly associated with poorer prognosis (OS and PFS) of patients with mCRPC, but not in case of patients with localized PCa. An elevated NLR was not significantly associated with poor OS in localized PCa (4). Meta-analysis conducted by Wang *et al* showed that a high PLR was correlated with poor DFS and OS in prostate cancer patients. In subgroup analysis PLR remained significant prognostic factor for OS independently from ethnicity or tumor stage (12). In our univariate analysis, elevated pre-treatment NLR (>4.66), PLT (>299x10^9/l), higher leukocyte level (>6.63x10^9/l), higher neutrophil (>4.32x10^9/l) and lymphocyte levels (>1.79x10^9/l) were associated with lower OS in prostate cancer patients. LMR (>3.26) or PLR (>89.6) did not affect overall survival. Multivariate analysis has showed that pre-treatment NLR, LMR, leukocyte levels or RBC were independently associated with prognosis in prostate cancer patients.

In some studies lymphocyte-to-monocyte ratio (LMR) was examined together with PSA as a risk prediction factors. It may be a useful tool at detecting prostate cancer, especially in patients with PSA value between 4 and 10 ng/dl (13). The nomogram incorporating age, PSA, digital rectal examination, abnormal imaging signals, PSA density, and LMR could be used to facilitate individual risk of prostate cancer in initial prostate biopsy (14). In our study, there was no association between PSA level and studied laboratory parameters except of lymphocyte level.

In conclusion, pre-treatment NLR, LMR, leukocyte levels or RBC were independently associated with prognosis in prostate cancer patients. Elevated pre-treatment PLR were close statistical significance with worse overall survival.

Table III. Univariate and multivariate analysis.

Laboratory and clinicopathological factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Leukocyte >6.63 vs. ≤6.63x10^9/l	2.05 (1.02-4.10)	0.043	3.14 (1.38-7.72)	0.007
Lymphocyte >1.79 vs. ≤1.79x10^9/l	2.10 (1.02-4.31)	0.043	-	-
Neutrophils >4.32 vs. ≤4.32x10^9/l	2.35 (1.20-4.63)	0.013	-	-
Monocyte >0.58 vs. ≤0.58x10^9/l	1.60 (0.80-3.21)	0.183	-	-
Platelets >299 vs. ≤299x10^9/l	3.40 (1.47-7.85)	0.004	-	-
Hemoglobin >14.2 vs. ≤14.2 g/dl	0.55 (0.26-1.15)	0.114	-	-
RBC >4.51 vs. ≤4.51x10^{12}/l	0.54 (0.27-1.08)	0.083	0.40 (0.17-0.92)	0.031
NLR >4.66 vs. ≤4.66	4.25 (1.49-12.11)	0.007	10.83 (2.79-42.0)	0.001
PLR >89.6 vs. ≤89.6	1.64 (0.63-4.24)	0.308	2.72 (0.90-8.29)	0.078
LMR >3.26 vs. ≤3.26	1.76 (0.88-3.52)	0.109	3.14 (1.38-7.17)	0.007
Gleason score >7 vs. ≤7	2.94 (1.39-6.21)	0.005	2.70 (1.14-6.39)	0.024
PSA >20 vs. ≤20 ng/ml	3.88 (1.93-7.78)	0.0001	2.63 (1.25-5.53)	0.011
Age >70 vs. ≤70 years	2.31 (1.15-4.64)	0.018	3.66 (1.62-8.30	0.002
Smoking Yes vs. No	3.00 (1.45-6.24)	0.003	3.40 (1.46-7.95)	0.005
Diabetes	0.72 (0.10-5.29)	0.748	-	-
Hypertension	0.71 (0.36-1.43)	0.340	-	-
Cardiological diseases	1.09 (0.47-2.52)	0.835	-	-
Cancer in family history	0.92 (0.47-1.83)	0.818	0.47 (0.20-1.11)	0.087

HR, hazard ratio; CI, confidence interval; PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLT, platelets; RBC, red blood cells; PSA, prostate-specific antigen.

Acknowledgements

The authors would like to thank Ms. Aleksandra Chmura (Analytics and Clinical Biochemistry Department, Maria Sklodowska-Curie National Research Institute of Oncology Gliwice Branch, Gliwice, Poland) for providing laboratory assistance.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JH was responsible for study design, acquisition of data and preparation of the manuscript. ZK was responsible for database preparation, statistical analysis and critical revision and preparation of the manuscript. JMK was responsible for analyzing data and critical revision of the manuscript. ET was responsible for acquisition of data and critical revision of the manuscript. BJ was responsible for acquisition of data and critically revising the manuscript. LM supervised the study and contributed to the conception of the study. All authors have read and approved the final manuscript. JH, ZK and JMK confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This was a retrospective analysis conducted on the medical records and results of laboratory tests. All patients provided written informed consent regarding the use of their biological material for clinical research (all were routine laboratory analyses).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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