Relationship between the Inflammation/immune Indexes and Deep Venous Thrombosis (DVT) following Tibial Plateau Fractures

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Research article

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Abstract

Objective To determine the relationship between inflammation/immune-based indexes and preoperative DVT of lower extremities following tibial plateau fractures

Methods Retrospective analysis of a prospectively collected data on patients undergoing surgeries of tibial plateau fractures between October 2014 and December 2018 was performed. Duplex ultrasonography (DUS) was routinely used to screen for preoperative DVT of bilateral lower extremities. Data on biomarkers (neutrophil-, lymphocyte-, monocyte- and platelet counts) at admission were collected, based on which neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte/lymphocyte (MLR) and systemic immune-inflammation index (SII, neutrophil* platelet/ lymphocyte) were calculated. Receiver operating characteristic (ROC) was used to determine the optimal cut-off value for each variable. Multivariate logistic regression analysis was used to evaluate the independent relationship of each biomarker or index with DVT, after adjustment for demographics, co-morbidities and injury-related variables.

Results Among 1179 patients included, 16.3% (192/1179) of them had (16.3%) had a preoperative DVT. Among the biomarkers and indexes, only platelet and neutrophil were identified to be independently associated with DVT, and their predictive ability was stable regardless of open fracture with or without included. The other independent variables were elevated D-dimer level (>0.55mg/L), male gender and hypertension in the sensitivity analysis with open fractures excluded.

Conclusion These identified factors are conducive to the initial screening for patients at-risk of DVT, individualized risk assessment, risk stratification and accordingly development of targeted prevention programs.

Introduction

Tibial plateau fracture represented 1%-2% of adult fractures and 32% of peri-knee fractures [1], with a population-based incidence of 10.3 per 100000 person-years [2]. As is generally accepted that, DVT is a significant cause of morbidity, pulmonary embolism and even mortality, especially in patients with trauma or undergoing major orthopaedic surgery [3, 4]. The previous reports showed 17.3–23.9% of patients with tibial plateau fracture would develop deep vein thrombosis (DVT) before they were operated [5, 6]. Extensive and deep understanding the epidemiologic characteristics of DVT, particularly the relevant risk factors, was of extreme importance in prevention of this key adverse event. By far, multiple risk factors associated with DVT have been identified, including advanced age, male gender, obesity, a history of DVT or pulmonary embolism, immobility, smoking or fracture itself [7–10].

In addition to external factors, there is increasing evidences that the internal factors, namely the systemic inflammation/immune response to traumatic fracture or major surgical trauma, played an important role in development of DVT. Alexandru et al [11] found the significant change of some inflammation/immune indexes (neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR)) after long-bone fracture.

Moreover, researchers have identified the significant correlation of NLR, PLR, or monocyte to lymphocyte ratio (MLR) with acute DVT after major orthopaedic surgery [12–14]. However, the role of these inflammation/immune indexes in development of DVT was not consistently significant [15]. Unlike other markers of inflammation, these indexes are calculated by the readily obtained biomarkers from a hemogram with an automated differential, which are routinely measured. If demonstrated to be predictive of preoperative DVT after traumatic fractures, these inexpensive and readily available indexes will help identify high-risk patients and the targeted application of ultrasound scanning for detection of DVT.

Review of the literature showed no data about relationship between inflammation/immune indexes and preoperative DVT occurrence after tibial plateau fractures. In this study, we used the prospectively collected data in a level I trauma center to address this issue. Our aims were: 1, to identify the optimal cut-off values of biomarkers or their derived indexes; 2, to evaluate their predictive ability for development of DVT; and 3, to evaluate their independent relationship with DVT after adjustment for demographics, co-morbidities and injury-related characteristics.

Methods

Data used in this study were obtained from the database of Surgical Site Infection in Orthopaedic Surgery (SSIOS), in which prospective method was used to collect data on patients who underwent orthopaedic surgeries between October 1 and December 31 2018, and surveillance of surgical site during hospitalization and telephone follow-up after discharge were conducted to identify surgical site infections. The ethics committee of the 3rd Hospital of Hebei Medical University approved the SSIOS (NO 2014-015-1), and all the participants had written the informed consent.

Inclusion and exclusion criteria

Patients meeting the following criteria were included: age of 18 years or older, definite diagnosis of tibial plateau fracture, and complete data available. Pathological (metastatic) fracture, old fracture (> 3 weeks from injury), concurrent fractures in other locations, patients with history of DVT or other thrombotic events, or current use of anticoagulants due to chronic comorbidities were excluded from this study.

According our policy, all patients received basic thromboprophylaxis after admission, consisting of chemical (low molecular weight heparin (LMWH), 2500-4100 IU once daily, subcutaneous injection) and elevation of the injured lower extremity for each patient.

Diagnosis of DVT

Guideline for the Diagnosis and Treatment of Deep Vein Thrombosis (3rd edition) proposed by Chinese Medical Association [16] was used to diagnose DVT. Before the operation, routine duplex ultrasonography (DUS) scanning of bilateral lower extremities was performed to detect potential DVT in femoral common vein, superficial and deep femoral vein, popliteal vein, posterior and anterior tibial vein and peroneal vein. The positive criteria of DUS scanning were set as noncompressibility, lumen obstruction or filling defect,

lack of respiratory variation in above knee segments, and inadequate flow augmentation to calf and foot compression maneuvers [17]. Due to the less clinical significance, superficial or intermuscular vein thrombosis (soleal or gastrocnemius vein thrombosis) were not included [18, 19].

Data collection and definition

Biomarkers or biomarker-derived inflammatory/immune indexes were obtained from hematologic tests carried out after admission and before the definite operation. These data included neutrophil-, lymphocyte-, monocyte- and platelet counts, The NLR was defined as the neutrophil count divided by lymphocyte count, PLR as the platelet count divided by the lymphocyte count, and MLR as monocyte count divided by lymphocyte count. The systemic immune-inflammation index (SII) was calculated as: platelet count * neutrophil count/lymphocyte count [20]. Given the importance in predictive ability or diagnosis of DVT, palsma D-dimer level was also included.

The other potential factors included demographics (age, gender, body mass index (BMI)), current cigarette and alcohol consumption, the comorbidities (hypertension, diabetes, chronic heart disease), fracture-related factors (injury mechanism (low- or high-energy trauma), open or cloded fracture, fracture classification based on Schatzker classification system).

The BMI (kg/m^2) was divided using the criteria recommended by the Chinese working group on obesity: normal (18.5-23.9), underweight (<18.5), overweight (24.0-27.9) and obesity (>=28.0) [21]. Low-energy injury was defined as an injury caused by a fall from a standing height, while fall from a height more than 2 meter or motor accidents was degined as high-energy injury.

Statistical analysis

Continuous variables were expressed by mean and standard deviation (SD), and evaluated by student-*t* test or Mann Whitney-*U* test, as appropriate. The categorical data were expressed as number and percentage (%), and were evaluated by chi-square or Fisher's exact test, as appropriate.

For biomarker (neutrophil-, lymphocyte-, monocyte- and platelet counts) and biomarker-derived inflammation/immune indexes (NLR, PLR, MLR and SII) and the plasma D-dimer level in continuous variable, we constructed receiver operating characteristic (ROC) to determine the optimal cut-off value for each variable, when Youden index (sensitivity+specificity-1) was maximum. The significance of the ROC curve was tested using the area under the curve (AUC) analysis, with $p<0.05$ as significance level. On basis of the cut-off values determined, each variable was divided in to two groups, and the chi-square or Fisher's exact test was performed, as appropriate. we also constructed ROC curve and used the generated AUC to evaluate the discriminatory ability of each biomarker or inflammation/immune index, when they were in dichotomous variable.

In the multivariate logistics regression model, the included variables were those tested as statistially significant in the univariate analyses. The stepwise backward elimination method was used to exclude

variables not significantly affecting the development of DVT. In the final model, variables with p<0.10 were retained, and the correlation strength is indicated by odd ratio (OR) and 95% confidence interval (95%CI). The significance level was p<0.05. Fitting degree of the final model was evaluated by Hosmer-lemeshow (H-L) test, and p>0.05 indicated the acceptable result. SPSS23.0 was used to perform all the tests (IBM, armonk, New York, USA).

Results

In this study, a total of 1179 patients with tibial plateau fractures were included, consisting of 742 males and 437 females, with an average of 45.6 years (Sd, 13.6; range, 18-82). Among them, 192 (16,3%) had a preoperative DVT.

The optimal cut-off value for each biomarker or inflammation/immune index was as follows: neutrophil count, $5.02*10^9$/L; lymphocyte count, $1.24*10^9$/L, monocyte, $0.78*10^9$/L, platelet count, $278*10^9$/L; NLR, 2.90; PLR, 207; MLR, 0.50; SII, 1066; and D-dimer, 0.55mg/L (Figure 1 and Table 1). When evaluated as categorical variables, the AUC showed the best discrimination ability for PLT (AUC, 0.615; 95%CI, 0.570-0.660), followed by D-dimer (AUC, 0.611; 95%CI, 0.570-0.652) (**Figure 2** and **Table 2)**.

From the univariate analyses, we could find that the rate of DVT was significantly different between patients and non-DVT patients in term of gender, prevalence of hypertension, current smoking, open fracture, fracture type based on Schartzker classification system, platelet, monocyte, neutrophile, NLR, PLR, MLR and SII (**Table 3**).

In the final multivariate logistic regression model, four risk factors were identified to be associated with DVT, including open fracture, neutrophil (>$5.02*10^9$/L), D-dimer level (>0.55mg/L), and PLT >$278*10^9$/L (**Table 4**). The H-L test showed the good fitness (X^2=2.428, p=0.787; Nagelkerke R^2=0.111).

We also performed the sensitivity analysis after excluding the 71 open fractures. the results showed neutrophil (>$5.02*10^9$/L), D-dimer level (>0.55mg/L), and PLT >$278*10^9$/L remained significant in the multivariate model. Also, the gender (male vs female) and hypertension were identified to be associated with occurrence of DVT (**Table 4**). The H-L test showed the good fitness (X^2=5.668, p=0.684; Nagelkerke R^2=0.127).

Discussion

This study demonstrated that several commonly used bimarker-based inflammatory/immune indexes as NLR, PLR, MLR, SII were not independently associated with the occurrence of preoperative DVT after tibial plateau fractures. Platelet count and neutrophil count were demonstrated to be independent risk factors associated with DVT, regardless of fracture type (with or without open fractures included). Specified at closed tibial plateau fractures, male gender and hypertension were also identified as independent risk factors for DVT.

Over the past decade, many peripheral hemogram-derived indexes such as NLR, PLR, LMR and SII were demonstrated to be closely associated with systemic inflammation/immune response status, and be of predictive value in prognosis of various infectious, oncological and antoimmune diseases [22–25]. The underlying mechanism might be that the cascade of inflammatory cytokines and chemokines, which was initiated by inflammation dysfunctional lymphocytes, provoked neutrophil and macrophage aggregation [26]. More recently, these inflammation/immune indexes have been increasingly used in major orthopaedic surgeries, and were demonstrated to be associated with injury severity or perioperative complications. Barker et al [12] found the positive relationship between increased NLR level (day 1 and day 2, pre- and postoperative) and the risk of venous thromboembolism after total knee arthroplasty. In addition, researchers have successively reported independent association of MLR [14], NLR [27] and PLR [27] with postoperative DVT in total joint arthroplasty.

Increasing evidences have showed that inflammatory response played an important role in development of DVT. In fact, coagulation activation and inflammation reaction are intimately related because multiple cellular factors are involved in both processes, including but not limited to monocyte, neutrophils, and platelets [28–30]. In an animal experiment, Bruhl et al [30] demonstrated the monocytes, neutrophils, and platelets cooperated to initiate and propagate venous thrombosis. In addition, inflammatory/immune response to trauma is the important contributing factor for development of DVT. Alexandru et al [11] evaluated the levels of hematology panel biomarkers in 148 patients with long-bone fractures, and found patients with fractures had significantly higher NLR level, compared to controls. However, in this study, we did not demonstrate the significant relationship between any of these inflammatory/immune indexes. This might be explained by the fact that these derived indexes would have more “intersections” with the original hemogram indexes, and it was possible that algorithm between biomarkers did not exhibit the significant independent predictive effect on DVT formation.

In contrast, platelet and neutrophil count were found to be independently associated with DVT following tibial plateau fractures, and the significance remained even if open fractures were excluded, indicating their stability in predicting DVT formation. The previous basic researches have described different mechanisms of DVT formation, including neutrophil extracellular traps (NETs), neutrophil histone modification [31–33] and trauma-induced activation of platelets and secondary cascade reaction via secretion of aggregatory mediators [34]. In this study, we also evaluate the predictive ability of them. The sensitivity neutrophil count > $5.02*10^9$/L was 0.807, a relatively high level, which could be used for initial screening of patients at-risk of DVT. The sensitivity of Platelet count > $278*10^9$/L was relatively low (0.505), but with a moderate specificity of 0.715; therefore, it might be a useful auxiliary tool to exclude patients without a DVT.

D-dimer in plasma reflects the secondary increased fibrinolytic activity and the hypercoagulability, which is a well-established highly sensitive marker of thrombotic events, although the specificity is poor [35]. Another consideration should be taken that the concentration of D-dimer varies in different settings. For example, D-dimer concentration increased with age, which resulted in a higher cut-off value of D-dimer concentration of 0.5 mg/L in the elderly. Therefore, several studies suggested the use of age-adjusted cut-

off values in patients with suspected DVT [36, 37]. In this study, we determined the optimal cut-off value of D-dimer was 0.55, slightly higher than the commonly used values, which might be associated with setting of trauma. The multivariate analysis showed DVT > 0.55 mg/L was associated with 2.42-fold risk of DVT in overall fractures included, and with 2.36-fold risk of DVT in closed fractures. this result demonstrated the stability of D-dimer in predicting or diagnosis of DVT in trauma patients. Our result re-confirmed the low specificity D-dimer, that was 0.451, higher than that of the previous studies in different settings, even with age-adjusted values used [37].

This study had some limitations. Firstly, as other multivariate analyses, we could not include all the potential factors that affect the occurrence of DVT, such as immolisation of the injured extremity. Secondly, C-reaction protein (CRP) was an important inflammatroy biomarker predictive of DVT formation, but only a fraction of patients had the relevant data, because it was not rountinely measured in our hospital. Thirdly, we determined the association rather than the causation between variables and DVT, therefore, these results should be interpreted with caution.

In summary, 16.3% of patients had preoperative DVT after tibial plateau fracture. Among the several biomarkers and bimarker-based inflammatory/immune indexes (neutrophil, lymphocyte, monocyte, platelet, NLR, PLR, MLR and SII), only platelet and neutrophil were identified to be associated with development of DVT indepdnet of fracture types and other clinical factors, and their predictive ability was moderate. In addition, open fracture, D-dimer level, male gender and past hypertension were identified as independent risk factors associated with DVT, in different settings. These factors are conducive to the initial screening for patients at-risk of DVT, individualized risk assessment, risk stratification and accordingly development of targeted prevention programs.

Abbreviations

DVT: deep venous thrombosis

SSIOS: Surgical Site Infection in Orthopaedic Surgery

BMI: body mass index

DUS: duplex ultrasonography

NLR: neutrophil to lymphocyte ratio

PLR: platelet to lymphocyte ratio

MLR: monocyte to lymphocyte ratio

SII: systemic immune-inflammation index

ROC: Receiver operating characteristic

SD: standard deviation

OR: odd ratio

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the 3rd hospital of Hebei Medical University. Informed consent was obtained from all the participants.

Consent for publication

Written informed consent was obtained from each patient to authorize the publication of their data.

Availability of data and materials

All the data will be available upon motivated request to the corresponding author of the present paper

Competing interests

The authors declare that they have no competing interests.

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Contributors

Yingze Zhang conceived the idea for the study; Yanbin Zhu and Wei Chen designed the study. Kuo Zhao, Junzhe Zhang, Hongyu Meng and Junyong Li collected the relevant data. Dawei Liu and Junyong Li prepared the figures and tables. Wei Chen performed the statistical analyses. All the authors interpreted the data and contributed to preparation of the manuscript. Dawei Liu and Wei Chen contributed equally to this manuscript.

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Tables

Table 1 The ROC and AUC to determine the optimal cut-off value for each index in continuous variable

Variable	Optimal cut-off value	AUC	95%CI		*p*
			lower limit	upper limit	
Lymphocyte	$1.24*10^9$/L	0.481	0.435	0.527	0.422
Platelet	$278*10^9$/L	0.598	0.548	0.648	0.000
Monocyte	$0.78*10^9$/L	0.562	0.514	0.610	0.009
Neutrophil	$5.02*10^9$/L	0.595	0.549	0.641	0.000
NLR	2.90	0.565	0.520	0.611	0.006
MLR	0.50	0.552	0.506	0.598	0.028
PLR	207	0.591	0.546	0.636	0.000
SII	1066	0.605	0.559	0.651	0.000
D-Dimer	0.55mg/L	0.628	0.588	0.669	0.000

Table 2 The ROC and AUC to evaluate the discriminatory ability of each index in categorical variable

Variable	Sensitivity	Specificity	AUC	95%CI		*p*
				Upper limit	Lower limit	
Lymphocyte	0.422	0.618	0.520	0.475	0.565	0.381
Platelet	0.505	0.715	0.615	0.570	0.660	0.000
Monocyte	0.469	0.655	0.562	0.517	0.607	0.007
Neutrophil	0.807	0.352	0.579	0.538	0.621	0.000
NLR	0.490	0.658	0.574	0.529	0.618	0.001
MLR	0.490	0.653	0.572	0.527	0.616	0.002
PLR	0.469	0.679	0.574	0.529	0.619	0.001
SII	0.557	0.719	0.581	0.536	0.626	0.000
D-dimer	0.771	0.451	0.611	0.570	0.652	0.000

Table 3 Univariate analyses of factors associated with preoperative DVT following tibial plateau fracture

Variables	DVTs/total (incidence)	*P*
Gender		0.003
Male	139/742 (18.7%)	
Female	53/437 (12.1%)	
18-44	81/558 (14.5%)	0.108
45-64	96/509 (18.9%)	
65 or older	15/ 112 (13.4%)	
BMI (kg/m^2)		
18.5-23.9	44/362 (12.2%)	
<18.5	2/21 (9.5%)	
24.0-27.9	102/511 (20.0%)	
≥28.0	44/286 (15.4%)	
Diabetes mellitus	23/154 (14.9%)	0.627
Hypertension	47/214 (22.0%)	0.013
Chronic heart disease	14/56 (25.0%)	0.070
Fracture type (Schatzker)		0.022
-	133/793 (16.8%)	
-	59/385 (15.3%)	
Mechanism (high-energy)	120/758 15.8%	0.571
Open fracture	22/71 31.0%	0.001
Current smoking	37/166 (22.3)	0.024
Alcohol consumption	20/107 (18.7%)	0.480
D-Dimer (>0.55 mg/L)	148/690 (21.4%)	<0.001
Neutrophil count (>5.02*10^9/L)	155/795 (19.5%)	<0.001
Lymphocyte (<1.24*10^9/L)	81/458 (17.7%)	0.299
Monocyte (>0.78*10^9/L)	90/431 (20.9%)	0.001
Platelet (>278*10^9/L)	97/368 (26.4%)	<0.001
NLR (>2.90)	94/432 (21.8%)	<0.001
PLR (>206)	90/407 (22.1%)	<0.001
MLR (>0.50)	94/436 (21.6%)	<0.001
SII (>1066)	85/362 (23.5%)	<0.001

Abbreviation: DVT, deep vein thrombosis; BMI, body mass index; **NLR**, neutrophil to lymphocyte rate; PLR, platelet to lymphocyte rate; MLR, monocyte to lymphocyte rate; SII, systemic immune-inflammation index

Table 4 Multivariate analysis of risk factors associated with DVT, with inclusion or exclusion of open fracture

Multivariate analysis with open fracture included			Sensitivity analysis with exclusion of open fracture		
Variables	OR and 95%CI	*P*	Variables	OR and 95%CI	*P*
Open fracture (vs close)	2.30 (1.30-4.07)	0.004	Gender (male vs female)	1.71 (1.17-2.49)	0.006
D-dimer (>0.55 mg/L)	2.20 (1.47-3.28)	<0.001	D-dimer (>0.55 mg/L)	2.36 (1.59-3.50)	<0.001
Neutrophil count (>5.02*10^9/L)	1.75 (1.13-1.71)	0.012	Neutrophil count (>5.02*10^9/L)	1.59 (1.05-2.41)	0.030
Platelet count (>278*10^9/L)	2.42 (1.71-3.42)	<0.001	Platelet count (>278*10^9/L)	2.66 (1.88-3.75)	<0.001
			Hypertension	1.71 (1.13-2.58)	0.011

Figures

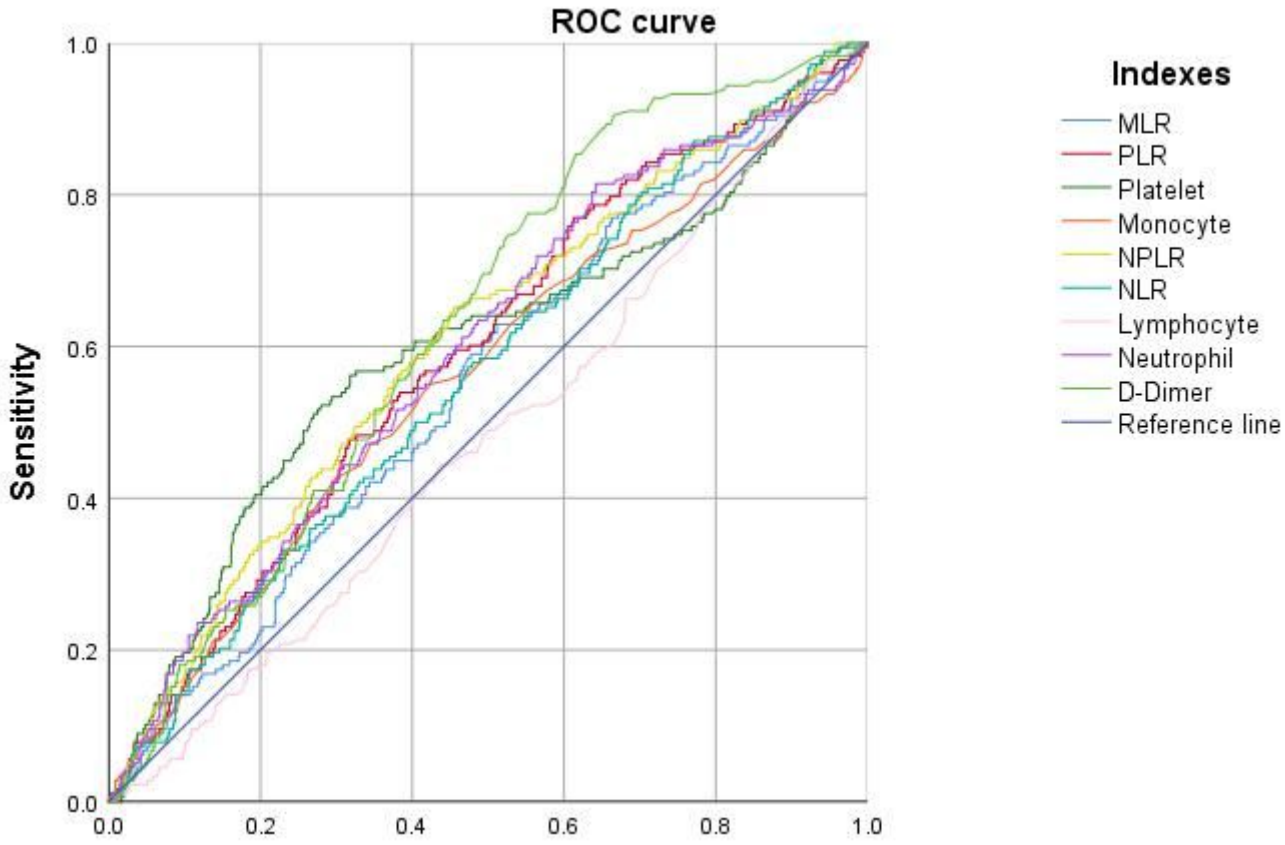

Figure 1

ROC to determine the optimal cut-off value for each biomarker or inflammatory/immune index, when in continuous variable

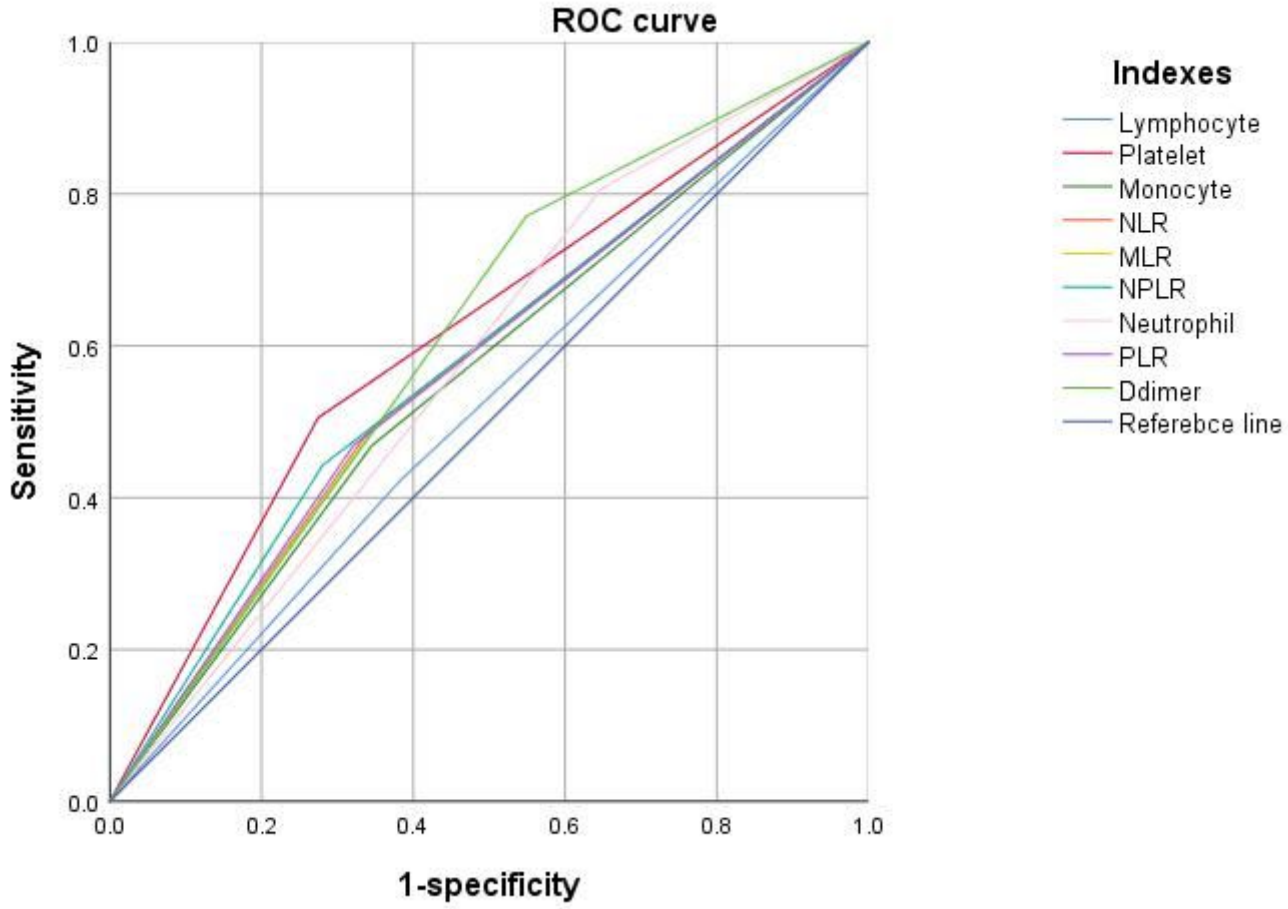

Figure 2

The predictive ability (sensitivity, specificity and AUC) of each biomarker or inflammatory/immune index, when in dichotomous variable