Research Square

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Alterations of coagulofibrinolytic-related markers in children with severe Mycoplasma pneumoniae pneumonia

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Abstract

Objective Severe

Mycoplasma pneumoniae pneumonia (SMPP) in children can cause multiple systemic complications. This study aimed to explore changes in coagulofibrinolytic biomarkers and their predictive value for SMPP.

Methods

A total of 133 hospitalized children with *Mycoplasma pneumoniae* pneumonia (MPP) were retrospectively enrolled from March 2025 to April 2026. Patients were divided into the general MPP (GMPP, n = 63) and severe MPP (SMPP, n = 70) groups according to Guideline for management of community-acquired pneumonia in children (2024 version). Demographic, clinical features, inflammatory and coagulofibrinolytic laboratory data were extracted from electronic medical records. erformance of candidate biomarkers.

Results

Compared with the GMPP group, children with SMPP exhibited significantly higher neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), fibrinogen (FIB), D-dimer, fibrin degradation products (FDP), tissue plasminogen activator-inhibitor complex (t-PAIC), thrombin-antithrombin complex (TAT), and plasmin-α2-plasmin inhibitor complex (PIC) ($P < 0.05$). Multivariate logistic regression demonstrated that elevated PIC (OR = 1.004, 95%CI:1.002–1.005, $P < 0.001$) and NLR (OR = 1.514, 95%CI:1.037–2.210, $P = 0.032$) were independent risk factors for SMPP. The threshold value of PIC for predicting SMPP was 1185.5 ng/mL (AUC = 0.838, sensitivity 81.4%, specificity 77.8%). The combined model of PIC and NLR achieved an AUC of 0.876 with improved specificity (84.1%). D-dimer levels were markedly higher in patients with endobronchial mucus plugs than those without mucus plugs ($P = 0.035$).

Conclusions

Activation of the coagulation-fibrinolysis system is prominent in children with SMPP. PIC and NLR serve as risk factors for severe MPP. The combination of PIC and NLR shows good predictive efficacy for SMPP in pediatric patients.

Introduction

As a cell wall-deficient prokaryote, *Mycoplasma pneumoniae* (MP) is the primary pathogen of *Mycoplasma pneumoniae* pneumonia (MPP). It represents one of the most prevalent etiologies of community-acquired pneumonia (CAP) in children over age 5, accounting for 40% of childhood CAP [1].

Although most of children with MPP usually recover by macrolide antibiotic administration, MPP can progress to refractory MPP (RMPP) or severe MPP (SMPP), like necrotizing pneumonia, pleural effusion, atelectasis, lung consolidation, pulmonary fibrotic lesions, pulmonary embolism, thrombosis involving other systems, and pulmonary hemorrhage [2–4]. These complications are associated with unfavorable prognosis and even mortality [2, 5].

Inspired by recent research findings, we considered that conventional coagulation assays are affected by hepatic maturation in children as well as the adhesion of MP to respiratory epithelial cells. Therefore, we collected data on systemic inflammatory indices (white blood cell count (WBC), monocyte percentage, neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP)), platelet count, factor VIII (FVIII), von Willebrand factor activity (vWF:Ac), von Willebrand factor antigen/FVIII ratio (vWF:Ag/FVIII), fibrinogen (FIB), D-dimer, fibrin degradation products (FDPs), soluble thrombomodulin (sTM), thrombin-antithrombin complex (TAT), plasmin-α2-plasmin inhibitor complex (PIC) and tissue plasminogen activator-inhibitor complex (t-PAIC) to investigate whether alterations in coagulation and fibrinolytic systems correlate with the severity of MPP [6–9].

Materials and Methods

133 children admitted to our hospital as MPP between March 2025 and April 2026 were enrolled in this study. We retrospectively analyzed demographics, clinical manifestations, laboratory data, radiological and bronchoscopy results retrieved from the hospitalized electronic records.

Criteria

MPP was diagnosed according to Guideline for the diagnosis and treatment of *Mycoplasma pneumoniae* pneumonia in children (2023 version) [10], including (1) fever, cough, and abnormal lung auscultation; (2) lung lobar infiltration confirmed by radiologic image; and (3) a positive detection of *M. pneumoniae* via polymerase chain reaction (PCR) in a nasopharyngeal swab or bronchoalveolar lavage fluid or MP antibody (IgM) in sera via an automated chemiluminescence immunoassay system. In addition to the baseline MPP enrollment criteria, severe MPP (SMPP) was categorized based on Guideline for management of community-acquired pneumonia in children (2024 version)[11], including (1) persistent fever for more than five days; (2) hypoxemia: oxygen saturation less than 92%; cyanosis; tachypnea; nasal flaring; retractions; (3) chest imaging revealed infiltration in multiple lung lobes or involving two-thirds of the lung; atelectasis, necrosis and abscess; (4) extra-pulmonary complications: rash; epistaxis; abnormal myocardial enzyme profile; gastrointestinal dysfunction; (5) anorexia or poor feeding. All the other patients were divided into GMPP group, and all patients were treated by macrolide antibiotics.

The exclusion criteria were as follows: (1) incomplete clinical data; (2) congenital heart disease, chronic kidney disease (CKD), immunodeficiency or tumors; (3) co-infection with bacteria (e.g. *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginiosa, Haemophilus influenzae* and

Stenotrophomonas maltophilia); (4) usage of corticosteroids or anticoagulants within one week; (5) history of surgery, trauma or blood transfusion recently.

Sample collection and measurements

(1) The nucleic acid of MP from deep sputum, nasopharyngeal swab or bronchoalveolar lavage fluid was detected by a 3500XL-Dx Genetic Analyzer (Thermo Fisher Scientific, Foster City, CA, USA) using a multiplex PCR profile covering 13 viral pathogens, i.e., MP, human rhinovirus (HRV), human respiratory syncytial virus (HRSV), human parainfluenza virus (HPIV), human coronavirus (HCoV), human metapneumovirus (HMPV), human bocavirus (HBoV), human adenovirus (HADV), *chlamydia pneumoniae* (Ch), and influenza virus (InfA, InfA H1/H3, InfB). In addition, herpesvirus and *Tropheryma whipplei* were analyzed by metagenomic next generation-sequencing (mNGS); (2) Sera detection: MP-IgM was analyzed by YHLO iFlash 3000 chemiluminescence analyzer (YHLO Biotech, Shenzhen, Guangdong, China) and sera were collected in procoagulant tubes with separator gel (centrifuged at 5000xg for 5 minutes). When the cutoff index (COI) was ≥ 1.0, MP-IgM was identified as positive, with sensitivity ≥ 90% and specificity ≥ 85%; (3) Inflammatory parameters: Peripheral blood (PB) was collected into dipotassium ethylenediaminetetraacetic acid (EDTA-K_2) tubes for hematology analyses. Complete blood cell counts (CBCs) were analyzed on a hematology analyzer (Sysmex XN-1000; Sysmex Corporation, Kobe, Japan). C-reactive protein (CRP) was performed by an immunoturbidimetric assay on the JOINSTAR JET-iSTAR 3000 Immunoanalyzer (Joinstar Biomedical Technology Co., Ltd., Hangzhou, Zhejiang, China); (4) Coagulofibrinolytic indicators: Plasma was obtained from anticoagulated PB with 109 mmol/L sodium citrate (1:9) (centrifuged at 1500xg for 15minutes) within 24 hours after admission. Factor VIII, vWF:Ac, vWF:Ag/VIII were analyzed on CS-5100 automated coagulation analyzer (Sysmex Corporation, Kobe, Japan). sTM, TAT, PIC and t-PAIC were detected via chemiluminescent immunoassay using the Sysmex HISCL 5000 analyzer (Sysmex Corporation, Kobe, Japan). Fibrinogen, D-dimer and FDPs were measured on Stago STA Compact coagulation analyzer (Diagnostica Stago, Asnieres-sur-Seine, France).

Statistical analysis

The Kolmogorov-Smirnov test or the Shapiro—Wilk test was used for checking the normal distribution of continuous data. An independent sample *t*-test was performed for comparing continuous data with a normal distribution, expressed as mean ± standard deviation. Mann—Whitney *U* test was conducted for non-normally distributed data comparison, using median with interquartile range (IQR). The *Chi-square* test or Fisher's exact test was used for comparing categorical data, expressed as the n (%). FDPs were originally measured as a continuous variable. Because of the linearity range, FDP values below the lower limit (< 4μg/mL) and values within the linear range (4-150μg/mL) were treated as a categorical variable for statistical analyses. No FDPs results were greater than 150μg/mL. Univariate and multivariate logistic regression analyses were performed to identify risk factors associated with SMPP. Prior to multivariate logistic regression analysis, multicollinearity among candidate variables was examined. The

variance inflation factor (VIF) was less than 5 and the tolerance was greater than 0.1. PIC and NLR were analyzed by receiver operating characteristic (ROC) curve with its sensitivity, specificity, area under the curve (AUC) and optimal threshold values for predicting SMPP. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 31.0 and GraphPad Prism 11.0 software.

Results

In this study, there were 62 boys and 71 girls with median age of 4.1 (IQR 2.2-6.8) years (minimum age: 5 months and 22 days; maximum age: 14.3 years). Of these patients, 63 children were diagnosed with GMPP and 70 were classified as having SMPP. Of 70 children with SMPP, four had atelectasis of the right middle and lower lobes (one complicated by pulmonary consolidation), two exhibited consolidations with concurrent pleural effusion, and one showed minimal fibrous foci within the right middle lobe.

No statistically significant differences in age, gender, white blood cell count, monocyte percentage, and platelet count on admission were observed between the GMPP and SMPP groups ($P>0.05$). Length of hospital stay, NLR and CRP showed higher levels in the SMPP group than the GMPP group, with statistically significant differences ($P<0.05$) (Table 1).

Table 1 Demographic, clinical features and inflammatory parameters of children with GMPP and SMPP

Variables	GMPP (N=63)	SMPP (N=70)	$\chi 2$/ Z Value	P-Value
Age (years)	3.9 (2.2, 5.9)	4.8 (1.9, 7.9)	1.242	0.214
Gender, male (%)	30 (47.6)	32 (45.7)	0.048	0.826
Hospital stay (days)	6.0 (5.0, 7.0)	6.0 (5.0, 7.3)	2.078	0.038
WBC (10^9/L)	7.5 (6.0, 9.8)	7.3 (6.1, 8.7)	0.117	0.907
MONO (%)	7.6 (6.3, 9.6)	8.5 (6.6, 10.9)	1.319	0.187
NLR	1.6 (1.1, 2.2)	1.9 (1.2, 3.0)	2.012	0.044
CRP (mg/L)	5.8 (1.1, 9.2)	6.6 (2.9, 14.2)	2.028	0.043
PLT (10^9/L)	274 (224, 335)	264 (218, 316)	0.121	0.903

Abbreviations: WBC, white blood cell count; Mono, monocyte percentage; NLR, neutrophil-to-lympocyte ratio; CRP, C-reactive protein; PLT, platelet count.

Viral co-infections

There were no significant differences in mono-infection and viral co-infection of MP between the GMPP and SMPP groups ($P>0.05$). In the SMPP group, viral co-infections accounted for 50.0% (35/70), with

human respiratory syncytial virus being the most detected (Table 2). Among them, two cases had mixed infection of *Chlamydia pneumoniae* and rhinovirus, and one case had co-infection between *Tropheryma whipplei* and rhinovirus; these cases were all classified as viral co-infections.

Table 2 Pathogens of children with GMPP and SMPP

Etiologic agents	**Total**	**GMPP (N=63)**	**SMPP (N=70)**	***P* Value**
1000. Pneumoniae mono-infection	63	28 (44.4%)	35 (50.0%)	0.522
M. Pneumoniae co-infection	70	35 (55.6%)	35 (50.0%)	
Virus				
HADV	2	1	1	
Boca	5	4	1	
Boca+HRV	2	1	1	
Hcov	2	2		
HMPV	2	2		
HPIV	6	4	2	
HPIV+HRV	4	3	1	
HRSV	25	10	15	
HRV	12	5	7	
HRV+HMPV	2		2	
HRV+HPIV	2	2		
HRV+HRSV	1	1		
HRV+CP	2		2	
HRV+TW	1	1		
HHV-6B	1	1		
HSV-I+HPIV	1		1	

Abbreviations: M. pneumoniae, *Mycoplasma pneumoniae*; ADV, human adenovirus; Boca, human bocavirus; HRV, human rhinovirus; Hcov, human coronavirus; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; HRSV, human respiratory syncytial virus; CP, *Chlamydia pneumoniae*; TW, *Tropheryma whipplei*; HHV-6B, human herpesvirus type 6B; HSV-I, herpes simplex virus type I.

Comparison of coagulofibrinolytic parameters between the GMPP and SMPP groups

As shown in Table 3, factor VIII, vWF:Ac, vWF:Ag/VIII and sTM were no different significantly between the two groups (*P*>0.05). FIB, FDPs, D-dimer, t-PAIC, TAT and PIC were significantly higher in the SMPP than GMPP group (*P*<0.05, Table 3).

Table 3 Coagulofibrinolytic indicators of children with GMPP and SMPP

Parameters	GMPP (N=63)	SMPP (N=70)	χ2 / Z value / t value	*P*-Value
Factor VIII (%)	51.5 (39.4, 68.8)	58.3 (42.1, 70.5)	1.568	0.117
vWF:Ac (%)	123.4 (86.4, 187.2)	140.7 (93.9, 197.7)	1.543	0.123
vWF:Ag/FVIII	2.6±0.5	2.8±0.7	-1.722	0.087
FIB (g/L)	4.0 (3.4, 4.8)	4.3 (3.6, 5.5)	2.400	0.016
D-dimer (μg/mL)	3.2 (2.4, 4.5)	5.1 (3.7, 7.9)	5.184	<0.001
FDPs, n (%)	62 (98.4%)	61 (87.1%)	4.544	0.033
sTM (TU/mL)	7.7 (6.5, 8.7)	8.0 (6.3, 10.1)	0.730	0.465
t-PAIC (ng/mL)	2.0 (1.5, 2.7)	2.3 (1.9, 3.4)	3.627	<0.001
TAT (ng/mL)	1.2 (0.8, 2.5)	2.2 (1.4, 3.1)	3.627	<0.001
PIC (ng/mL)	882.0 (680.0, 1151.0)	1457.5 (1227.8, 1793.0)	6.714	<0.001

Abbreviations: vWF:Ac, von Willebrand factor Activity (or VWF:GPIbM); vWF:Ag/FVIII, von Willebrand factor Antigen/ factor VIII; FIB, fibrinogen; FDPs, Fibrin Degradation Products; sTM, soluble thrombomodulin; t-PAIC, tissue plasminogen activator-inhibitor complex; TAT, thrombin-antithrombin complex; PIC, plasmin-α2-plasmin inhibitor complex.

Comparison of thrombus biomarkers in children with *Mycoplasma Pneumoniae* pneumonia in different bronchoscopic groups

Twenty-six pediatric patients underwent fiberoptic bronchoscopy for examination and intervention. Mucus plug-induced luminal obstruction was observed in eight cases, including two cases of GMPP and six cases of SMPP. Three of the six SMPP patients had plug occlusion within the right upper bronchial lumen. The levels of FIB, FDPs, sTM, t-PAIC, TAT, PIC showed no statistically significant differences in different bronchoscopic manifestations (*P*>0.05). The concentration of D-dimer elevated in the mucus plug group than the non-mucus plug group (*P*=0.035, Table 4).

Table 4 Clinical characteristic and thrombus indicators of children with MPP in different bronchoscopic groups

Indicators	Non-mucus plug group (n=18)	Mucus plug group (n=8)	Z value/*t* value	*P*-value
FIB (g/L)	4.1±1.1	4.8±1.7	-1.225	0.232
D-dimer (μg/mL)	3.5 (2.3, 5.2)	8.3 (3.2, 16.7)	2.113	0.035
FDPs, n (%)	15 (83.3%)	6 (75.0%)	-	0.628
sTM (TU/mL)	7.6±2.2	8.4±2.6	-0.857	0.400
t-PAIC (ng/mL)	2.8 (2.1, 3.9)	2.8 (1.6, 3.3)	-0.334	0.765
TAT (ng/mL)	2.3 (0.8, 2.6)	2.0 (1.1, 3.0)	-0.056	0.978
PIC (ng/mL)	866.5 (637.5, 1706.8)	1232.0 (945.0, 1490.8)	1.111	0.285
SMPP, n (%)	12 (66.7%)	6 (75.0%)	-	1.000

Note: - means missing χ2 values for Fisher's exact test

Risk factors for SMPP

Variables showing inter-group differences between GMPP and SMPP were entered into logistic regression models. Univariate logistic regression analysis was initially performed to screen candidate coagulofibrinolytic-related biomarkers. Parameters with $P<0.05$, including D-dimer, FIB, t-PAIC, TAT, PIC and NLR, were subsequently enrolled into the multivariate logistic regression model for identification of independent risk factors for the SMPP patients. Since FDPs measurements cloud not be standardized, and 92.5% of the values were below the lower limit of linear quantification (4.0μg/mL), stratification based on FDP levels was not feasible. FDP was therefore excluded from the multivariate regression analysis to avoid instability of the regression model. VIF analysis confirmed no substantial multicollinearity for these variables (all VIF<3 and tolerance >0.4). PIC (OR=1.004, 95%CI: 1.002-1.005, $P<0.001$) and NLR (OR= 1.514, 95%CI: 1.037-2.210, $P=0.032$) were significant coagulofibrinolytic-related risk factors for SMPP children (Table 5).

Table 5 Multivariate logistic regression analysis of the coagulofibrinolytic-related risk factors associating with the SMPP

Parameters	B	SE	Wald χ2	*P*-value	OR (95%CI)
D-dimer (μg/mL)	0.000	0.001	0.133	0.716	1.000 (0.998, 1.003)
FIB (g/L)	-0.436	0.285	2.335	0.126	0.647 (0.370, 1.131)
t-PAIC (ng/mL)	0.343	0.225	2.317	0.128	1.409 (0.906, 2.190)
TAT (ng/mL)	0.090	0.112	0.652	0.420	1.095 (0.879, 1.363)
PIC (ng/mL)	0.004	0.001	17.666	<0.001	1.004 (1.002, 1.005)
NLR	0.415	0.193	4.611	0.032	1.514 (1.037, 2.210)

Abbreviations: OR, odds ratio; CI, confidence interval; SE, standard error.

ROC curve analysis of PIC

ROC curve was constructed for PIC and NLR. The threshold value of PIC was 1185.5 ng/mL, which generated an AUC of 0.838 (95%CI: 0.769-0.907, *P*<0.001), with a sensitivity of 81.4% and a specificity of 77.8%. The threshold value for NLR was 1.868, accompanied by an AUC of 0.601 and limited discriminatory power. When PIC was combined with NLR for predicting MPP severity, the sensitivity declined to 77.1%, whereas the specificity increased slightly to 84.1% (Fig. 1).

Discussion

Although the majority of children with MPP attain remission or fully recovery under macrolide treatment, persistent fever, clinical deterioration, the rising prevalence of RMPP and macrolide-resistant MP, together with the worldwide resurgence of MPP, have been documented after COVID-19 pandemic restrictions (2023-2024), accompanied by an increasing burden of complications [12-14]. Obstructive disease and pleural effusions have been exhibited higher incidence in the post-COVID-19 era (2022-2025) [15]. Against this background, we investigated the clinical profiles and coagulation-fibrinolysis-asssociated biomarkers in children with SMPP.

Several research illustrated that co-infection with bacteria and pneumonia might be associated with inflammation and disorders of the coagulation and fibrinolysis systems [16, 17]. In this study, only patients with viral-*Mycoplasma pneumoniae* co-infection were included, while bacterial co-infections were excluded. Although viral co-infection was not associated with greater MPP severity in our cohort, HRSV was the predominant virus in mixed infections in both MPP and SMPP cases. This finding is consistent with the results reported by de Groot RCA et al [18].

In our study, there were no significant different changes statistically, in terms of Factor VIII, vWF:Ac, vWF:Ag/FVIII, sTM and PLT, between the GMPP and SMPP groups. This may indicate that the dysfunction of coagulation-fibrinolysis system of SMPP may not be initiated by endothelial cells. We found elevated NLR and CRP expressions in SMPP group compared with GMPP group, which is in accordance with the findings from Qiu et al [19]. Our findings also indicated that MPP tended to

deteriorate when NLR was ≥1.9, in agreement with Li et al [20]. In addition, we observed higher levels of FIB, TAT, PIC, t-PAIC, FDPs and D-dimer in SMPP group. Thrombin binds to antithrombin at 1:1 ratio to yield the thrombin-antithrombin complex (TAT), a stable and detectable complex, which initiates the activation of the coagulation system [21]. Similarly, plasmin combines with α2-plasmin inhibitor1 by 1:1 ratio to produce PIC, an indicator of fibrinolytic-system activation [22]. Beyond this biomarker property, PIC works together with plasminogen activator inhibitor-1 (PAI-1) to regulate fibrinolysis. PAI-1 suppresses fibrinolysis by forming the t-PAIC after binding with tissue-plasminogen activator (t-PA) [23]. Collectively, the detected biomarkers reflect concurrent inflammation, hypercoagulability and fibrinolytic disorder among patients with SMPP. Blanch-Ruiz et al demonstrated the neutrophil secretome as a vital link between inflammation and thrombosis [24]. Therefore, the hypercoagulability and fibrinolytic disorder of SMPP may be triggered by inflammation, such as neutrophils. Neutrophils may facilitate early thrombus resolution by releasing elastase within inflammatory microthrombi, and inflammatory factors can activate neutrophils, trigger neutrophil extracellular traps, inhibit fibrinolytic potential via elevated PAI-1 during thromboinflammation [25, 26]. Moreover, PIC >1185.5 ng/mL and NLR > 1.868 were identified as risk factors for SMPP. Although NLR was an independent risk factor for SMPP, its single-index discrimination ability remained limited. The combination of PIC and NLR sacrificed partial sensitivity and achieved satisfactory specificity and efficacy with AUC=0.876, which is suitable for predicting SMPP.

Some studies have demonstrated that elevated D-dimer levels are observed in children with MPP complicated with thrombosis or endobronchial mucus plugs, which is consistent with our finding that D-dimer concentrations were significantly increased in the mucus plug group [8, 27]. Accordingly, elevated D-dimer together with clinical manifestations such as refractory fever or compromised airway ventilation may serve as helpful warning signs. Under these circumstances, clinicians may perform timely bronchoscopic mucus-plug clearance to recover adequate respiratory ventilation for pediatric patients with MPP.

Study Limitations

There are several limitations in our study. First, it was a retrospective study in a single medical centre, and the sample size of pediatric patients receiving bronchoscopy was small, which may introduce selection bias. Second, the threshold values derived from ROC analyses should be considered as exploratory and need further validation in independent external cohorts.

Conclusion

Children with SMPP present with prolonged hospital stay, robust inflammatory response, and a hyperactive coagulation-fibrinolytic system. NLR (>1.868) and PIC (>1185.5 ng/mL) are independent risk factors for SMPP. The combination of PIC and NLR shows good predictive efficacy for SMPP in pediatric patients.

Declarations

Human Ethics and Consent to Participate declaration

This retrospective study was approved by the Medical Ethics Committee of the Children's Hospital of Soochow University (Approval NO. 2026CS136). All data were collected from electronic medical records.Written informed consent was waived by the ethics committee due to the retrospective nature of the study using de-identified clinical data.

Data availability

The data underlying this article will be shared on reasonable request.

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CRediT authorship contribution statement

Fang Chen: Writing – review & editing, Writing – original draft, Methodology. **Lei Yin**: Visualization, Validation. **Yang Li**: Writing – review & editing, Investigation. **Qiuxia Tan**: Conceptualization. **Xuejun Shao**: Supervision. **Hanjun Shen**: Data curation, Software, Resources.

Disclosure statement:

The authors have declared no conflicts of interests.

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Figures

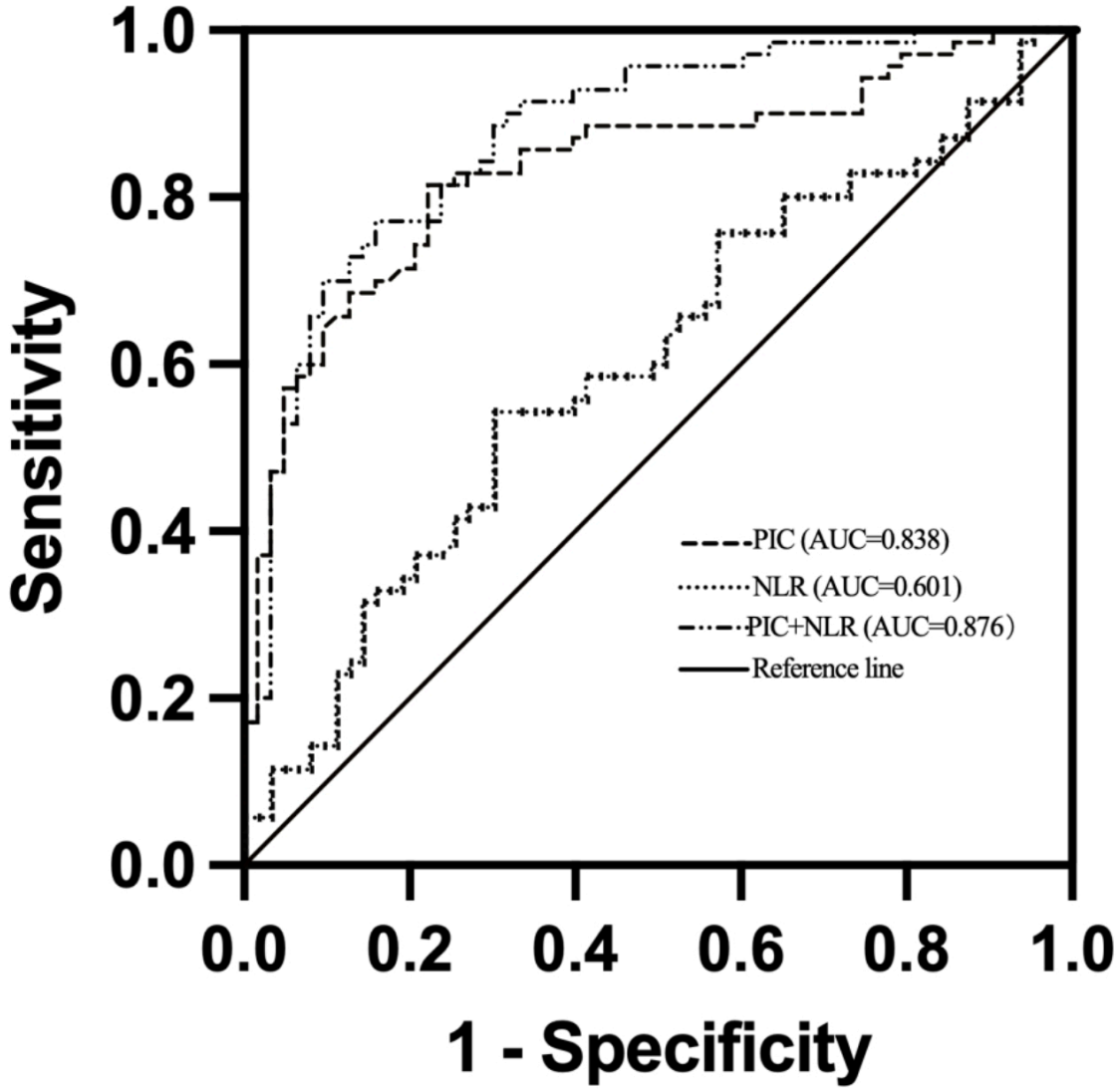


Figure 1

ROC curve analysis of PIC and NLR.