Clinical Significance of D-dimer Level in Refractory Mycoplasma Pneumoniae Pneumonia

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Abstract

Background

Levels of serum D-dimer (D-D) in children with mycoplasma pneumoniae pneumonia (MPP) were assessed to explore the clinical significance of D-D level in refractory MPP(RMPP).

Method:

A total of 430 patients with MPP were enrolled between January 2015 and December 2015, and divided into a genera MPP (GMPP) group (n = 306) and a RMPP group (n = 124). Clinical data, D-D level, white blood cell (WBC) count, C-reactive protein (CRP), blood sedimentation (ESR), and lactate dehydrogenase (LDH) were compared between the two groups.

Results

(1) Hospitalization time, fever duration, WBC, CRP, LDH, ESR, and D-D were significantly higher in the RMPP group than in the GMPP group, (all $P < 0.05$). (2) Correlation analysis showed that D-D was positively correlated with WBC, CRP, ESR, and LDH, and could be used to jointly evaluate the severity of the disease. (3) The predictive values of WBC, CRP, ESR, LDH, and D-D for RMPP were further compared using area under the receiver operating characteristic curve(AUC) analysis. D-D had the highest predictive power for RMPP (AUC = 0.923, $P < 0.01$). When the D-D level was > 738 ng/ml, the predicted sensitivity of RMPP occurrence was 79.8% and the specificity was 93.5%. D-D level also had a good ability to predict pleural effusion and liver injury (AUC = 0.740, $P < 0.01$ and AUC = 0.812, $P < 0.01$, respectively). (4) After 1 week of treatment, the levels of D-D in both groups were lower than those before treatment ($p < 0.01$), but remained outside the normal range in 91.4% of participants, and were moderately or severely increased in 27.1% of the participants, all of whom were in the RMPP group.

Conclusion

Serum D-D levels were significantly increased in patients with RMPP, indicating that severe hypercoagulability and vascular endothelial injury with prolonged duration existed in this patient population. Increased levels of serum D-D may be used as an early predictor of RMPP and the occurrence of complications. Our findings provide a theoretical basis for the early diagnosis of RMPP, early intervention of hypercoagulability, and improvement of microcirculation therapy.

Background

Mycoplasma pneumoniae pneumonia (MPP) is a common etiology of childhood community-acquired pneumonia (CAP), accounting for 10–40% of cases, of which, nearly 20% require hospitalization [1–3].

The clinical manifestations of MPP are complex and varied. In addition to pulmonary involvement, MPP is frequently accompanied by intrapulmonary and extrapulmonary multi-system damage. Refractory Mycoplasma pneumoniae pneumonia (RMPP) has become increasingly common in recent years. RMPP frequently shows no improvement in clinical and radiological findings despite appropriate macrolide treatment, and even may present with necrotizing pneumonia, airway occlusion, or thrombosis [4]. Therefore, early identification and active treatment are needed. Several cases of MPP complicated with thrombus have recently been reported [4–5], indicating that children with MPP have abnormal coagulation. Serum D-dimer (D-D) level can be used as a molecular marker for hypercoagulability [4], as well as an indicator for monitoring inflammation and severe infection [6]. The present study further explored the role of hypercoagulability in the pathogenesis of RMPP by evaluating D-D levels and changes in D-D levels in children with MPP.

Methods

Study population

Children with MPP admitted to the respiratory department of our hospital from January 2015 to December 2015 were eligible for participation in the present study. Inclusion criteria were as follows: (1) age ≥ 1 year old; (2) signs and symptoms indicative of pneumonia on admission, including fever, cough, abnormal lung auscultation, and a new infiltrate on chest radiography; (3) diagnosis of MP infection based on positive serologic test results (MP IgM positive and antibody titer ≥ 1:160) with positive results for M. pneumoniae DNA detected in nasopharyngeal secretions; exclusion of other respiratory tract infections and tuberculosis using the following tests: protein purified derivative (PPD), blood cultures, pleural effusion cultures, nasopharyngeal aspirate/swab cultures, nasopharyngeal aspirate/swab for virus antigen detection (respiratory syncytial viruses, influenza viruses, metapneumovirus, adenovirus, and parainfluenza virus), and serology for Chlamydia pneumoniae and Legionella pneumophila.

Exclusion criteria were (1) immunodeficiency disease and (2) respiratory diseases such as primary ciliary dystrophy, cystic fibrosis, congenital bronchopulmonary dysplasia, vascular ring malformation, bronchial foreign body, asthma, pulmonary tuberculosis, pulmonary tumor and non-infectious interstitial pulmonary disease.

RMMP was defined as follows: 1) Prolonged fever for 7 days or more or 2) persistent consolidation of more than one lobe of the lung despite appropriate antibiotic treatment, including macrolides. All other participants were considered to have general mycoplasma pneumoniae pneumonia (GMPP). The parents of all participating children provided written informed consent form prior to inclusion in the study.

Data Collection

All children were admitted to hospital within 24 h after routine screening for infection, including peripheral white blood cell (WBC) count, C-reactive protein (CRP), blood sedimentation (ESR), sputum culture, M.

pneumoniae DNA, phlegm and blood respiratory etiology examination, levels of serum D-D, liver and kidney function, X-ray chest radiograph (or chest CT), and electrocardiogram (ECG).General information including sex, age, history, medical history, physical examination, and complications were documented, as well as an assessment of the patient's condition. Patients with significantly increased levels of D-D (≥ 1400 ng/ml) were reviewed after treatment for 1 week, and WBC and CRP were also reviewed at this time point.

Diagnostic criteria for myocardial injury were as follows: (1) clinical manifestations of cardiac insufficiency; (2) cardiac enlargement; (3) ECG changes such as ST-T changes and arrhythmias; increased levels of CK-MB or positive cardiac troponin, excluding children with previous underlying heart disease. Diagnostic criteria for liver injury were ALT ≥ 3 times normal value upper limit (ULN) and ratio of ALT measured value/ALT normal value upper limit and ALP measured value/ALP normal value upper limit ≥ 5. Viral hepatitis, metabolic diseases, and other diseases involving the liver were excluded.

The levels of serum D-D were determined by immunoturbidimetry using an ACLTOP700 automatic blood coagulation analyzer (Wofen Inc., USA) in accordance with the manufacturer's instructions. The normal range of serum D-D was ≤ 280 ng/ml. In the present study, the degree of D-D elevation was defined as follows: mild increase: < 5-fold increase (> 280 to < 1400 ng/ml), moderate increase: < 10-fold increase (≥ 1400 to < 2800 ng/ml), and severe increase: >10-fold increase (≥ 2800 ng/ml).

Statistical Analyses

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version. 22.0 (IBM Corp., Armonk,NY, USA). For continuous variables, comparison of means was conducted using a t-test. For categorical variables, $\chi 2$ or Fisher's exact test was used. For ordinally scaled data, the Wilcoxon rank-sum test was used. Skewed distribution data were expressed as median values (25th-75th interquartile ranges) and comparisons between two groups were conducted using the Mann-Whitney U rank sum test. The Wilcoxon rank sum test was used to compare serum D-D levels before and after treatment. Multi-scale logistic regression analysis was used to analyze the relationship between D-D level and complications. Values of $P < 0.05$ were considered statistically significant. The critical value of the diagnostic value of each predictor was obtained using receiver operating characteristic (ROC) curve analysis.

Results

Characteristics of study subjects

A total of 944 patients with community-acquired pneumonia aged ≥ 1 year were screened for inclusion in the study. Of these, 135 patients with incomplete data were removed from further analysis, and the remaining 809 patients underwent the study assessments. Among these 809 patients, 508 (62.8%) had a positive MPP PCR result or a significant antibody response, including 78 cases of mixed infection with

mycoplasma and or other pathogens. After exclusion of mixed infection, a total of 430 patients with MPP were selected for further analysis and included 306 patients in the GMPP group with an average age of (4.7 ± 2.5) years and 124 patients in the RMPP group with an average age of (5.7 ± 2.7) years. Age and sex were compared between the two groups (Table 1). There was no statistically significant difference in sex between the two groups (P = 0.116); however, the RMPP group had a higher mean age than that of the GMPP group, with a statistically significant difference (P = 0.000).

Table 1
Comparison of clinical data and laboratory sanalyses between the GMPP and RMPP groups.

Characteristics	GMPP (n = 306)	RMPP (n = 124)	$t/\chi^2/Z$	*P*-value
Male/female	176/130	61/63	2.47	0.116
Age in years	4.7 ± 2.5	5.7 ± 2.7	-3.8	0.000
Hospitalization time(d)	8.1 ± 2.5	12.7 ± 5.9	-11.2	0.000
Total fever duration(d)	5.0 ± 3.8.	9.3 ± 4.6	-9.6	0.000
WBC($\times 10^9$/L)	8.5 ± 3.7	10.1 ± 4.8	-3.7	0.000
CRP(mg/L)	11.4 ± 15.2	40.0 ± 45.6	-9.72	0.000
LDH(U/L)	328.3 ± 467.4	467.4 ± 259.7	-7.156	0.000
ESR(mm/h)	32.0 ± 15.4	44.5 ± 23.3	-6.539	0.000
D-D(ng/ml)	247(173.0-385.8)	1718.5(819.5-3057.5)	-13.7	0.000

Compared with the GMPP group, hospitalization time and fever duration were longer in the RMPP group; while the levels of WBC, CRP, ESR, LDH, and D-D were higher in the RMPP group; these differences were all statistically significant (P < 0.05; Table 1).Among these assessments, a moderate- to- severe increase in serum D-D (≥ 1400 ng/ml) was more likely to be observed in the RMPP group (Fig. 1).

Correlation analysis of D-D level with WBC, CRP, LDH, and ESR

D-D level was found to be positively correlated with WBC, CRP, LDH, and ESR (*P* < 0.01; Table 2).

Table 2
Correlation analysis of serum D-D level with WBC, CRP, LDH, and ESR

	WBC	CRP	LDH	ESR
r	0.194	0.519	0.336	0.340
P	0.000	0.000	0.000	0.000

Predictive Value Of D-d Level For Rmpp

The predictive value of WBC, CRP, ESR, LDH, and D-D for RMPP werer compared using area under the ROC curve (AUC) analysis. D-D was found to have the highest predictive power for RMPP (AUC = 0.923, P = 0.000). When the D-D level was > 738 ng/ml, the predicted sensitivity of RMPP occurrence was 79.8% and the specificity was 93.5% (Fig. 2).

Predictive Value Of D-d Level For Mpp With Complications

AUC analysis was used to further evaluate the value of D-D level in predicting complications such as atelectasis, pleural effusion, liver injury, erythema, myocardial damage, and pulmonary embolism. The results showed that the serum D-D level could robustly predict pleural effusion and liver injury (AUC = 0.740, P = 0.000 and AUC = 0.812, P = 0.000, respectively) (Fig. 3). For D-D level > 930 ng/ml, the sensitivity and specificity of the prediction for pleural effusion were 80.6% and 60.5%, respectively.For D-D level > 2100.5 ng/ml, the sensitivity and specificity of the prediction for liver injury were 93.3% and 72.7%, respectively.

Degree Of D-d Elevation And Complications

Levels of D-D were classified as normal, mildly increased, moderately increased, and severely increased. Pleural effusion was the most prevalent complication across the four classifications, The incidence of pleural effusion increased with increasing D - D level and differed significantly among the normal, mild increase, and moderate increase groups (P < 0.01); however, the difference between the moderate increase group and the severe increase group was not statistically significant (P > 0.05; Fig. 4). The incidence of atelectasis was significantly higher in the group with mildly elevated D-D level compared with in the normal group (P < 0.01), but did not further increase with increasing D-D level (moderately elevated group, P = 0.622; severely elevated group, P = 0.421).

Serum D-d Level After Treatment For 1 Week

A total of 74 children were reviewed for D-D level, WBC, and CRP after treatment for 1 week, including 5 patients with GMPP and 69 patients with RMPP. After treatment, the levels of WBC and CRP in most children were reduced to normal (63.0% and 81.5%, respectively). In both the GMPP and RMPP groups, D-D level decreased significantly with treatment (P < 0.05, Table 3), although 91.4% of children had D-D levels that remained above the upper limit of normal (> 280 ng/ml) and 27.1% of children had a moderate-to-severe increase in D-D, all of which were within the RMPP group (Fig. 5). According to the D-D level after a further 1-week interval, patients were divided into a normal group and an abnormal group. More pleural effusions were observed in the abnormal group than in the normal group (28.6% and 67.2%, respectively, P = 0.04; Fig. 6).

Table 3
Comparison of serum D-D levels between GMPP group and RMPP group before and after treatment

Treatment time	D-D(ng/ml)	
	GMPP (n = 5)	RMPP (n = 69)
0d	1816(1368.0-2696.5)	2984.0(2134.0-3757.0)
1W	450.0(259.0-633.5)	1060.0 (670.0-2134.0)
z	-2.02	-6.45
P	0.043	0.000

Discussion

MPP is a common respiratory disease in children. In recent years, the prevalence of RMPP has been increasing, particularly in Asian countries [7, 8]. The specific pathogenesis of RMPP remains unclear, however, pathogenic substances or other host factors may be the cause of lung injury associated with an excessively strong immune response [9–11]. Previous studies have reported that RMPP is associated with more serious lung injury and higher levels of clinical indicators such as CRP, ESR, and LDH, as well as longer recovery time [8, 10, 12]. Therefore, early use of immune modulators is recommended in RMPP rather than waiting for antibiotic treatment to exert an effect; this approach can reduce MP-mediated immune injury and improve treatment efficacy [13–15]. However, there is no specificity in early clinical manifestations of RMPP and early diagnosis is difficult, meaning that early predictors need to be identified.

Clinical cases of MPP complicated with thrombosis are not unusual, and MPP complicated with deep vein thrombosis is frequently reported [4–5]. At present, the mechanism by which Mycoplasma pneumoniae pneumonia causes vascular embolization is not fully understood, and it is primarily considered to be related to immune mediation after vascular injury [16]. Under normal circumstances, the coagulation and fibrinolytic systems are in a dynamic equilibrium state. When coagulation occurs in vivo, thrombin acts on fibrin to activate the fibrinolytic system, and D-D can be formed [17]. D-D is primarily used in clinical settings for the initial diagnosis of pulmonary embolism, and shows diagnostic accuracy in the diagnosis of acute pulmonary embolism. However, D-D has been shown not only to be a special marker of fibrinolytic system but also to be an indicator for monitoring inflammation and severe infection [6]. Levels of D-D are also closely related to the inflammatory response and may reflect the effects of infection on coagulation in infectious diseases. Some studies have reported that the levels of D-D are closely related to the severity of CAP [18].

Previous studies [19, 20] have reported that levels of D-D in children with MPP were higher than those in healthy children and were also higher in severe cases of MPP compared with mild cases, especially in

severe MPP with extrapulmonary complications [20]. However, few studies have reported on D-D levels in RMPP or on the monitoring of D-D levels after treatment. Consistent with previous reports, we found that levels of D-D in the GMPP and RMPP groups were all above the normal range, and that levels in the RMPP group were significantly higher than those in the GMPP group. Elevated D-D levels may imply that hypercoagulability is prevalent in children with MPP and is more severe in children with RMPP, and that vascular endothelial cell injury caused by an excessive inflammatory response may be involved in the mechanism of lung injury in RMPP. In a previous study, the levels of D-D were found to have decreased significantly after a period of treatment, and the final levels after treatment were higher in a group with severe pneumonia compared with a group having mild pneumonia [20]. Our study found 1 week of treatment was associated with a significant decrease in D-D level, although levels remained abnormal in most cases, indicative of a prolonged state of high coagulation and endothelial injury in RMPP.

LDH and CRP, which are elevated in several pulmonary diseases, have previously been associated with RMPP and can be used as early predictors of the condition [10, 11, 21]. In the present study, D-D level was positively correlated with WBC, CRP, and ESR. The increased levels of these analytes may represent a stronger systemic inflammatory response in RMPP, while the positive correlation of D-D with these inflammatory indicators means that D-D level may be used to evaluate the inflammatory response and jointly evaluate the severity of the disease. The average age of patients in the RMPP group was 5.7 years, which was older than that in the GMPP group and was consistent with previous studies [8], indicating that older children have a stronger immune inflammatory response that can more readily lead to refractory conditions. A previous study showed that CRP $\geq$ 50 mg/L and LDH $\geq$ 480 U/L were associated with longer time to radiographic clearance [22], while the percentage of neutrophils, CRP, and LDH were found in ROC curve analysis to be useful in differentiating patients with RMPP from those with GMPP [8]. In the present study, we found that D-D levels and LDH were positively correlated, and after comparing the predictive value of WBC, CRP, ESR, LDH, and D-D for RMPP by AUC analysis, we found that D-D was better able to predict RMPP compared with the other indexes and may therefore be used in the early detection of refractory cases.

Regarding complications, previous studies have reported that D-D level was positively correlated with extra-pulmonary complications in pediatric patients with MPP [20]; however, extensive research on D-D level and complications has not been reported to date. In a previous study, a higher level of D-D was associated with more extensive and serious thrombosis [8]. Our results show that elevated levels of D-D had a good predictive ability for pleural effusion and liver injury and that the incidence of pleural effusion increased with increasing D-D level. However, there was no significant difference between the moderately elevated group and the severely elevated group. The incidence of atelectasis was only significantly different between the normal D-D level group and the mildly elevated group and the incidence of rash and myocardial damage did not differ significantly between the four groups, which suggested that severely elevated D-D might not be associated with more complications. However, further research including case studies is needed to verify this hypothesis and thus avoid overtreatment.

At present, controversy remains over the use of anticoagulant treatment in pneumonia [23]. Further research on D-D and pneumonia is therefore needed to clarify the relationship between dynamic changes in D-D and the course and progression of disease, thus allowing the appropriate anticoagulant treatment strategy to be selected.

Conclusion

Children with RMPP were shown to have significantly increased serum levels of D-D, indicating that severe hypercoagulability and vascular endothelial injury with prolonged duration may exist in this patient population. Increased serum levels of D-D may therefore represent an early prediction index for RMPP, pleural effusion, and liver injury, thus facilitating the early diagnosis of RMPP, early intervention in hypercoagulability, and improved microcirculation therapy.

Abbreviations

D-D
d-dimer; MPP:mycoplasma pneumoniae pneumonia; RMPP:refractory MPP; GMPP:genera MPP; WBC:white blood cell; ESR:sedimentation; LDH:lactate dehydrogenase; CRP:C-reactive protein; AUC:area under the receiver operating characteristic curve; ROC:Receiver operating characteristic; CAP:community-acquired pneumonia; PPD:protein purified derivative; ECG:electrocardiogram

Declarations

Ackowlegements

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Authors' contributions

XH wrote the main manuscript text; XH and DL collected and analyzed clinical data; XH, FL and DZ contributed to study design and project implementation as well as critically reviewed and edited the manuscript. XH and YZ performed statistical analyses for the study. HT was principal investigators for the study and critically revised the manuscript.All authors reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All the information supporting our conclusions are included in the manuscript. There are no datasets related to this case report.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Children's Hospital of Nanjing Medical University. Individual informed consent was waived by the ethics committee listed above because this study used currently existing sample collected during the course of routine medical care and did not pose any additional risks to the patients. All patient data were anonymized prior to the analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

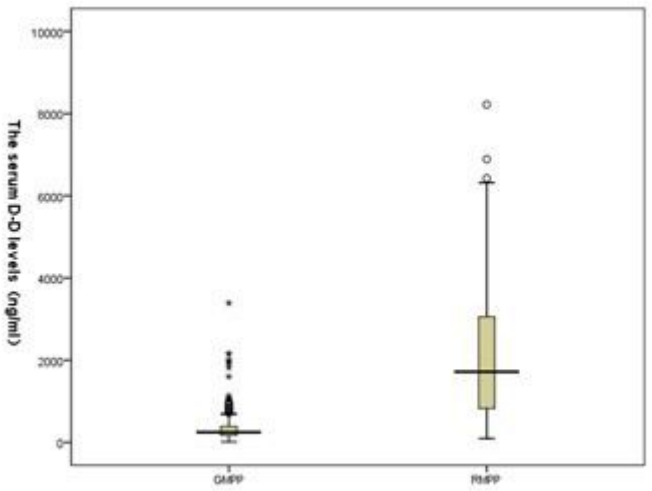

Figure 1

Comparison of D-D level between the RMPP and GMPP gourps.

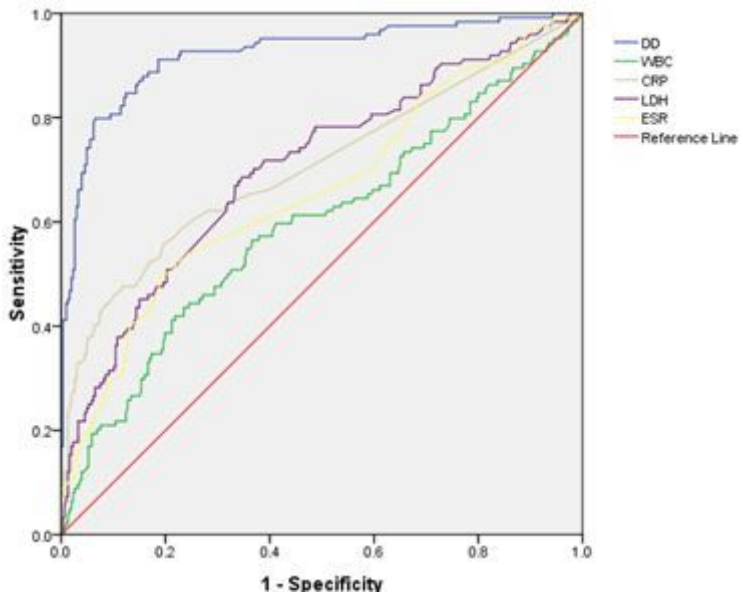

Figure 2

ROC curve of WBC, CRP, LDH, ESR and D-D level for predicting RMPP

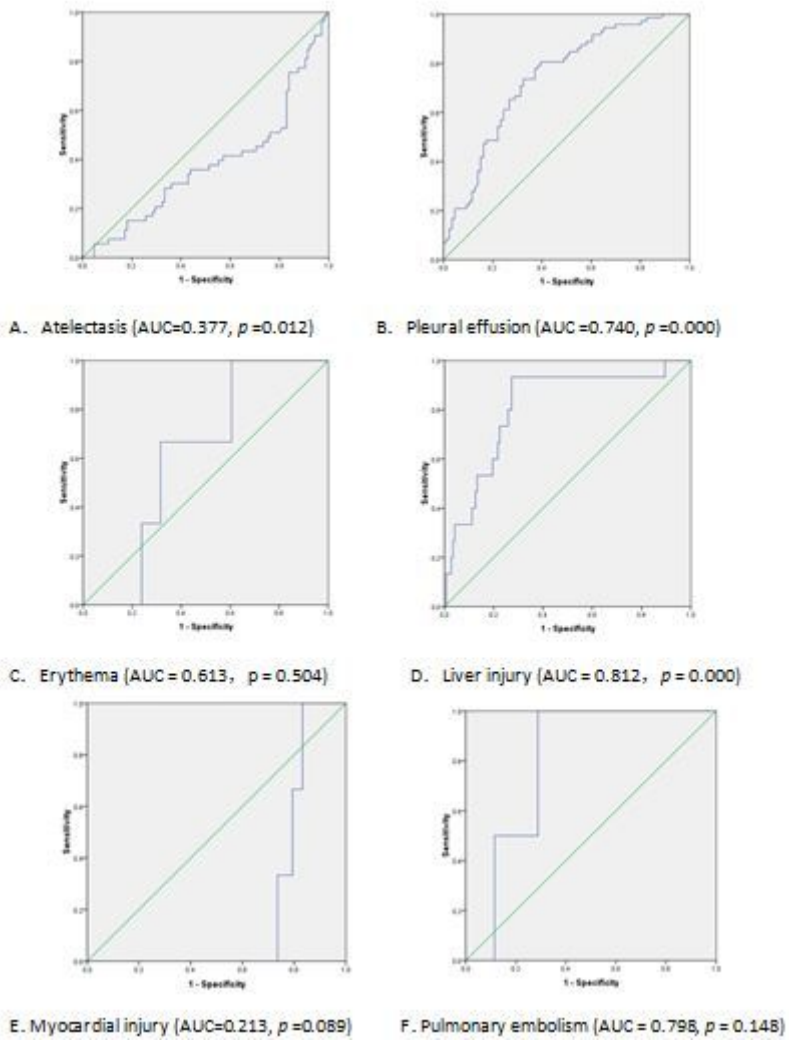

Figure 3

ROC curve analysis of D - D for predicting the complications atelectasis (A) pleural effusion (B), erythema (C), liver injury (D), myocardial injury (E), and pulmonary embolism (F)

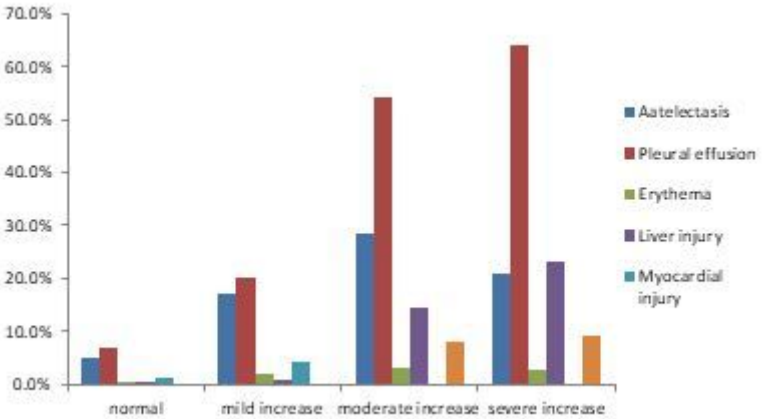

Figure 4

Relationship between degree of D-D elevation and prevalence of complications

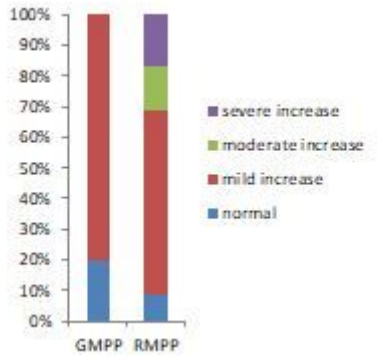

Figure 5

Serum D-D level after 1 week of treatment

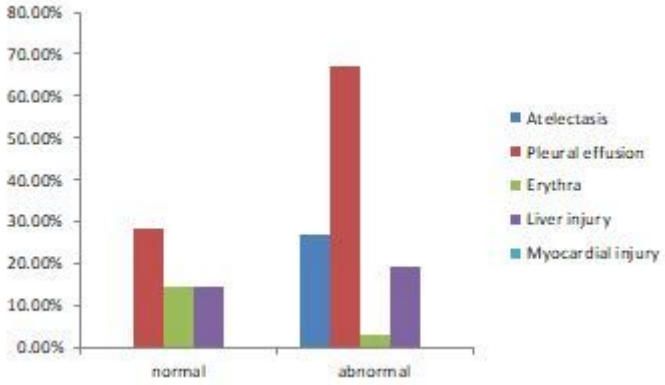

Figure 6

Complications associated with normal and abnormal serum D-D levels after treatment for 1 week