Thrombocytosis and thrombocytopenia are markers of poor outcome in pediatric patients with community-acquired pneumonia

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Abstract

Abstract Background: This study aimed to investigate the prevalence of thrombocytopenia and thrombocytosis in hospitalized pediatric patients with community-acquired pneumonia (CAP), and determine whether thrombocytopenia and thrombocytosis are associated with patient outcome. Methods: A total of 9,372 consecutive patients, who were 1-168 months old, diagnosed with CAP and admitted in the Children's Hospital of Soochow University, were enrolled in the present retrospective observational study. Their clinical and laboratory data were collected. According to the platelet count on admission, these patients were divided into three groups: thrombocytopenia, normal platelet count, and thrombocytosis groups. The clinical characteristics and etiologic pathogens were compared among these groups. The multivariate logistic regression model was applied to identify risk factors for severe CAP, length of hospitalization ≥10 days and respiratory complications. The correlations between platelet count and clinical features were determined by Spearman's correlation. Results: Thrombocytosis and thrombocytopenia were found in 3,376 (36.0%) and 43 (0.5%) patients, respectively. Normal platelet count was observed in 5,953 (63.5%) patients. Thrombocytopenia was an independent risk factor of severe CAP (OR, 6.206; 95% CI, 2.209-17.436; P=0.001), while thrombocytosis was associated with length of hospitalization of ≥10 days (OR, 1.315; 95% CI, 1.177-1.470; P<0.001). In addition, thrombocytosis was associated with respiratory complications (OR, 1.658; 95% CI, 1.171-2.346; P=0.004). Platelet count (median 350.0 [IQR 270.2-447.0] × 109/L) was positively correlated with length of hospitalization (median 7.0 [IQR 6.0-9.0] days) (r = 0.101, P<0.001), but negatively correlated with age (median 12.0 [IQR 3.0-36.0] months) (r = -0.401, P<0.001) and C-reactive protein (median 2.0 [IQR 0.3-10.7] mg/dl) (r = -0.191, P<0.001). Conclusion: Thrombocytosis is highly prevalent, while thrombocytopenia has low prevalence in pediatric CAP patients. Both thrombocytosis and thrombocytopenia are associated with clinical outcomes in pediatric CAP patients.

Background

Platelet plays a fundamental role in the development of thrombosis and hemostasis. Increasing evidences have recognized that platelet is an important component in the immune response to infection [1-3]. In the process of infection and inflammation, thrombocytes may secrete various substances, such as cytokines, pro-coagulants, oxidants and antimicrobial peptides, which are involved in beneficial or harmful activities [4-6]. Therefore, an abnormal platelet count may be a critical biomarker for assessing disease severity.

The impact of thrombocytopenia or thrombocytosis on the outcomes of pediatric patients with community-acquired pneumonia (CAP) has been scarcely studied, although previous studies have confirmed that thrombocytopenia and/or thrombocytosis were associated with mortality in adult CAP patients [7-10]. Thrombocytosis is actually more common in childhood [11]. Two studies on pediatric CAP revealed that thrombocytosis is frequently observed in severe bacterial infections, and that thrombocytosis is associated with more severe and protracted diseases [12, 13]. However, the sample

size of these studies was limited. Furthermore, the differences in clinical and etiologic characteristics between patients with thrombocytosis and normal platelet count have not been clarified.

To the best of our knowledge, few large-scale studies have investigated the impact of abnormal plate count on the outcomes of pediatric patients with CAP. The present study evaluates the prevalence of thrombocytopenia and thrombocytosis in pediatric CAP patients, and determines whether thrombocytopenia and thrombocytosis is associated with clinical outcomes.

Methods

In the present retrospective observational study, consecutively admitted pediatric patients, who were diagnosed with CAP at the Children's Hospital of Soochow University (a tertiary teaching hospital), Suzhou, China, between January 2012 and December 2017, were included.

The inclusion criteria were as follows: (1) patients within 1-168 months old; (2) patients with new-onset pulmonary infiltrate on chest X-ray at admission, which may be accompanied by other signs consistent with pneumonia, such as fever, cough, or auscultatory findings.

The exclusion criteria were as follows: (1) patients who received immunosuppressive therapy; (2) patients with primary hematological disorders (immune thrombocytopenia, leukemia, myelodysplastic syndrome, etc.); (3) patients with active tuberculosis; (4) patients hospitalized within the preceding 21 days; (5) patients who experienced trauma or surgery within the preceding two weeks; (6) patients with chronic gastrointestinal disorders; (7) patients with haemolytic anaemias.

The present study was approved by the Ethics Committee of the Children's Hospital of Soochow University. A signed consent was obtained from the patient's guardian.

Data collection and microbiologic evaluation

Clinical and laboratory data were collected. The collected variables included the patient's demographical information, basic diseases, clinical signs and symptoms, comorbidity, laboratory and chest X-ray findings. The laboratory results were obtained within six hours after admission. The criteria for the microbiologic diagnosis have been previously described [14, 15].

Study definitions

Thrombocytopenia was defined as a platelet count of <100,000/L, while thrombocytosis was defined as a platelet count of > 400,000/L. CAP was defined the appearance of a new pulmonary infiltrate on chest X-ray at admission, in combination with fever, cough, or auscultatory findings [16]. Severe CAP was determined when the World Health Organization criteria for severe pneumonia was met [17]. Pleural effusion or empyema and lung abscess were considered as respiratory complications in the present study [16]. Fever was defined as an axillary temperature exceeding 38.0°C. A diagnosis of tachypnea was made when the respiratory rate was higher than the WHO classification categorized by age: 0-2 months

old: >60 breaths/min; 2-12 months old: >50 breaths/min; 1-5 years old: >40 breaths/min; >5 years old: >20 breaths/min [16].

The cut-off for length of hospitalization was 10 days, considering the sample size and the percentage of children hospitalized for more or less than 10 days. The overall median length of hospitalization was 7.0 days (range: 3.0-56.0 days; interquartile range [IQR]: 6.0-9.0). The percentage of patients with a length of hospitalization of ≥10 days was 19.34% (*n*=1,813).

Statistical analysis

Statistical analyses were performed using SPSS 21.0 software. Data normality was tested using the Kolmogorov-Smirnov test. Continuous variables with non-normal distribution were expressed as median and IQR (25^{th}-75^{th} percentile). Non-normally distributed continuous variables were analyzed using the Mann-Whitney U-test or kruskal-Wallis test. Categorical variables were compared using chi-squared test or Fisher's exact test. The correlations between variables were determined by spearman correlation. Variables with a univariate *P*-value ≤0.1 were included in the multivariate logistic regression models. *P*<0.05 was considered statistically significant.

Results

During the study period, a total of 9,372 consecutive patients were enrolled in the present study. The study flowchart was presented in Figure 1. Thrombocytosis was found in 3,376 (36.0%) patients, while thrombocytopenia was found in 43 (0.5%) patients. Normal platelet count was observed in 5,953 (63.5%) patients. The patient characteristics are presented in Table 1.

Patients with thrombocytopenia were more likely to have severe CAP (*P*=0.009), neuromuscular disorders (*P*=0.004), and lower peripheral leukocyte counts (*P*=0.009), when compared to patients with normal platelet counts. Patients with thrombocytosis were younger (*P*<0.001), had longer length of hospitalization (*P*<0.001), more frequently had a length of hospitalization of ≥10 days (*P*<0.001), and more commonly had severe CAP (*P*<0.001), cough (*P*=0.024), wheezing (*P*<0.001), and a higher peripheral leukocyte count (*P*<0.001), while these patients less commonly to had asthma (*P*<0.001), fever (*P*<0.001), and lower C-reactive protein (*P*<0.001).

An etiologic diagnosis was identified in 4,186 (44.7%) patients (Table 2). There was no significant difference in pathogens between patients with thrombocytopenia and patients with normal platelet count. Parainfluenza virus (*P*=0.004), respiratory syncytial virus (*P*<0.001), human bocavirus (*P*<0.001), and rhinovirus (*P*=0.004) were more frequently identified in patients with thrombocytosis, when compared to patients with normal platelet counts. Adenovirus (*P*<0.001) and Mycoplasma pneumoniae (*P*<0.001) were less frequently identified in patients with thrombocytosis, when compared to patients with normal platelet counts.

Factors associated with severe CAP, length of hospitalization ≥10 days and respiratory complications were analyzed (Table 3). Age, bronchopulmonary dysplasia, congenital heart disease, neuromuscular disorder, wheezing, fever, gastrointestinal symptoms, tachypnea and C-reactive protein were independent predictors of severe CAP. When platelet count was included as a categorical variable, the association between thrombocytopenia and severe CAP was confirmed (OR, 6.206; 95% CI, 2.209-17.436; *P*=0.001). Asthma, bronchopulmonary dysplasia, congenital heart disease, neuromuscular disorder, wheezing, fever, gastrointestinal symptoms, tachypnea and C-reactive protein were independent predictors of length of hospitalization ≥10 days. When platelet count was taken as a categorical variable, the association between thrombocytosis and length of hospitalization ≥10 days was observed (OR, 1.315; 95% CI, 1.177-1.470; *P*<0.001). Age, asthma, wheezing, fever and C-reactive protein were independent predictors of respiratory complications. Platelet count, as a categorical variable, was associated with respiratory complication (OR, 1.658; 95% CI, 1.171-2.346; *P*=0.004).

The correlation between platelet count at admission and clinical characteristics and outcomes were analyzed. Platelet count (median 350.0 [IQR 270.2-447.0] × 10^9/L) was positively correlated with the length of hospitalization (median 7.0 [IQR 6.0-9.0] days) (r = 0.101, P<0.001), but was negatively correlated with age (median 12.0 [IQR 3.0-36.0] months) (r = -0.401, P<0.001) and C-reactive protein (median 2.0 [IQR 0.3-10.7] mg/dl) (r = -0.191, P<0.001).

None of the patients in the present study developed hemorrhagic or thromboembolic complications, 9,357 (99.8%) patients recovered after treatment, and 15 (0.2%) patients died of respiratory failure.

Discussion

The present study evaluated the prevalence of thrombocytopenia and thrombocytosis in hospitalized pediatric patients with CAP, and the contributions of these two to clinical outcomes. These present results revealed that thrombocytopenia occurred in a considerable pediatric population, and that both were correlated with poorer outcome.

Thrombocytosis was identified in approximately one-third of the studied pediatric CAP patients, which is consistent with the previously reported percentage (9-48%) of thrombocytosis in patients with respiratory tract infections [18-20]. In addition, it was found that platelet count was negatively correlated with age, which could be explained by the fact that bone marrow precursor cells in young children are more sensitive to external stimuli, such as infection and inflammation [11].

The prevalence of thrombocytopenia was merely 0.5% in the present study, indicating that thrombocytopenia is not common in pediatric patients with CAP. In a previous study, the researchers found that patients with thrombocytopenia tended to be older [8]. However, the exact underlying mechanism remains unclear and warrants further investigation.

Thrombocytosis is associated with multiple pathogens. It was observed that parainfluenza virus, respiratory syncytial virus, human bocavirus and rhinovirus are more frequently identified in patients with

thrombocytosis, when compared to patients with normal platelet counts. However, it has not been fully elucidated why infection could promote thrombocytosis. Similarly, the incidence of respiratory syncytial virus and rhinovirus was also reported to be greater in the thrombocytosis group, when compared to the normal group, in a previous study [21]. However, contrary to these previous findings, the thrombocytosis caused by parainfluenza virus and human bocavirus infection have not been described at present. The investigators speculate that specific viral agents causing CAP may induce the production of interleukin-6, and lead to thrombocytosis. The increased release of interleukin-6 was reported during parainfluenza virus and human bocavirus infection *in vitro* and mice experiments [22, 23]. Interleukin-6 induces and increases expression of hepatic thrombopoietin mRNA and consequential thrombocytosis. Thus, the inflammation-associated platelet production depends on interleukin-6 [24]. Adenovirus and Mycoplasma pneumoniae were less frequently identified in patients with thrombocytosis, when compared to patients with normal platelet counts. This could be partly explained by the fact that adenovirus and Mycoplasma pneumoniae infection predominated in older children who less frequently developed thrombocytosis [25].

In the present study, CAP patients with asthma were associated with a lower incidence of respiratory complication. This finding is consistent with that from previous studies [26]. Furthermore, the severity of CAP is largely correlated to comorbid conditions, such as cardiopulmonary and immune status [16]. In agreement with these previous findings, the investigators also found that the conditions of bronchopulmonary dysplasia, congenital heart disease and neuromuscular disorder were independent predictors of severe CAP in the present study.

Thrombocytopenia in adult severe CAP has already been studied [9, 27, 28]. However, few studies have explored the impact of thrombocytopenia on the severity of CAP in pediatric patients. In the present study, it was demonstrated that thrombocytopenia is an independent predictor of severe CAP in pediatric patients.

These present findings revealed that thrombocytosis was independently associated with length of hospitalization ≥10 days and respiratory complications, which is consistent with two previous studies in adult patients, although the exact mechanism for the association of thrombocytosis with respiratory complication remains unclear [7, 8]. As expected, it was found that platelet counts at admission were positively correlated with length of hospitalization. In addition, platelet count at admission was negatively correlated with C-reactive protein, indicating that lower platelet count might be associated with a stronger inflammatory response in patients with CAP. This was consistent with a previous study that revealed that sepsis shock patients were more likely to have lower platelet counts [29].

There are several limitations associated with the present study. First, the changes in platelet count were not dynamically monitored, and merely the values on admission were included. According to previous studies, the serial measurements of platelet counts during hospitalization could differentiate between a transient event and sustained derangements in platelet count [30-32]. Second, the present findings derived from a single medical center might not applicable to patients in other areas. Hence, a multi-center

study is necessary in the future. Third, related cytokines were not concurrently analyzed, which limited our understanding of the underlying mechanism.

Conclusions

Thrombocytosis is highly prevalent in pediatric CAP patients, while thrombocytopenia less frequently occurs. Parainfluenza virus, respiratory syncytial virus, human bocavirus and rhinovirus are more frequently identified in CAP patients with thrombocytosis. Both thrombocytosis and thrombocytopenia may serve as useful prognostic markers for pediatric CAP.

Abbreviations

CAP: community-acquired pneumonia

IQR: interquartile ranges

Declarations

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

HMS and SXL and ZRC and WJ were responsible for the study design, literature search and manuscript drafting. HMS and SXL were responsible for the data collection and statistical analysis. HMS and SXL and WJ were mainly responsible for the data interpretation. CLH and YQW and CHZ were responsible for the study concept and critical revision. All authors contributed to the discussion, writing and reviewing the manuscript and all authors have approved the final manuscript.

Ethics approval and consent to participate

The study protocols were approved by the Ethics Committee of the Children's Hospital of Soochow University. Written informed consent was obtained from their legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no conflicts of interest.

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Tables

Table 1. Clinical characteristics of the study population

Parameters	Thrombocytopenia (n=43)	Normal Platelet Count (n=5953)	Thrombocytosis (n=3376)	*P*
General characteristics				
Age, median (IQR), months	31.0 (12.0-53.0)	19.0 (6.0-45.0)	5.0 (2.0-13.0)[b]	<0.001
Male, n (%)	28 (65.1)	3662 (61.5)	2156 (63.9)	0.074
Length of hospitalization, median (IQR), days	7.0 (6.0-10.0)	7.0 (6.0-9.0)	7.0 (6.0-9.0)[b]	<0.001
Length of hospitalization ≥ 10 days, n (%)	11 (25.6)	1030 (17.3)	772 (22.9)[b]	<0.001
Antibiotic therapy during the preceding 2 weeks, n (%)	42 (97.7)	5911 (99.3)	3345 (99.1)	0.160
Duration of symptoms before admission, median (IQR), days	7.0 (5.0-10.0)	7.0 (5.0-12.0)	6.0 (4.0-13.0)	0.424
Severe CAP	6 (14.0)[a]	247 (4.1)	204 (6.0)[b]	<0.001
Underlying medical conditions				
Asthma, n (%)	1 (2.3)	397 (6.7)	88 (2.6)[b]	<0.001
Bronchopulmonary dysplasia, n (%)	0 (0.0)	104 (1.7)	81 (2.4)	0.087
Congenital heart disease, n (%)	0 (0.0)	111 (1.9)	74 (2.2)	0.457
Neuromuscular disorder, n (%)	3 (7.0)[a]	43 (0.7)	18 (0.5)	0.003
Respiratory complication	1 (2.3)	146 (2.5)	59 (1.7)	0.061
Pleural effusion, n (%)	1 (2.3)	142 (2.4)	59 (1.7)	0.094
Pulmonary abscess, n (%)	0 (0.0)	9 (0.2)	0 (0.0)	0.070
Clinical symptoms and signs				
Cough, n (%)	40 (93.0)	5794 (97.3)	3311 (98.1)[b]	0.011
Fever, n (%)	28 (65.1)	3637 (61.1)	1300 (38.5)[b]	<0.001
Wheezing, n (%)	12 (27.9)	2189 (36.8)	1639 (48.5)[b]	<0.001

Tachypnea, n (%)	8 (18.6)	621 (10.4)	393 (11.6)	0.053
Gastrointestinal symptoms, n (%)	2 (4.7)	687 (11.5)	424 (12.6)	0.117
Laboratory findings				
Peripheral leukocyte count, median (IQR), x 10^9/L	6.6 (4.8-9.4)[a]	8.3 (6.2-11.0)	11.2 (8.7-14.7)[b]	<0.001
C-reactive protein, median (IQR), mg/dl	3.8 (0.6-10.9)	3.0 (0.5-11.8)	1.0 (0.2-7.0)[b]	<0.001

CAP = community-acquired pneumonia

Gastrointestinal symptoms include diarrhea and vomiting

[a] Differences between the thrombocytopenia and normal platelet count group

[b] Differences between the thrombocytosis and normal platelet count group

Table 2. Etiologic diagnosis of the study population

	Thrombocytopenia (n=43)	Normal Platelet Count (n=5953)	Thrombocytosis (n=3376)	*P*
Virus, n (%)				
Adenovirus	0 (0.0)	57 (1.0)	9 (0.3)[b]	<0.001
Influenza virus	0 (0.0)	65 (1.1)	25 (0.7)	0.217
Parainfluenza virus	0 (0.0)	223 (3.7)	168 (5.0)[b]	0.008
Respiratory syncytial virus	4 (9.3)	580 (9.7)	547 (16.2)[b]	<0.001
Human metapneumovirus	1 (2.3)	17 (0.3)	13 (0.4)	0.085
Human bocavirus	2 (4.7)	324 (5.4)	248 (7.3)[b]	0.001
Rhinovirus	4 (9.3)	594 (10.0)	402 (11.9)[b]	0.014
Mycoplasma pneumoniae	4 (9.3)	1032 (17.3)	425 (12.6)[b]	<0.001
Bacteria, n (%)	0 (0)	70 (1.2)	48 (1.4)	0.615
Hemophilus parainfluenzae	0	1	0	
Haemophilus influenzae	0	9	5	
Streptococcus pneumoniae	0	42	30	
Human staphylococcus	0	1	3	
Enterobacter aerogenes	0	2	0	
Staphylococcus epidermidis	0	4	1	
Staphylococcus aureus	0	2	3	
Pseudomonas aeruginosa	0	6	2	
Klebsiella pneumoniae	0	1	1	
Escherichia coli	0	1	3	
Enterococcus	0	1	0	

[b] Differences between the thrombocytosis and normal platelet count group

Table 3. Risk factors for severe CAP, length of hospitalization ≥10 days, and respiratory complication

Variables	Severe CAP		Length of hospitalization ≥ 10 days		Respiratory complication	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	0.976 (0.969-0.984)	< 0.001	...	...	1.027 (1.023-1.030)	< 0.001
Asthma	0.479 (0.215-1.067)	0.07	0.580 (0.435-0.772)	< 0.001	0.176 (0.054-0.572)	0.004
Bronchopulmonary dysplasia	3.801 (2.453-5.891)	< 0.001	4.131 (3.053-5.590)	< 0.001	...	...
Congenital heart disease	1.926 (1.156-3.208)	0.01	2.033 (1.481-2.789)	< 0.001	0.162 (0.014-1.953)	0.152
Neuromuscular disorder	6.773 (3.274-14.010)	< 0.001	2.212 (1.290-3.791)	0.004	...	...
Wheezing	1.224 (1.057-1.419)	0.01	1.143 (1.036-1.262))	0.008	0.431 (0.273-0.678)	< 0.001
Fever	0.745 (0.588-0.944)	0.02	0.798 (0.711-0.895)	< 0.001	1.122 (1.014-1.242)	0.027
Gastrointestinal symptoms	1.718 (1.296-2.276)	< 0.001	1.357 (1.159-1.587)	< 0.001	...	...
Tachypnea	10.323 (8.359-12.749)	< 0.001	1.498 (1.281-1.752)	< 0.001	1.606 (0.955-2.702)	0.074
C-reactive protein	1.008 (1.004-1.011)	< 0.001	1.007 (1.004-1.009)	< 0.001	1.013 (1.010-1.016)	< 0.001
Platelets						
Normal range	1	Reference	1	Reference	1	Reference
Thrombocytosis	1.096 (0.884-1.358)	0.405	1.315 (1.177-1.470)	< 0.001	1.658 (1.171-2.346)	0.004
Thrombocytopenia	6.206 (2.209-17.436)	0.001	1.681 (0.827-3.419)	1.151	1.093 (0.142-8.390)	0.932

CAP = community-acquired pneumonia

Gastrointestinal symptoms include diarrhea and vomiting

Figures

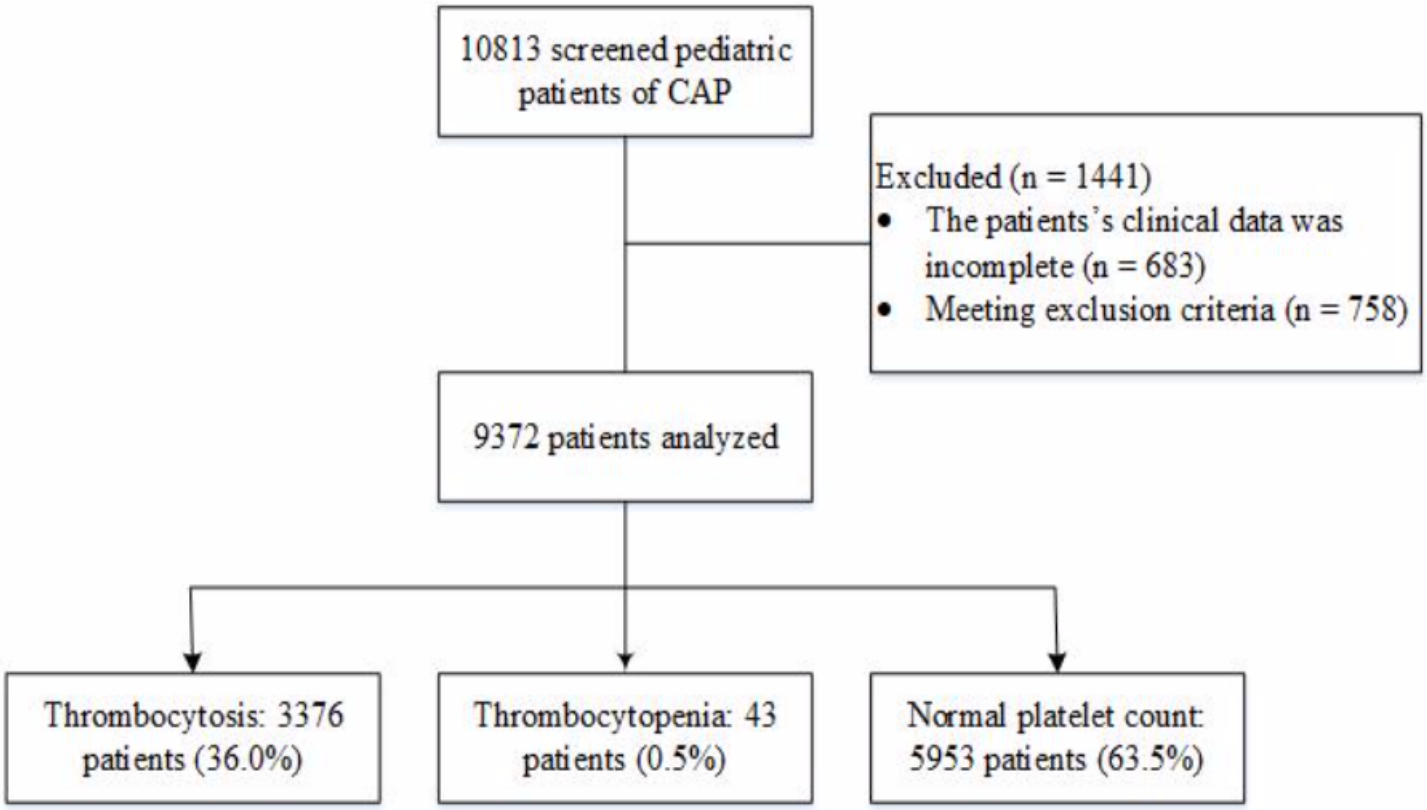

Figure 1

Flowchart of the selected population CAP: community-acquired pneumonia