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The Investigation on the Role of Spleen Tyrosine Kinase in Hospitalized Pneumonia Patients: A Potential Biomarker for Pneumonia Process

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Abbreviations: WBC: White Blood Cell Count; CRP: C Reactive Protein; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BUN: Blood Urea Nitrogen; LDH: Lactate Dehydrogenase; APTT: Activated Partial Thromboplastin Time; A. baumannii, Acinetobacter baumannii; K. pneumoniae, Klebsiella pneumoniae; P. aeruginosa, Pseudomonas aeruginosa; M. tuberculosis, Mycobacterium tuberculosis; H. influenzae, Haemophilus influenzae; S. maltophilia, Stenotrophomonas maltophilia; S. marcescens, Serratia marcescens; B. cepacia, Burkholderia cepacian; S. aureus, Staphylococcus aureus; HSV-1, Herpes simplex virus-1; CMV, Cytomegalovirus; Flu-A, Influenza A; Flu-B, Influenza B; EV, Enterovirus; PIV-3, Human Parainfluenza III; RHV, Rhinovirus; CoVOC43, Coronavirus OC43; CoVNL63, Coronavirus NL63

ABSTRACT

Background: The clinical importance of pneumonia relates to infected pathogens as well as pathologic changes in the immune system. Spleen tyrosine kinase (SYK) is a critical immune signaling molecule and therapeutic target and plays an important role in inflammatory response mediated by macrophage, neutrophils, or complement.

Methods: To understand the potential role of SKY in the pneumonia process, we collected the clinical data, investigated the SYK levels and etiological spectrum by ELISA, sputum culture or/and real-time PCR, and analyzed the correlation of SYK with clinical symptoms, infected pathogens, or blood laboratory tests in a total of 257 hospitalized adult pneumonia patients.

Results: The median age of the 257 patients with detectable fever in 54 (23.18%) patients on admission was 62 (IQR, 48-72) years. The median value of CURB-65 indexes was 1 (IQR,0-2) in these patients. Sputum culture or PCR showed that pathogenic bacteria or viruses were detected in 23 (10.55%) out of 218 patients and 32 (15.84%) out of 202 patients, respectively. ELISA results showed that the levels of SYK were significantly much higher in sera of pneumonia patients on admission than in that of the healthy population. But no statistical differences were observed between patients with fever and patients without fever on admission, and between patients with different CURB-65 index, as well as between patients with viral or bacterial infection although the levels presented higher in patients with each infection than healthy humans. The SYK presented significantly higher levels in patients with abnormal AST (>40U/L), ALT (>50U/L), eosinophils (>0.5×109/L), basophils (>0.1×109/L) or LDH (>250U/L) than patients with normal AST, ALT, eosinophils, basophils or LDH. Whereas the levels have no statistically significant difference between patients with normal or abnormal WBC, Monocytes, Neutrophils, Lymphocytes, CRP, BUN, Creatinine, D-Dimer, or APTT. The correlation analysis showed that the levels of SKY presented a significant correlation with levels of AST, ALT, eosinophils, basophils, LDH, or APTT.

Conclusion: The results suggested that SYK contributes the extrapulmonary injury in pneumonia patients and is a potential measure or biomarker for clinical assessment of pneumonia through its potential contribution to immune regulation in the pathogenesis of pneumonia.

Keywords: Pneumonia; Spleen Tyrosine Kinase; Infection; Immune Regulation

Introduction

Pneumonia is defined as infectious inflammation of alveoli, distal airways, or/and pulmonary interstitium, usually caused by viruses or/and bacteria [1]. It is the fourth most common cause of death globally, responsible for 3.1 million deaths annually, and is the deadliest communicable disease [2]. The clinical importance of pneumonia relates to infected pathogens as well as pathologic changes in the immune system. The etiology of pneumonia is often different between countries and changes over time. In many countries, even atypical pathogens are one of the main pathogens of community-acquired pneumonia [3]. Whereas, immune responses, including the infiltration of inflammatory cells and the release of cytokines, are critical for clearance of invader and a return to homeostasis but often are also responsible for disease complications and tissue injury in pneumonia [4]. Previous studies have suggested that the pulmonary innate immune response determines the outcome of inflammation during pneumonia [5].

Spleen Tyrosine Kinase (SYK), a critical immune signaling molecule and the therapeutic target are widely expressed in hematopoietic cells including neutrophils, monocytes, and macrophages [6]. SYK participating in the cascade transmission is necessary for the activation of physiological signals and the process of immune cell proliferation and differentiation. It also mediates many other unexpected biological functions, including cell adhesion, innate immune recognition, osteoclast maturation, platelet activation, and vascular development. Previous studies have shown that SYK played an important role in inflammatory response mediated by macrophage, neutrophils, or complement, and SYK inhibitors displayed active roles in the treatment of allergies, autoimmune diseases, and acute lung injury although its therapeutic mechanism was unclear yet [7,8]. In addition, a recent study indicated that SYK-dependent STAT1 activation played a critical role in innate antiviral immunity [9]. Another recent study indicates that gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice [10]. However, to be our knowledge, it is unclear whether or not SYK is related to pneumonia so far.

In order to observe the role of SYK in the pneumonia, in this study, we investigated the SYK levels, and analyzed the correlation of SYK levels with the clinical symptoms, infected pathogens, or blood laboratory tests spectrum of a total of 257 hospitalized adult patients with community acquired pneumonia.

Materials and Methods

Patients

A total of 257 hospitalized patients with pneumonia were enrolled in this study. These patients included 142 hospitalizing from January to September 2018, and 115 hospitalizing from September to November 2020 in the Second Affiliated Hospital, Anhui Medical University in Anhui province. All patients were clinician diagnosed as community acquired pneumonia with imaging signs and were excluded from COVID-19. Relevant information was collected demographic, clinical, and laboratory data recorded in the electronic medical record of the patient. Throat swab and serum were sampled from these patients on the day or second day after hospitalization. Throat swab specimen was maintained in a viral-transport medium. The samples were frozen at -80°C for etiological or SYK detection. Among this, of which 218 patients were conducted sputum culture for identifying potentially bacterial infection, 202 patients were conducted by PCR detection on throat swab specimens for identifying potentially viral infection. Moreover, 186 patients were conducted sera SYK assay by ELISA.

RNA/DNA Extraction and Real-Time PCR Detection for Identification of Pathogens

The RNA/DNA was extracted from 200μL throat-swab by an automatic nucleic acid extractor using an automatic nucleic acid extraction kit. RNA/DNA was obtained in a 50-μL volume for each sample according to the introduction of the kit. Specific real-time Polymerase-Chain-Reaction (PCR) or reverse-transcriptase PCR (RT-PCR) assays were used for the identification of 14 pathogens including two kinds of DNA virus (HSV-1 and CMV) and 12 kinds of RNA virus (Flu-A, Flu-B, EV, PIV-1, PIV-2, PIV-3, RHV, CoVOC43, CoVNL63, CoV229E, HMPV, and RSV). The PCR detections use a fluorescently labeled TaqMan probe to enable continuous monitoring of amplicon formation. The primers and probes of the above pathogens were as previously published [11-13]. To increase the detection efficiency, multiple detections with two sets of primer and probe were conducted in a vial for each sample. The assays were performed in a total volume of 25 μL system, with 5μL RNA/DNA, 15 mmol/L each primer, and 10 mmol/L each probe. The thermal cycling conditions used for the assays were as follows: for RNA targets, reverse transcription at 45°C for 10 minutes, 1 cycle at 95°C for 10 minutes, then 40 cycles at 95°C for 15 seconds and at 60°C 45 seconds; For DNA, 1 cycle at 95°C for 3 minutes, then 40 cycles at 95°C for 3 seconds and at 60°C 20 seconds.

Enzyme-Linked Immunosorbent Assay (ELISA) to Detect the Content of SYK in Patients' Setum

The sera SYK levels of 186 patients and 10 healthy population were detected through a human Spleen Tyrosine Kinase (SYK) ELISA Kit according to the manufacturer's instructions. In brief, 100μL of 5-fold diluted serum was added into a 96-well microplate with pre-coated antibodies against SYK. The 96-well microplate was incubated at 4°C overnight. After 3 times washing, a biotin-

labeled antibody against SYK, HRP-labeled second antibody, and Tetramethylbenzidine (TMB) stabilized substrate was respectively added into the 96-well microplate after necessary incubation and washing. The absorbance of sample wells was measured immediately by a microplate reader under 450nm after provided stop solution was added.

Statistical Analysis

The quantitative SYK tests were compared by unpaired t-test. The Pearson's correlation analysis was conducted between levels of SYK and blood laboratory tests. Differences were considered significant at P < .05 with a two-tailed test. All analyses were performed using Instat software (Vision 8.0; GraphPad Prism).

Results

Demographic and Clinical Characteristics of Pneumonia Patients

As shown in Table 1, the median age of these patients was 62 (IQR, 48-72) years. There were 118 (45.91%) females in these pneumonia patients. The median duration of hospitalization was 10 (IQR, 7-14) days. On admission, 54(23.18%) patients had a detectable fever. The median value of CURB-65 indexes was 1 (IQR,0-2) in 257 patients.

Table 1: Clinical characteristics of Pneumonia patients.

Variable	Pneumonia patients (n=257)
Age, median (interquartile range)	62 (48-72)
Female (%)	118 (45.91)
Day of duration, median (interquartile range)	10 (7-14)*
Fever (%)	54 (23.18)**
CURB-65, median (interquartile range)	1(0-2)

Note: * Total 232 out of 257 patients had available information on duration.** Total 233 out of 257 patients had available information about fever record.

Clinical Laboratory Results of Pneumonia Patients

We analyzed the data of clinical laboratory tests associated with infection or inflammation (Table 2). The WBC included 12.5% (<4×10^9/L, 7 of 216) and 21.3% (>10×10^9/L, 46 of 216) abnormal levels were 6.7 (range, 1.79~67.7) ×10^9/L in mean. The monocytes and neutrophils including 3.6% (>1.3×10^9/L, 9 of 250) and 34.52% (>6.3×10^9/L 87 of 252) abnormal levels were 0.4 (range, 0~12.6) ×10^9/L and 4.14 (range, 0.14~303) ×10^9/L in mean, respectively. The lymphocytes including 15.94% (>4 ×10^9/L 40 of 251) were 1.72 (range, 0.13~445) ×10^9/L in mean. Eosinophils and Basophils including 26.69% (> 0.5×10^9/L, 67 of 251) and 15.94% (> 0.1×10^9/L, 40 of 251) abnormal levels respectively were 0.16 (range, 0.00~3.90) and 0.02 (range, 0.00~5.00) ×10^9/L in mean, respectively. The CRP including 82.23% (>4mg/L, 162 of 197) abnormal levels was 1.28 (range, 0.5~312.7) mg/L in mean. The ALT and AST including 15.54% (>50U/L, 39 of 251) and 18.73% (>40U/L, 47 of 251) abnormal levels were 25.21(range, 5~2738) U/L and 23.31(range, 5~3921) U/L in mean, respectively. The BUN and creatinine including 34.24% (>7.1 mmol/L, 88 of 257) and 5.6% (>133μmol/L, 15of 252) abnormal levels were 5.01 (range, 0.6~806) mmol/L and 66.29 (range 1.7~1120) μmol/L in mean, respectively. The LDH including 17.95% (>250U/L, 42of 234) was 178.3 (range, 6.9~2138) U/L in mean. The APTT and D-Dimer including 7.86% (>43s, 18 of 229) and 68.89% (>0.5mg/L 155 of 225) abnormal levels respectively were 36.51s (range, 10.2~114s) and 0.29 (range 0.01~408) mg/L respectively.

Table 2: Laboratory Results of Pneumonia Patients.

Variable (Normal Range)	Values
WBC (4-10×10^9/L), mean (range)	6.70 (1.79-67.7)
<4	27/216(12.5%)
>10	46/216(21.3%)
Monocytes (0.002-1.3 ×10^9/L), mean (range)	0.40(0.00-12.6)
>1.3	9/250(3.6%)
Neutrophils (1.8-6.3×10^9/L), mean (range)	4.14 (0.14-303)
>6.3	87/252(34.52%)
Lymphocytes (0.8-4×10^9/L), mean (range)	1.72(0.13-445)
>4	40/251(15.94%)
Eosinophils (0.05-0.5×10^9/L), mean (range)	0.16(0.00-3.90)
>0.5	67/251(26.69%)
Basophils (0〜0.1×10^9/L), mean (range)	0.02 (0.00-5.00)
>0.1	40/251(15.94%)
CRP (0-4mg/L), mean (range)	1.28(0.5-312.7)
>4	162/197(82.23%)
>60	74/197(37.56%)
ALT(9-50U/L), mean (range)	25.21(5-2738)
>50	39/251(15.54%)
AST (15-40 U/L), mean (range)	23.31(5-3921)
>40	47/251(18.73%)
BUN (3.2-7.1mmol/L), mean (range)	5.01(0.6-806)
>7.1	88/257 (34.24%)
Creatinine (44-133μmol/L), mean (range)	66.29(1.7-1120)
>133	15/252 (5.6%)
LDH (120-250U/L), mean (range)	178.3(6.9-2138)
>250	42/234(17.95%)
APTT (31-43s), mean (range)	36.51(10.2-114)
>43	18/229(7.86%)
D-Dimer (0-0.5mg/L), mean (range)	0.29(0.01-408)
>0.5	155/225(68.89%)

Pathogen Identification in Respiratory Samples of

Pneumonia Patients

Table 3: Laboratory identification results of pathogenic microorganisms.

Variable	Positive sample numbers (%)
Sputum culture (n=218)	23 (10.55)
Candida	5(2.3)
A. baumannii	2(0.92)
K. pneumoniae	2(0.92)
P. aeruginosa	5(2.3)
M. tuberculosis	3(1.38)
H. influenzae	1(0.46)
S. maltophilia	1(0.46)
Co-infection	4(1.84)
K. pneumoniae, S. marcescens, B. cepacia	1(0.46)
A. baumannii, Candida	1(0.46)
P. aeruginosa, Candida, K. pneumoniae	1(0.46)
S. aureus, Candida	1(0.46)
PCR detection (n=202)	32 (15.84)
HSV-1	15(7.43)
CMV	1(0.50)
FLU-A	2(1)
FLU-B	1(0.50)
EV	1(0.50)
PIV-3	1(0.50)
RHV	2(1)
CoVOC43	3(1.49)
CoVNL63	3(1.49)
Co-infection	3(1.5)
HSV-1, CMV	1(0.50)
CMV, RHV	1(0.50)
CMV, PIV-3	1(0.50)
Bacterial and viral co-infection (n= 202)	3(1.5)
Candida, FLU-B	1(0.50)
Candida, HCV-1	2(1)

Among those pneumonia patients, sputum culture and real-time PCR of throat swab were conducted to identify pathogenic bacteria or virus pathogens in 218 and 202 patients, respectively. As shown in Table 3, pathogenic bacteria or viruses were detected in sputum of 23 (10.55%) patients and swabs of 32 (15.84%) patients, respectively. These bacteria included *Candida* [n=5 (2.3%)], *A. baumannii* [n=2(0.92%)], *K. pneumoniae* [n=2 (0.92%)], *P. aeruginosa* [n=5 (2.3%)] and co-infection with *K. pneumoniae* & *S. marcescens* & *B. cepacia*, *A. baumannii* & *Candida* or *P. aeruginosa* & *Candida* & *K. pneumoniae* or *S. aureus* & *Candida* [n=1 (0.46%)]. Viruses included HSV-1 [n=15（7.43%）], CMV [n=1 (0.5%)], Flu-A virus [n=2 (1%)], Flu-B virus [n=1 (0.5%)], EV [n=1 (0.5%)], PIV-3 [n=1 (0.5%)], RHV [n=2 (1%)], CoVOC43 [n=3 (1.49%)], CoVNL63 [n=3 (1.49%)] and co-infection with HSV-1 & CMV [n=1 (0.5%)], CMV & RHV [n=1 (0.5%)] or CMV & PIV-3 [n=1 (0.5%)]. In addition, combined with the results of sputum culture, there were one patients (0.50%) with coinfection FLUB and Candida, and two patients (1%) with coinfection of HSV-1 and Candida.

SKY Levels in Pneumonia Patients

The ELISA results showed that the SYK presented significantly much higher Optical Density (OD) in sera of pneumonia patients on admission than healthy humans (Figure 1A), suggesting that SYK level was significantly much higher in sera of pneumonia patients than healthy humans. However, no statistical differences were observed between the SYK OD of patients with fever and patients without fever on admission, males and females, less than 10 days hospitalized duration and more than 10 days hospitalized duration, and as well as between patients with different CURB-65 index (Figures 1B-1E). Additionally, if the infection of these patients was classified into viral, bacterial, co-infection, or unknown pathogen, the OD of SYK had no statistically significant difference between patients with viral, bacterial, co-infection, or unknown pathogen although the levels presented significantly much higher in pneumonia patients with each infection than healthy humans (Figure 1F).

The Correlation Between SYK Levels and Blood Laboratory Tests of Pneumonia Patients

As shown in Figure 3, the SYK respectively presented significantly higher levels in patients with abnormal AST (>40U/L), ALT (>50U/L), or LDH (>250U/L) than patients with normal these biomarkers while the SYK respectively presented significantly lower levels in patients with abnormal eosinophils (>0.5×10^9/L) or basophils (>0.1×10^9/L) than patients with normal eosinophils or basophils. Whereas the levels have no significant difference between patient with normal or abnormal WBC, monocytes, neutrophils, lymphocytes, CRP, BUN, creatinine, D-Dimer or APTT. Among the 14 biomarkers, however, both patients with normal levels and patients with abnormal levels presented significantly remarkable higher SYK levels than healthy humans. The correlation analysis showed that the levels of SKY presented a significant correlation with levels of AST, ALT, eosinophils, basophils or LDH. In addition, a significant correlation was observed between SYK levels and APTT levels.

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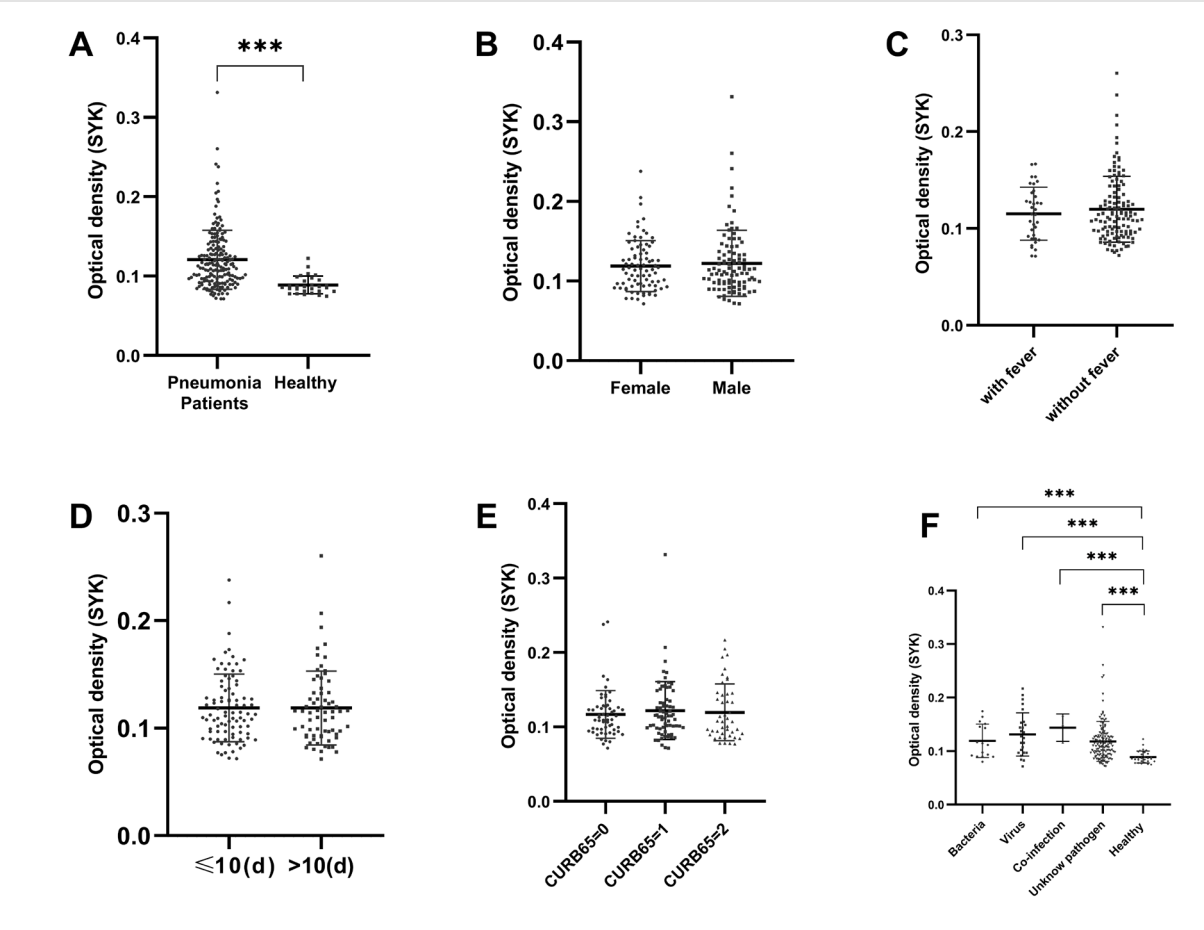

Figure 1: The SYK levels in pneumonia patients.

A. The SYK optical density (OD) values in sera of pneumonia patients and healthy humans.

B. The SYK OD values in male patients or female patients.

C. The SYK OD values in pneumonia patients with or without detectable fever.

D. The SYK OD value in pneumonia patients with hospitalization longer than 10 days and less than 10 days.

E. The SYK OD values in pneumonia patients with CURB-6 index 0, 1 or 2.

F. The SYK OD values in pneumonia patients with detectable bacteria, viruses, coinfection, or unknown pathogen.

Statistical p values were obtained by two-tailed t-test. ***p<0.001.

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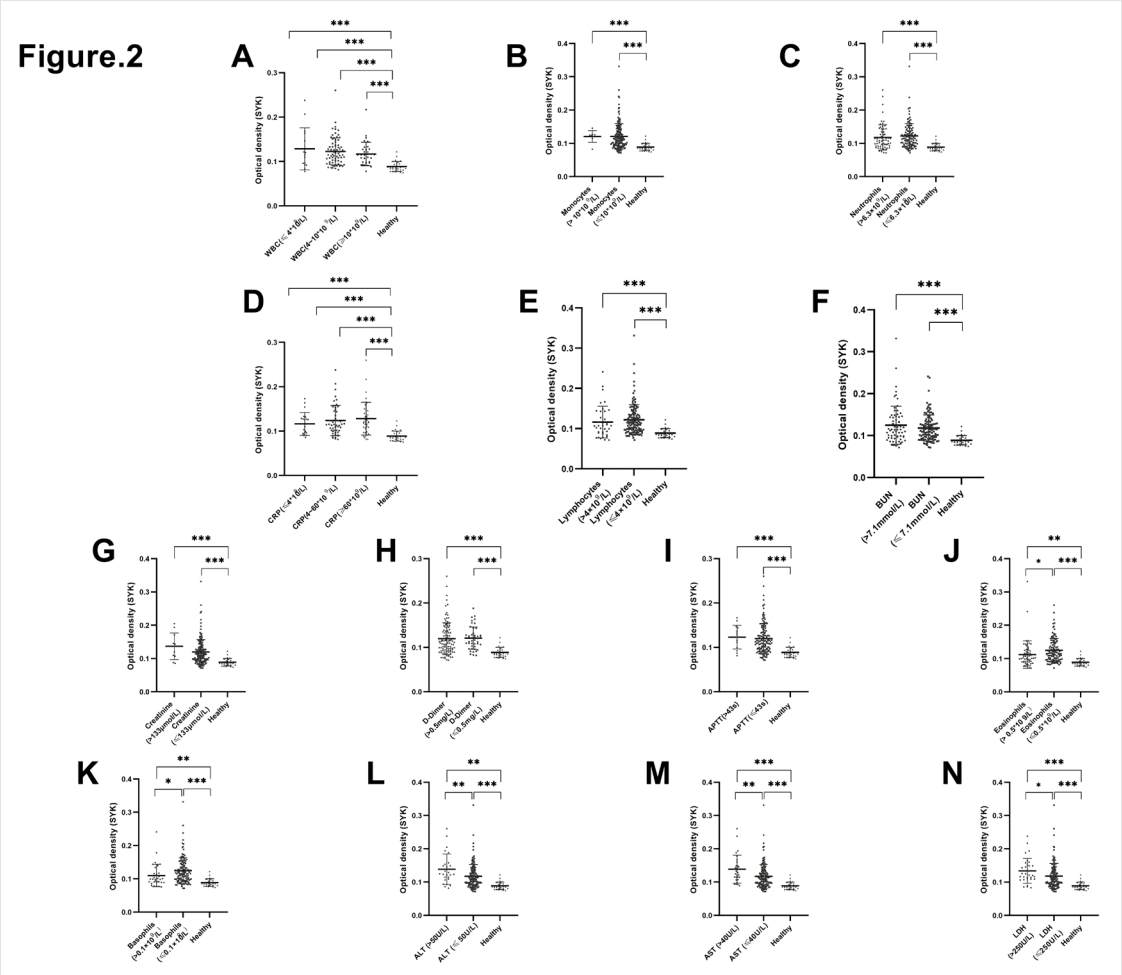

Figure 2: The Comparative analysis of SYK levels between patients with variable blood laboratory tests and healthy humans. SKY OD values in patients with normal or abnormal

A. WBC

B. Monocytes

C. Neutrophils

D. CRP

E. Lymphocytes

F. BUN

G. Creatinine

H. D-Dimer

I. APTT

J. AST

K. ALT

L. Eosinophils

M. Basophils

N. LDH

The SYK OD values from healthy humans were listed in each panel. Statistical p values were obtained by two-tailed unpaired t-test. *p<0.05, **p<0.01, ***p<0.001.

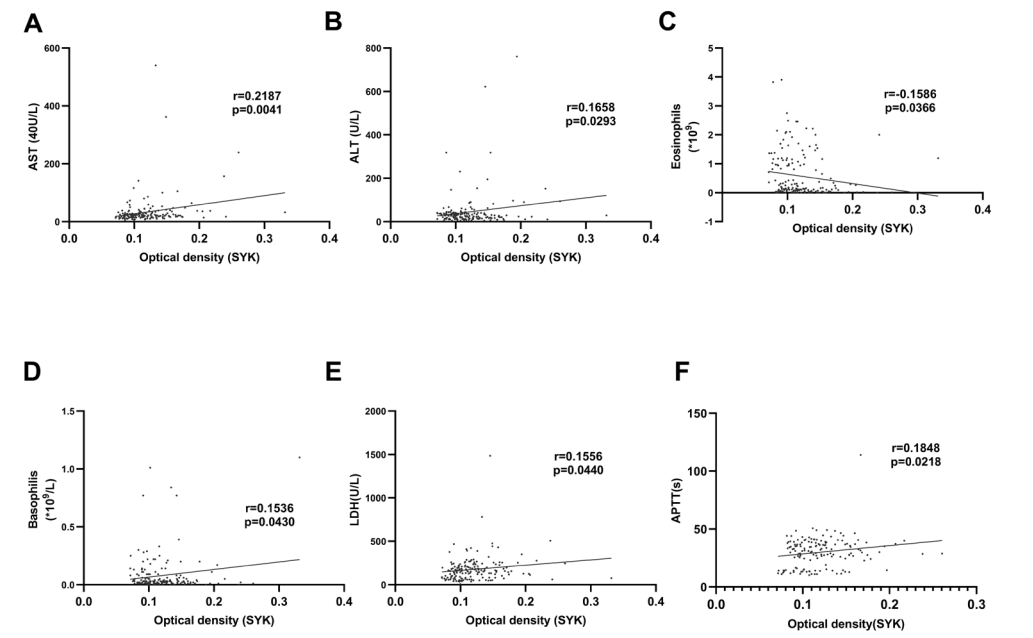

Figure 3: The correlation between SKY levels and levels of

A. AST

B. ALT

C. eosinophils

D. basophils

E. LDH

F. APTT

Statistical p values were obtained by Pearson correlation test.

Discussion

The severity of pneumonia is determined by 2 processes, immune resistance and tissue resilience which owes to host pathways [14]. The finding of novel molecular or biomarkers associated with the pathways would help understand the pathogenesis of pneumonia or the development of potential targets for the treatment of pneumonia. In this study, we report a descriptive analysis on SYK levels and its correlation with clinical symptom, infected pathogens and blood laboratory tests in 257 hospitalized pneumonia patients. The results showed that SYK levels were remarkably higher in pneumonia patients than healthy humans, and presented a significant correlation with AST, ALT, eosinophils, basophils, LDH or APTT although no statistically significant difference was observed between SYK levels of patients with fever symptom, or with different CURB-65 index which is a severity score to predict mortality secondary to community acquired pneumonia.

Previous studies showed that ischemic hepatitis or liver damage was caused frequently in severe respiratory tract infections by bacterium (e.g. mycoplasma pneumoniae, streptococcus pneumoniae) or virus (e.g. influenza virus, SARS-CoV-2) [15-18], and indicated that elevated transaminase levels in patients with severe respiratory viral infections on the intensive care unit may not just indicate collateral damage due to an immunological process but may more commonly be an indicator of myocardial decompensation [15]. Additionally, studies showed that SYK inhibition prevented tissue damage after ischemia-reperfusion or remote lung tissue damage after mesenteric ischemia-reperfusion injury [19,20]. In this study, our results showed that SYK level presented remarkably higher levels in patients with increased AST or ALT and had a significantly positive correlation with AST or ALT level. Liver injury indicated by increasing AST or ALT is frequent in severe pneumonias [21]. Whereas SYK signaling pathway has been suggested to contribute to the pathogenesis of liver injury [22-24]. Hence, our data suggest that SYK may play a role on extrapulmonary injury in pneumonia patients and it would be valuable to perform further study on the mechanism of the damage.

Our results showed that SYK levels presented lower levels in patients with abnormally increased eosinophils or basophils than patients with normal eosinophils or basophils, whereas higher

levels in patients with abnormally increased LDH than patients with normal LDH. Both eosinophils and basophils contribute significantly to Th2 immunity such as allergic inflammation and Chronic Obstructive Pulmonary Disease (COPD). Previous studies have evidenced that eosinophils and basophils were present in all anatomical compartments of COPD-affected lungs and increased significantly in very severe COPD [25]. LDH is one of the potential parameters presented in the literature as a possible indicator of lung damage and is a predictor of worse outcomes in several pulmonary disorders including community-acquired pneumonia [26,27]. In addition, to be different from the above biomarkers, SYK levels also presented a significant correlation with APTT level although SYK level has no significant difference between patients with normal APTT and patients with abnormally increased APTT. APTT is a measure used in patients to detect coagulation or thrombosis generally. Prolonged APTT was frequently seen and may affect the disease progress in pneumonia caused by viral infections (e.g. influenza, SARS-CoV-2, hantavirus) [28,29]. Taken together, SYK is a promising indicator or biomarker for clinical use in the assessment of the pneumonia.

In addition, our data also suggested that SYK may contribute to immune regulation in the pathogenesis of pneumonia. SYK is a key protein related to many immune-related cells and factors [7]. Recent studies showed that inhibition of the SYK-CARD9 (Caspase recruitment domain family member 9) pathway is an ideal therapeutic target for severe influenza pneumonia, and SYK/JNK signaling pathway may play a vital role in the inflammasome activation and modulate host immune responses against S. pneumoniae [30,31]. Our data showed that, no matter which infection with virus or bacteria, the SYK levels of the pneumonia patients were significantly higher than those of healthy humans and were correlated with eosinophils level negatively but positively correlated with APTT level. Eosinophils are increasingly understood to be positioned centrally within mammalian immune and inflammatory networks, possessing receptors for an array of inflammatory mediators and capable of producing numerous pro-inflammatory and homeostatic mediators, and play a major role in the modulation of allergic inflammation and the repair of damaged tissues in diseases characterized by eosinophilic infiltration [32]. Hence, our results indicated that increased SYK may result in damage to those eosinophilic functions in associated diseases. Whereas APTT is a measurement of the intrinsic pathway of coagulation disorders that may be associated with the infection including both bacterial and nonbacterial [33]. For example, coagulopathic characteristics, such as increased D-dimer concentration and von Willebrand factor activity, are common complications in influenza infection, triggering life-threatening cytokine storm and vascular thrombosis [34]. Consequently, increased SYK level may alert a risk factor for triggering complications of coagulation disorders in pneumonia patients.

In summary, we described the SYK levels and the correlation of SYK with the clinical symptom, infected pathogens, or blood laboratory tests in 257 hospitalized adult patients. The results indicated that SYK may join in the immune regulation in the pneumonia process and contributes to the extrapulmonary injury in pneumonia patients. It would have potentially been valuable for further study on SKY as a measure or biomarker for the clinical assessment of the pneumonia process. The study also has the limitation that we cannot exclude the influence of chronic medical conditions on the correlation of SKY with pneumonia.

Declaration

Ethics Statement

All the methods were performed in accordance with the relevant guidelines and regulations of the Chinese Center for Disease Control and Prevention and the Second Affiliated Hospital, Anhui Medical University. All the procedures were performed in accordance with the Declaration of Helsinki. This retrospective data analysis has been approved by the Ethics Research Committee of the national institute for viral disease control and prevention, the Chinese Center for Disease Control and Prevention and the Second Affiliated Hospital, Anhui Medical University. The need for patient consent was considered waived by the Ethics Research Committee of the national institute for viral disease control and prevention, the Chinese Center for Disease Control and Prevention and the Second Affiliated Hospital, Anhui Medical University because of the retrospective nature of the study.

Consent for Publication

Not applicable. Availability of data and materials. All datasets used and/or analyzed during the current study are available from the corresponding/first author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contribution

RGao and DZhao designed the study. YGao and RGao performed data analysis and wrote the report. YGao, LL and ZZhang did lab experiments. DZhao, PLiu, JZhang, CMa, RLi and XZhao sampled throat swab of patients and gathered clinical data. All authors contributed to the review and revision of the manuscript and have read and approved the final version.

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Disclosure

The contents of this article are solely the responsibility of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention in China or other organizations.

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