Early predictors of lung necrosis severity in children with community-acquired necrotizing pneumonia

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Abstract

Abstract Objective: To analyze baseline clinical and laboratory characteristics and explore the possible predictors of lung necrosis severity in children with community-acquired necrotizing pneumonia (NP). Methodology: This retrospective observational study was performed in a tertiary referral center. A total of 104 patients aged <15 years with community-acquired pneumonia and radiologically confirmed NP were included. Patients were classified into the mild, moderate, or massive necrosis groups. Results: Among them, 29, 41, and 34 patients had mild, moderate, and massive necrosis, respectively. Moreover, 34.6% of the patients were admitted to the pediatric intensive care unit. Massive necrosis was more likely to occur during winter (p<0.05) and was associated with more severe clinical outcomes, such as longer duration of fever, longer hospitalization, increased mortality, and a higher risk of subsequent surgical intervention (p<0.05). Multivariate analysis demonstrated that the following were independent risk factors for massive necrosis: C-reactive protein (CRP) [?] 122 mg/L (adjusted odds ratio [aOR], 8.780; 95% confidence interval [CI], 3.320–21.089; p=0.003), serum albumin [?] 30.8 g/L (aOR, 11.608; 95% CI, 5.147–27.058; p=0.001), and immunoglobulin M (IgM) [?] 95.7 mg/dL (aOR, 7.152; 95% CI, 2.240–17.692; p=0.021). Receiver operating characteristic analysis demonstrated that these variables showed good diagnostic performance for differentiating patients with massive necrosis from all patients with NP. Conclusion: NP is a potentially severe complication of pediatric community-acquired pneumonia. Different severities of lung necrosis can lead to different clinical outcomes. CRP, serum albumin, and IgM levels are independent predictors of the degree of lung necrosis.

INTRODUCTION

Community-acquired pneumonia (CAP) remains the leading cause of morbidity and mortality worldwide in children aged between 28 days and 5 years\textsuperscript{1}. Most children with CAP recover; however, some develop pulmonary or systemic complications. Among them, necrotizing pneumonia (NP) is a rare but severe complication and is observed in up to 7% of all cases of pediatric CAP\textsuperscript{2}. NP is characterized by extensive destruction and liquefaction of lung tissue. Over the last 2 decades, an increasing number of cases of NP in previously healthy children have been reported, with special emphasis on clinical, laboratory, pathologic, and radiologic aspects\textsuperscript{3}.

The pathophysiology of NP remains unclear; however, pneumococci and \textit{Staphylococcus aureus} are the most common pathogens associated with NP. Masters et al. reported that approximately 197 bacterial and fungal pathogens were detected in previous cases of NP\textsuperscript{2}. On the other hand, viruses are rarely the sole cause of NP; however, virus-induced epithelial damage leads to an increased risk of a bacterial-activated necrotizing process\textsuperscript{4}. 
The clinical outcomes of NP range from mild to life-threatening depending on the lung necrosis severity. Patients with mild or moderate lung necrosis may be adequately treated with prolonged antibiotic regimens and hospitalization. In contrast, massive lung necrosis may require surgical intervention and mechanical ventilation and is associated with an increased risk of life-threatening late complications and death \(^5\)\(^-\)\(^8\). Therefore, it requires early recognition and treatment.

In this study, we described the clinical characteristics, etiology, and outcomes of children diagnosed with community-acquired NP. We analyzed baseline clinical characteristics and laboratory data of children with community-acquired NP to identify possible predictors of lung necrosis severity.

**METHODS**

**Study design**

This retrospective observational study was conducted at a tertiary referral center in Zhejiang, China. We conducted a computer database search to identify patients younger than 15 years who were diagnosed with CAP and radiologically confirmed NP from March 2011 to March 2021. A total of 104 patients were enrolled in the study. Medical records, including demographic characteristics, clinical signs and symptoms, laboratory and radiologic findings, diagnoses, treatments, and outcomes, were collected and stored in an electronic database.

This study was approved by the ethics committee of our hospital. Written informed consent was obtained from the guardian of each patient.

**Study population**

Patients who fulfilled the diagnostic criteria for CAP and NP were included in the study. CAP was diagnosed when acute respiratory infection symptoms, such as fever, cough, or wheezing, and infiltrates were noted on physical examination and chest imaging, respectively \(^9\). NP was diagnosed based on the presence of lung cavitation or radiolucency within the area of consolidation on serial plain films or computed tomography (CT) images. Patients with the following characteristics were excluded from the study: 1) other causes of pulmonary cavities, such as secondarily infected congenital lung malformations and traumatic pseudocysts; 2) nosocomial NP or cavitary pneumonia due to mycobacteria and fungi; and 3) incomplete medical data.

**Etiologic diagnosis**

Microbiologic data were reviewed to identify potential pathogens. A causative pathogen was identified when any of the following criteria were met: 1) a microorganism was isolated from the blood or pleural fluid; 2) a microorganism was identified from a sputum sample with >25 neutrophils and <10 squamous epithelial cells per lower-power field, collected within 24 h of admission, and with compatible Gram stain findings (MicroScan Walkaway 96; Beckman Coulter, Brea, CA, USA); 3) *Mycoplasma pneumonia* was isolated from nasopharyngeal secretions and demonstrated positive immunoglobulin M (IgM) or polymerase chain reaction (PCR) test results; or 4) respiratory virus antigens were identified using the D³ Ultra 8 DFA Respiratory Virus Screening & Identification Kit (Quidel, San Diego, CA, USA) or multiplex PCR (SureX 13 Respiratory Pathogen Multiplex Kit; Cat. No. 1 060 144, Ningbo Health Gene Technology, Ningbo, China).

**Radiologic assessment of lung destruction**

Chest radiographs and CT images were independently reviewed by two radiologists (Bo Chen and Wei Chen) who were blinded to the patients’ clinical information. A final decision was reached by consensus if the reviewers disagreed regarding their readings. Serial chest radiographs and CT images were analyzed to determine whether patients presented with NP on admission or during the course of their hospitalization. Lung necrosis severity was determined by analyzing the relative ratio between the necrotic radiolucent space and total involved lobe area; this was calculated using ImageJ version 1.48 (National Institute of Health, Bethesda, MD, USA). Necrotic areas with ratios <30\%, 30\%–70\%, and >70\% were categorized as mild (N1), moderate (N2), and massive (N3) necrosis, respectively (Fig 1); accordingly, all patients were classified into the mild, moderate, and massive necrosis groups.
Statistical analysis

Data analysis was performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as either mean ± standard deviation or median with interquartile range, whereas categorical variables are expressed as frequencies with percentages. The Kolmogorov–Smirnov test was used to evaluate the normality of data distribution. The chi-squared test was used to assess group differences between the categorical variables, whereas one-way analysis of variance was utilized for continuous variables. White blood cell (WBC) and C-reactive protein (CRP) levels were analyzed after logarithmic transformation. Based on the results of univariate analysis, multivariate ordinal logistic regression analysis was performed to identify independent factors associated with the severity of lung necrosis. Receiver operating characteristic (ROC) curves were constructed to predict massive necrosis, and area under the curve (AUC) values were used to evaluate the effectiveness of the model in distinguishing massive necrosis from other severities of lung necrosis. Statistical significance was set at \( p < 0.05 \).

RESULTS

Comparison of the clinical characteristics among the three groups

A total of 104 patients with community-acquired NP were enrolled in this study. During the study period, NP was found in 7.5% (104/1386) of children with severe CAP and in 0.1% (104/103795) of all children with CAP. Among the 104 patients, 29 developed mild necrosis, 41 developed moderate necrosis, and 34 developed massive necrosis. Moreover, 34.6% (36/104) of the patients were admitted to the pediatric intensive care unit.

No significant difference was observed in age, sex, body mass index (BMI), fever prior to admission, and dyspnea symptoms among the three groups. In patients with massive necrosis, it was more likely that the condition developed during winter \( (p < 0.05) \). Furthermore, these patients had fewer underlying diseases than patients with mild and moderate necrosis, but the difference was not significant among the groups \( (p = 0.31) \). Additionally, patients with massive necrosis exhibited more severe clinical outcomes, such as longer duration of fever, longer hospital stay, increased mortality, and a higher risk of subsequent surgical intervention \( (p < 0.05) \); Table 1).

Comparison of the microbiologic data among the three groups

A summary of the microbiological data of our population is presented in Table 2. Eighteen pathogens were identified in 14/29 patients (48.3%) in the mild necrosis group, 22 pathogens were identified in 18/41 (43.9%) patients in the moderate necrosis group, and 34 pathogens were identified in 27/34 (79.4%) patients in the massive necrosis group. A significant difference was observed in the detection rate of pathogens among the three groups, with the massive necrosis group exhibiting the highest detection rate \( (p = 0.005) \). The most commonly detected pathogen in the massive necrosis group was \( S. aureus \) (n=10), followed by \( Pseudomonas aeruginosa \) (n=5). \( S. aureus \) (10 [37.0%] vs. 4 [12.5 %], \( p = 0.041 \)) and \( influenza A \) (4 [14.8%] vs. 0 [0%], \( p = 0.039 \)) were significantly more common in the massive necrosis group than in the mild and moderate necrosis groups. In contrast, \( M. pneumoniae \) (4 [14.8%] vs. 9 [50%], \( p = 0.017 \)) and \( Streptococcus pneumoniae \) (4 [14.8%] vs. 11 [78.6%], \( p = 0.000 \)) was significantly less common in the massive necrosis group than in the mild and moderate necrosis groups. However, no significant difference was observed in the detection rate of \( Streptococcus pneumoniae \) among the groups \( (p = 0.222) \).

Univariate analysis of laboratory characteristics associated with the severity of lung necrosis

The univariate analysis demonstrated significant differences in the median levels of WBC, CRP, lactate dehydrogenase (LDH), serum sodium, serum albumin, and IgM \( (p < 0.001; p < 0.001; p < 0.001; p < 0.001; p < 0.01, \) respectively) among the three groups. In particular, the massive necrosis group had higher levels of WBC, CRP, and LDH but lower levels of serum albumin, serum sodium, and IgM than the mild or moderate necrosis group \( (p < 0.05) \). Necrosis severity was inversely related to the median levels of IgA and IgG, but the relationship was not significant among the three groups \( (p = 0.394, p = 0.621) \); Table
3). No significant difference was noted in the level of cytokines, including interleukin (IL)-2, IL-4, IL-6, and IL-10; tumor necrosis factor-α, and interferon-γ among the groups.

**Multivariate analysis and ROC curves**

A multivariate ordinal logistic regression model was utilized to determine the independent predictive factors for lung necrosis severity. Based on the results of the univariate analysis, seven variables were included in the multivariate model. Among them, three were significant, namely, CRP ($p = 0.013$), serum albumin ($p = 0.011$), and IgM ($p = 0.019$) levels. We merged the data of the mild and moderate necrosis groups to better determine the clinical applicability of these indicators in screening patients with severe pulmonary necrosis. Continuous variables were converted to categorical variables and analyzed for sensitivity, specificity, and Youden’s index, and ROC curves and AUCs were calculated. The seven variables were analyzed again, and the three previously mentioned variables remained significant, indicating that they were independent risk factors for massive necrosis (Table 4). The ROC curve analysis showed that CRP, serum albumin, and IgM were useful for differentiating cases with massive necrosis among all patients with NP (Fig 2).

**DISCUSSION**

NP is a potentially severe complication of CAP characterized by necrosis of consolidated lung tissue, which can develop despite the administration of appropriate antibiotics. Different degrees of pulmonary necrosis can lead to different clinical outcomes. Most children with NP have favorable long-term outcomes; however, severe morbidity and prolonged hospitalization can inevitably and significantly increase medical risks and costs. To the best of our knowledge, this was the first study to evaluate the correlation between clinical and laboratory characteristics and lung necrosis severity in children with community-acquired NP, as well as the first study that attempted to identify the predictive factors in the early recognition of massive lung necrosis in children.

In this retrospective study, most patients (93.4%) were previously healthy. The increased importance of pathogen virulence compared with that of host susceptibility and the role of the host immune response were hypothesized to contribute to necrosis. To date, the underlying disease mechanisms for NP are poorly understood; however, multiple factors have been identified, including host susceptibility, bacterial virulence factors, and viral-bacterial interactions.

In our study, a significant difference was observed in the clinical outcomes among the study groups; particularly, more severe lung necrosis was associated with a more severe clinical course and poorer clinical outcomes. Our study found no significant differences in age, sex, BMI, and underlying diseases among the groups; however, severe lung necrosis more commonly developed during winter. We speculated that viral infection was more likely to occur in winter and that preceding viral illness (especially influenza) might be an important risk factor for NP in childhood.

*Influenza A* was also an important risk factor in our study. We detected influenza A in four children; among them, two needed long-term extracorporeal membrane oxygenation and one died. Severe or very severe pneumonia has been associated with bacterial and viral co-infection in some important reports. This co-pathogenesis is characterized by complex interactions between co-infecting pathogens and the host, which lead to disruption of physical barriers, dysregulation of immune responses, and delays in the return to homeostasis. The synergistic effects of co-infection also increase the mortality rate compared with infections with solitary viral or bacterial pathogens. This correlated with our findings, which demonstrated that co-infections were significantly more likely in patients with massive lung necrosis than in patients with mild and moderate necrosis.

Etiological analysis suggested that the composition of the pathogens among the three groups was very different. *S. aureus* and *P. aeruginosa*, the most common pathogens in the severe lung-necrosis group, are uncommon but serious pathogens of pediatric CAP. In our study, three previously healthy children separately died of *S. aureus*, *P. aeruginosa*, and influenza A combined with bacterial infection, which has been reported as pathogens of fatal NP. Our data also demonstrated that *M. pneumoniae* was the
primary etiology in the mild and moderate necrosis groups, which highlighted its importance in pediatric NP. The incidence of *M. pneumonia* -associated NP appears to be increasing according to recent reports, particularly in China\(^{20,21}\).

Previous studies have demonstrated significantly higher WBC, CRP, and LDH levels and lower serum albumin and sodium levels in the NP group than in the control groups\(^{20,22}\). Similarly, the univariate analysis showed that these indices were significantly correlated with lung necrosis severity. The mean serum sodium level in the massive necrosis group was as low as 131.6 mmol/L. Frank renal failure is uncommon in pediatric NP, but hyponatremia is quite common (73% in this study). A retrospective analysis of medical records suggested that hyponatremia was associated with pneumonia severity\(^{23}\). Hyponatremia on hospital admission is a risk factor for severity among critically ill patients and is independently associated with in-hospital mortality in adult patients with pneumonia\(^{24}\). Our data demonstrated that serum albumin was an independent predictor of lung necrosis severity, which is significantly associated with the prognosis of adult patients with pneumonia\(^{25,26}\).

Torre et al.\(^{27}\) demonstrated that the Ig levels were significantly lower in patients with CAP than in healthy controls. This is consistent with our findings, which showed an inverse relationship between serum Ig levels and lung necrosis severity; particularly, there was a significant difference in IgM levels among our groups. IgM plays a critical role in the immediate defense against severe bacterial infection. Reduced IgM levels have been observed in patients with CAP, sepsis, and severe pandemic influenza\(^{28-30}\). Post-hoc analyses of data from the CIGMA study demonstrated that administration of trimodulin (containing IgM, IgA, and IgG) improved the mortality outcomes of patients with severe CAP exhibiting elevated CRP levels, reduced IgM levels, or both\(^{31}\). We did not find a significant difference in cytokine levels among the three groups, which may be related to the small number of samples.

The severity of lung necrosis was identified based on the chest CT findings. However, the limitations of the application of CT in pediatric patients, such as radiation exposure and inconvenient availability, would discourage its early usage for the prompt detection of massive necrotizing changes. Our multivariate analysis showed that the CRP, serum albumin, and IgM levels were independent predictors of lung necrosis severity. ROC curve analysis was performed to identify the optimal cut-off values for these parameters and indicated that the optimal cut-off values of CRP, serum albumin, and IgM that demonstrated fair discriminative power in predicting massive lung necrosis were 122 mg/L, 30.8 g/L, and 95.7 mg/dL, respectively.

The present study has some limitations. First, it was a single-center, retrospective study, which made it prone to selection bias. Second, we did not collect data of a control group without NP, which may have led to decreased evidence regarding the efficacy of CRP, serum albumin, and IgM as markers for predicting lung necrosis severity. Rigorously matching the age, sex, etiology, and other factors of necrotic and control groups is challenging; therefore, we selected to analyze data from necrotic groups alone to identify the predictive factors. Thirdly, because etiology is not a baseline index at admission, we did not include it in the multivariate analysis. However, the etiology composition among the groups with different degrees of necrosis is significant, which might become a confounding factor. Nevertheless, we believe that these limitations do not significantly confound the main findings of our study. Our data would allow physicians to better screen patients and administer the appropriate therapy in a timely manner. Larger prospective studies with a control group are necessary to validate our findings.

In conclusion, we identified potential predictors of lung necrosis severity in children, which included the CRP, serum albumin, and IgM levels. Children exhibiting abnormal values in these parameters could be at a high risk and should be carefully managed. Further studies, preferably prospective multicenter observational ones, should be conducted to identify additional predictors of pulmonary necrosis and its severity.

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AUTHOR CONTRIBUTIONS
Conceived and designed the study: HZ, CL, and QB. Acquired and managed data: QL, BC, YJ, WC, SC, and MY. Performed statistical analysis: XZ and MX. Searched literature: QL. Grafted the manuscript: QL. Critical reviewing of the manuscript: HZ, CL, and XZ. Revised and approved the final version of the text: All authors.

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

REFERENCES


**Figure legends**

Fig 1. Computed tomographic grading of pneumonia with necrotizing changes. Severity of lung necrosis was measured on the basis of the relative ratio of the necrotic radiolucent area to the total involved lobe area. Necrotic areas that were <30%, between 30% and 70%, and >70% were further categorized into mild (N1), moderate (N2), and massive (N3) necrosis, respectively.
Fig 2. ROC curves obtained with CRP levels (decision point 122 mg/L; sensitivity 82.6% and specificity 73.5%), serum albumin (decision point 30.8 g/L; sensitivity 81.4% and specificity 70.6%), and IgM (decision point 95.7 mg/dl; sensitivity 78.3% and specificity 53.3%). Alb, serum albumin; ROC, receiver operating characteristic; CRP, C-reactive protein.

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