CLINICAL AND LABORATORY PREDICTORS OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN UNDER FOUR YEARS OF AGE

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Community-acquired pneumonia (CAP) is a major cause of pediatric morbidity and mortality. Currently, there is no common approach to determination of CAP severity in children, which hampers early diagnosis and treatment of the disease. The study was aimed to determine clinical and laboratory predictors of severe CAP in children under 4 years of age. Analysis of clinical data, parameters of complete blood count (CBC), C-reactive protein (CRP) using nonparametric methods for hypothesis testing, univariate correlation analysis, cross-tabulation (Statistica 10.0), logistic regression, and ROC analysis (SPSS Statistics 20.0) was performed in 72 children aged 1 month to 3 years 11 months admitted to hospital due to CAP. Severe CAP was diagnosed in 16.7% of children. Causes of severe CAP included respiratory distress (moderate — 58.3%, severe — 16.7% of cases) and sepsis (25%). We identified significant clinical predictors of severe CAP: vomiting (OR 4.2), tachypnea (OR 28.3), chest wall retractions (OR 6), wheezing (OR 4), and the absence of rhinitis (OR 0.21). Isolated assessment of the CBC and CRP did not allow to predict CAP severity. We have developed a prediction model predicting severe CAP in children under 4 years of age based on the presence of rhinitis, tachypnea, as well as leukocyte count (sensitivity and specificity 91.7%). Thus, currently the main cause of severe CAP in children under 4 years of age is respiratory distress, in which wheezing predominates. Physical examination with an emphasis on detection of rhinitis and respiratory distress is essential for diagnosing severe CAP. The use of a pneumonia severity prediction model may contribute to improvement of management of CAP in patients under 4 years of age.

Keywords: community-acquired pneumonia, children, severity assessment, prognosis, predictor

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КЛИНИКО-ЛАБОРАТОРНЫЕ ПРЕДИКТОРЫ ТЯЖЕЛОЙ ВНЕБОЛЬНИЧНОЙ ПНЕВМОНИИ У ДЕТЕЙ ДО ЧЕТЫРЕХ ЛЕТ

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Внебольничная пневмония (ВП) — одна из ведущих причин заболеваемости и смертности детей. В настоящее время отсутствует единый подход к определению тяжести ВП у детей, что затрудняет ее раннюю диагностику и терапию. Целью работы было определить клинико-лабораторные предикторы тяжелой ВП у детей до четырех лет. У 72 госпитализированных с ВП детей в возрасте от одного месяца до трех лет 11 месяцев проводили анализ клинических данных, показателей гемограммы, уровня С-реактивного белка с помощью непараметрических методов оценки статистических гипотез, однофакторного корреляционного анализа, кросстабуляции (Statistica 10.0), логистической регрессии и ROC-анализа (SPSS Statistics 20.0). Тяжелая ВП выявлена у 16,7% детей. Причинами тяжести были дыхательная недостаточность (ДН) II и III степени (58,3 и 16,7% случаев соответственно), сепсис (25%). Выявлены значимые клинические предикторы тяжелой ВП: наличие рвоты (отношение шансов OR — 4,2), тахипноэ (OR — 28,3), втяжение уступчивых мест грудной клетки (OR — 6), синдром бронхообструкции (БОС; OR — 4) и отсутствие ринита (OR — 0,21). Изолированная оценка показателей гемограммы и уровня С-реактивного белка не позволяла прогнозировать степень тяжести ВП. Построена модель прогнозирования тяжелой ВП у детей до четырех лет, включающая наличие ринита, тахипноэ, количество лейкоцитов (чувствительность и специфичность — 91,7%). Таким образом, на современном этапе основной причиной тяжести ВП у детей до четырех лет является ДН, в патогенезе которой преобладает БОС. Физикальное обследование с оценкой синдромов ринита и ДН остается ведущим в диагностике тяжелой ВП. Модель прогнозирования тяжелой ВП может способствовать оптимизации тактики лечения.

Ключевые слова: внебольничная пневмония, дети, оценка тяжести, прогноз, предиктор

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Community-acquired pneumonia (CAP) remains the leading infectious cause of pediatric morbidity and mortality. According to the World Health Organization (WHO), about 150 million cases of CAP in children under the age of five all over the world were reported before the pandemic of novel coronavirus infection. Severe course was reported in 7–13% of CAP cases, which results in up to 20 million hospitalizations and up to 1 million deaths annually. Children under one year are most at risk of severe pneumonia, especially in the countries of South Asia and Africa [1, 2]. According to Rospotrebnadzor, in 2019, the CAP incidence in Russia was 518.9 per 100,000 population with the highest values in children (977.5 per 100,000 population); mortality rate for CAP was 3.73 per 100,000 population, including 0.28 per 100,000 population in children [3]. To date, the long-term average annual morbidity and mortality in CAP showed no downward trend, which was due to high variability of respiratory pathogens and the increase in the share of children at risk of CAP (premature babies, children with congenital malformations, organic central nervous system disorders, etc.) [4]. The emergence of new etiopathogens has a significant effect on epidemiological parameters and clinical manifestations of CAP, including severity. Thus, in the first year of the pandemic of novel coronavirus infection (2020), the number of fatal cases increased by almost 12 times and reached 44.45 per 100,000 population [3, 5].

Currently, there is no common approach to determination of CAP severity in children. This is enabled by polymorphic clinical manifestations of the disease, significant impact of the child's body response to infection, and changes in the CAP etiological structure over time. The clearly demonstrated increase in the share of viral pneumonia in children under the age of five and the decrease in the rate of local complications (pleural empyema, lung tissue destruction) determine the need to reassess the contribution of various symptoms in the disease severity [6, 7]. Different criteria of CAP severity in children have been proposed. According to the WHO, severe CAP is diagnosed in cases of children's refusal to drink, repeated vomiting, seizure, lethargy, stridor or severe protein calorie malnutrition. British Thoracic Society (BTS) has proposed 12 criteria of pneumonia severity in children, while Pediatric Infectious Diseases Society/Infectious Diseases Society of America (PIDS/IDSA) has proposed four major and 11 minor criteria, however, their diagnostic value needs clarification [8, 9]. Thus, more than a half of children having severe CAP based on the PIDS/IDSA criteria did not require hospitalization [10]. The majority of authors believe that hypoxemia, impaired mental status, age of a baby less than 3–6 months, dyspnea, multilobar infiltrates and pleural effusion on the chest X-ray (CXR) are sensitive, but mildly specific predictors of severe CAP [9].

The diagnostic significance of laboratory biomarkers associated with severe CAP in children is poorly understood, and the data available are controversial. A number of papers convincingly show that isolated WBC elevation is a significant predictor of severe CAP in children [11, 12]. The association of leukopenia below 4×10^9 kL/L with the complicated CAP and increased mortality rate (OR 6.5; 95% CI 2.7–15.6) has been revealed [13]. It has been shown that absolute neutrophil count (ANC) can be a predictor of systemic complications of pediatric CAP, including bacteremia. Elevated C-reactive protein (CRP) levels and serum levels of procalcitonin are associated with the severe course of CAP, including the development of complications (pleural empyema, lung tissue destruction, bacteremia), in cases of typical bacterial disease etiology only [14, 15]. However, no association of CRP and serum procalcitonin levels with CAP severity, including the development of hypoxemia, dyspnea and tachycardia, has been revealed [16].

The study was aimed to determine clinical and laboratory predictors of severe CAP in children under the age of four.

METHODS

Clinical follow-up of 72 children with community-acquired pneumonia (CAP) was performed January 2021 to June 2022 at the Pediatric Research and Clinical Center for Infectious Diseases of FMBA of Russia and St.Olga City Children's Hospital. Inclusion criteria: patients' age between 1 months and 3 years 11 months 29 days; availability of clinical, anamnestic and objective data allowing one to suspect pneumonia; detection of infiltration on CXR; pneumonia meeting the criteria for community-acquired pneumonia (occurred outside the hospital or within 72 h after hospital admission); antibiotic therapy duration at admission not exceeding 24 h. Exclusion criteria: chronic somatic disorder (including disorders of respiratory and cardiovascular systems, diabetes mellitus, confirmed immunodeficiency, etc.); history of hospital admission during previous 14 days; positive PCR test of nasopharyngeal and oropharyngeal discharge for SARS-CoV-2. The median and interquartile range (Me (IQR)) of the children's age were 2.53 (1.71–2.99) years, the male to female ratio was 1.17/1. Me (IQR) of time until hospital admission was 3 (2–4) years. The criteria for severe pneumonia were as follows: impaired vital functions resulting in the need for the child's admission to an intensive care unit (ICU), i.e. severe progressive respiratory failure (RF), impaired consciousness, peripheral microcirculation and systemic hemodynamics determined together with the critical care physician.

Admission complaints were collected and medical history was taken (disease duration, presence and type of fever, cough, catarrhal condition of the upper respiratory tract, facts of intoxication, dyspnea, vomiting, diarrhea, abdominal and chest pain), the facts of taking antibacterial drugs at the outpatient stage, vaccination against pneumococcal, hemophilic infections and influenza were clarified. Physical examination involved evaluation of the presence and severity of fever, intoxication, RF, local changes in the lungs based on percussion and auscultation, bronchial obstructive syndrome (BOS), catarrhal condition of the upper respiratory tract (based on ENT examination), lymphoproliferative syndrome, hepatomegaly and splenomegaly. Peripheral microcirculatory status was determined based on the capillary refill time (CRT): CRT < 2 s was considered as normal range. The RF symptoms were as follows: tachypnea, dyspnea (labored breathing, nasal flaring, accessory muscles involvement in respiration, grunting breathing, retractions of the chest), cyanosis, blood oxygen levels (SpO_2) decrease to less than 96% during atmospheric respiration. Age dependent criteria for tachypnea were used in accordance with the WHO guidelines: respiratory rate ≥ 60/min in children under the age of 2 months, ≥ 50/min in children aged 2–12 months, ≥ 40/min in children over the age of 12 months [1]. BOS was diagnosed when hearing prolonged expiration with a lot of bilateral wheezing. Intoxication syndrome included a number of symptoms that were considered separately: loss of appetite, decline in activity, irritability, refusal to eat or drink, drowsiness, unusual crying, lack of eye contact, impaired consciousness [17]. When there were nausea, vomiting, diarrhea (n = 17), intestinal infection was excluded by testing feces for bacteria of the genera *Shigella*, *Salmonella*, *Campilobacter*, as well as for diarrheagenic *Escherichia*, group A rotavirus, genotype II noroviruses, astroviruses, subgroup F

Table 1. Distribution of patients' complaints with significant differences depending on CAP severity

Symptom	CAP severity				OR (95% CI)	Significance level (*p*)
	Moderate		Severe			
	n	%	n	%		
Rhinorrhea	52	86.7	7	58.3	0.21 (0.05–0.8)	0.02
Dyspnea	21	35	8	66.7	3.71 (1.01–13.8)	0.04
Vomiting	15	25	7	58.3	4.2 (1.2–15.2)	0.02
Refusal to drink	2	3.3	3	25	9.7 (1.4–66)	0.03

adenoviruses by PCR (AmpliSense OKI screen-FL reagent kit; Central Research Institute of Epidemiology of Rospotrebnadzor, Russia; FRT detection format). Pulse oximetry, chest radiography with two projections, complete blood count test and serum CRP test were performed in all children. The complete blood count test performed in the Sysmex XP-300 hematological analyzer (Sysmex; Japan) involved assessment of the following parameters: white blood count (WBC), red blood cell count, hemoglobin, platelet (PLT) count, mean platelet volume and platelet distribution width, platelet larger cell ratio, erythrocyte sedimentation rate. Blood smear microscopy was used to determine the percentage of each type of white blood cells (segmented and band neutrophils, myelocytes, metamyelocytes, eosinophils, basophils, lymphocytes (Lym), plasma cells). Absolute neutrophil count (ANC) and absolute band count (ABC) were calculated considering total WBC and WBC differential.

Serum CRP levels were determined with the Taurus automated analyzer (Instrumentation Laboratory; Italy) using reagents manufactured by Vector-Best (Russia) and BioSystems (Spain).

Statistical processing of the results was performed using the Statistica 10.0 software package (TIBCO; USA) to test quantitative data for normality (Shapiro–Wilk test), calculate Me, IQR. When describing extensive characteristics, 95% confidence interval (95% CI) was calculated by the Wilson's method. Significance of differences between groups was assessed using Mann–Whitney U test (quantitative data), Fisher's exact test or Pearson's chi-squared (χ^2) test (qualitative data). Correlations between quantitative data were assessed using the Spearman's rank correlation coefficient (*r*), correlations between nominal variables in a four-column table were assessed using a φ coefficient and calculation of odds ratio (OR), while correlations between ordinal variables in the contingency tables were assessed using Somers' D. Sensitivity (Se), specificity (Sp), negative (NPV) and positive (PPV) prognostic value represented the diagnostic test characteristics. Binary logistic regression implemented in SPSS Statistics v. 20.0 (IBM; USA) was used to analyze the relationship between the independent and dependent variables; direct selection of predictors based on the likelihood function, step selection criteria (inclusion — 0.05, exclusion — 0.1) with the significance level set as $p < 0.05$ were used. The threshold values of continuous characteristics were determined by ROC analysis according to the requirement of maximum total Se and Sp. The binary classifier quality was assessed based on the area under the ROC curve (AUC). All statistical tests involved the use of critical significance level set as $p \leq 0.05$ [18, 19].

RESULTS

The condition of 12 children (16.7%; 95% CI: 9.8–26.9%) at admission was considered to be severe. In 9 children out of 12 (75%), the disease severity was determined by respiratory failure: stage II RF — 7 patients (58.3%), stage III RF — 2 patients (16.7%). Three patients out of 12 (25%) were admitted to the ICU with severe CAP due to complications: sepsis (*n* = 3; 25%) and pleural empyema (n = 1; 8.3%).

In cases of severe CAP, patients were significantly younger (Me (IQR) = 1.66 (0.96–2.59) years) compared to the cases of moderate CAP (Me (IQR) = 2.6 (2.02–3.11) years); $p = 0.008$. The logistic regression analysis showed that the likelihood of severe CAP decreased 2.6 times with increasing age factor per unit ($p = 0.009$; OR 0.39, 95% CI: 0.19–0.78).

Assessment of the patients' complaints at admission revealed significant differences for some of them depending on the pneumonia severity (Table 1).

Gender-related characteristics, features of antenatal period, duration of breastfeeding, indicators of children's physical development (at birth and at admission), as well as vaccination status against pneumococcal, hemophilic infections and influenza did not affect the risk of severe CAP ($p > 0.2$). There was also no correlation between CAP severity and body temperature increase, duration of fever, facts of intoxication and cough.

Physical examination revealed significant differences depending on pneumonia severity for some symptoms (Table 2).

We found a significant, direct, relatively strong correlation between the RF stage and CAP severity in children (Somers' D 0.68; $p < 0.001$). The relationship between BOS and various

Table 2. Distribution of physical findings with significant differences depending on CAP severity

Symptom	CAP severity				OR (95% CI)	Significance level (*p*)
	moderate		severe			
	n	%	*n*	%		
RF of any kind	29	48.3	11	91.7	11.8 (1.4–96.8)	0.005
Tachypnea	9	15	10	83.3	28.3 (5.3–151.3)	<0.001
Retraction of the chest	20	33.3	9	75	6 (1.5–24.6)	0.007
SpO_2 < 96%	18	30	8	66.7	4.7 (1.2–17.5)	0.02
Acrocyanosis	0	0	2	16.7	–	0.02
Local medium bubbling rales	18	30	0	0	–	0.03
Diffuse bilateral wheezes (BOS)	14	33.3	8	66.7	4 (1.07–14.9)	0.03

Table 3. Significant differences in hemogram parameters of children depending on CAP severity

Laboratory parameter (units)	CAP severity		OR (95% CI)*	Significance level (*p*)
	moderate Me (IQR)	severe Me (IQR)		
WBC (*10^9/L)	10 (7.6–15.1)	14.5 (11.2–22.9)	1.08 (1.004–1.17)	0.01
ANC (*10^9/L)	5 (3.1–7.6)	9.9 (4.6–15.1)	1.12 (1.01–1.24)	0.02
ABC (*10^9/L)	0.24 (0.08–0.94)	0.9 (0.3–2.5)	1.4 (1.01–2.1)	0.01
Lym (%)	31.5 (20–44.5)	19 (7–36)	0.94 (0.9–0.99)	0.02
PLT (*10^9/L)	280 (223–335)	428 (270.5–549)	1.009 (1.003-1.015)	0.02

Note: *when the laboratory parameter value increases by one.

stages of RF depending on CAP severity was analyzed. It was found that the contribution of BOS to RF was significantly larger in individuals with severe CAP (8 cases out of 11; 72.7%) compared to the cohort with moderate CAP (14 cases out of 29; 48.3%), $p = 0.03$. BOS was significantly associated with the RF stage (Somers' D 0.49; $p < 0.001$), and the correlation strength was significantly higher in the cohort with severe CAP (Somers' D 0.53; $p = 0.005$) compared to individuals with moderate CAP (Somers' D 0.25; $p = 0.03$). Laboratory parameters, for which significant differences have been revealed depending on CAP severity, are provided in Table 3.

When performing ROC analysis, cut-off points were determined for these laboratory parameters, enabling optimal differentiation between severe and moderate CAP (Table 4).

The logistic regression analysis, in which CAP severity was a dependent variable, while the listed above clinical and hematological parameters showing significant differences depending on the disease severity were independent variables, was performed to estimate rationality of the integrated assessment of clinical and laboratory parameters for diagnosis of severe CAP. We have constructed a significant ($p < 0.001$) regression model for prediction of severe CAP in children under the age of four:

$$y = \frac{1}{11+e^{(4.86+2.69*X1-4.99*X2-0.17*X3)}},$$

where y is the likelihood of severe CAP; X1 is rhinorrhea (no — 0, yes — 1); X2 is tachypnea (no — 0, yes — 1); X3 is WBC (×10^9/L). Table 5 provides characteristics of the regression model independent variables.

We determined the best cut-off probability value, $y \geq 0.305$, by ROC analysis: in case of satisfying inequality, severe CAP is predicted with Se 91.7%, Sp 91.7%, PPV 68.9%, NPV 98.2% (AUC 0.947; 95% CI: 0.889–1). When $y < 0.305$, moderate CAP is predicted with Se 91.7%, Sp 91.7%, PPV 98.2%, NPV 68.9%. In the third phase of construction the prognostic model has the following statistical characteristics: –2Log likelihood = 30.2 ($p < 0.001$), Nagelkerke's R squared coefficient 0.64 ($p < 0.001$), Hosmer–Lemeshow goodness-of-fit test 0.82 ($p = 0.66$). The lack of multicollinearity between predictors ($|r|_{max.} = 0.5$) and the distribution of resudials close to normal (Shapiro–Wilk test 0.76; $p = 0.05$) have been revealed, which suggest that the analysis conducted is correct.

DISCUSSION

The identified distribution of CAP by severity across children under the age of four is generally consistent with the literature data. The prevalence of severe CAP in the study (16.7%) is slightly higher than that in general pediatric population (7–13%) [20] and, according to other data, by at least 3% [21]. This confirms a significant impact of age factor on the likelihood of severe CAP and the maximum medical and social significance of this issue in infants and young children [22, 23]. It has been found that nowadays severity of the majority of CAPs in children under the age of four does not result from the features of early stages of ontogeny and nutrition, which can be related to improvement of the population quality of life, including reduced exposure of children to household pollutants (biofuel used for cooking, second-hand smoke, etc.) [24]. In our study, the fact of vaccination against pneumococcal, hemophilic infections and influenza had no significant effect on CAP severity in children, which was inconsistent with the available literature data [9, 24]. It can be assumed that this observation reflects alteration of CAP etiological structure in children with the increase in the share of primary viral pneumonia [6, 7].

It has been found that stage II–III respiratory failure (75%), in the structure of which bronchial obstructive syndrome significantly predominates (72.7%), is currently the main cause of severe CAP in children under the age of four. The leading role of BOS in pathogenesis of severe pneumonia is probably due to predominance of respiratory viruses in etiology of CAP in young children [6, 7]. The history of dyspnea was a weak predictor of CAP severity, which could be explained by vague understanding of the term by parents. In contrast, detection of age-depenent tachypnea (according to the WHO criteria) and retractions of the chest during physical examination significantly, many times increased the chance of severe disease (28.3 and 6 times, respectively).

Dyspepsia in the form of vomiting made a significant contribution to the development of severe CAP, increasing

Table 4. Disgnostic ability of laboratory parameters in detection of severe CAP

Laboratory parameter (units)	Cut-off point	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUC (95% CI)
WBC (*10^9/L)	≥11.05	83.3	61.7	30.4	94.9	0.732 (0.6–0.86)
ANC (*10^9/L)	≥8.31	58.3	78.3	35	90.4	0.71 (0.56–0.86)
ABC (*10^9/L)	≥0.3	83.3	53.3	26.3	94.1	0.729 (0.6–0.86)
Lym (%)	≤22	66.7	71.7	32.1	91.5	0.711 (0.53–0.89)
PLT (*10^9/L)	≥423.5	58.3	90	53.9	91.5	0.714 (0.53–0.89)

Table 5. Traits included in the logistic regression model for prediction of severe CAP in children under the age of four

№ п/п	Predictors and their gradation	Code	Coefficient (B_i)	Standard error (S_i)	Wald test (W_i)	Significance level (p)	Odds ratio (95% CI)
1	Rhinorrhea: no — 0; yes — 1	X1	–2.69	1.33	4.05	0.04	0.68 (0.005–0.931)
2	Tachypnea: no — 0; yes — 1	X2	4.99	1.51	10.9	0.001	147 (7.6–2851)
3	WBC, *10^9 cells/L	X3	0.17	0.07	5.4	0.02	1.19 (1.03–1.38)
4	Constant	–	–4.86	1.97	6.1	0.01	–

the chance on average 4 times. The emergence of reflex vomiting in the structure of endogenic intoxication and faster development of exicosis in young children can constitute possible pathogenetic substantiation of this observation. The fact of vomiting is among CAP severity criteria according to BTS [8, 9], which confirms the importance of assessing this symptom in children with pneumonia.

The fact attracts attention that some symptoms earlier proposed as criteria for severe pneumonia were seldom (refusal to drink — 25%, acrocyanosis — 16.7%) or never (nasal flaring, refusal to eat, cyanosis, apnea and groaning in infants, increased CRT, impaired consciousness) reported in our study [9]. The rhinitis syndrome and local medium rales in auscultation were negative predictors of severe CAP. This interesting observation can reflect predominant involvement of upper respiratory tract and bronchi of medium caliber in individuals with mild pneumonia.

Among leukocyte indicators, absolute WBC, segmented and band neutrophil counts, relative lymphocyte counts were potential predictors of the disease severity. When assessing diagnostic value of laboratory biomarkers, the inequality $0.7 < AUC < 0.8$ was fulfilled in all cases, which was indicative of good discriminatory ability [19]. It has been found that assessment of leukocyte indicators does not improve the detection rate of severe pneumonia (positive prognostic value < 50%), but makes it possible to exclude it with high probability (negative prognostic value > 90%). It should be noted that platelet counts in individuals with severe CAP were significantly higher (1.52 times) compared to individuals with moderate CAP. Activation of the platelet component of hemostasis in severe CAP can be associated with significant involvement of the lungs being the main site of platelet formation in the disease process [25]. Other hemogram indicators, such as relative counts of immature neutrophils (band neutrophils, meta- and myelocytes) and CRP concentration were not predictors of severe pneumonia.

A significant model for prediction of severe CAP in children under the age of four was constructed using binary logistic regression. This made it possible to substantiate the feasibility of integrated assessment of clinical and hematological characteristics during examination of children with CAP aimed at early diagnosis of severe pneumonia and optimization of treatment tactics. Statistical analysis showed good quality of model approximation to hypothetic real situation, no significant differences between the reported and predicted values of the response factor and its high share of dispersion explained by the model. The model advantages include accessibility and simplicity of assessment of the proposed combination of parameters, enabling early and effective prediction of CAP severity in children under the age of four.

CONCLUSIONS

The goal of the study was achieved: clinical and laboratory predictors of severe CAP in children under the age of four were identified and assessed. Currently, respiratory failure, in the pathogenesis of which BOS predominates, is the main cause of severe pneumonia. Clinical assessment of patient's condition focused on detection of the rhinitis syndrome and RF, including age-dependent tachypnea and retraction of the chest, plays a leading role in the diagnosis of pediatric CAP. Isolated assessment of hematological parameters and serum CRP levels makes it impossible to predict pneumonia severity. A model for early prediction of CAP severity in children under the age of four has been proposed, the use of which can contribute to the treatment tactics improvement. Given small size of the sample used in the study (72 patients) and no consensus about the criteria of severe CAP diagnosis based on the literature data, further research with the prospect of creating a validated quantitative system for assessment of pneumonia severity in children is necessary.

References

1. World Health Organization. Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities: Evidence Summaries. Geneva: World Health Organization, 2014; 34 p.
2. World Health Organization. Pneumonia in children [cited 2023 Jul 07]. Available from: https://www.who.int/news-room/fact-sheets/detail/pneumonia.
3. Federal'naja sluzhba po nadzoru v sfere zashhity prav potrebitelej i blagopoluchija cheloveka. O sostojanii sanitarno-jepidemiologicheskogo blagopoluchija naselenija v Rossijskoj Federacii v 2022 godu: Gosudarstvennyj doklad. M.: Federal'naja sluzhba po nadzoru v sfere zashhity prav potrebitelej i blagopoluchija cheloveka; 368 s.
4. Gorbich OA. Jepidemiologicheskaja harakteristika i profilaktika vnebol'nichnyh pnevmonij u detej [dissertacija]. Minsk, 2018. Russian.
5. Nesterenko ZV, Prokopeva NJe, Matalygina OA, Shestakova MD, Polunina AV. Vnebol'nichnaja pnevmonija u detej v period koronavirusnoj jepidemii. Medicina: teorija i praktika. 2021; 6 (4): 12–20. Russian.
6. O'Brien KL, Baggett HC, Brooks WA, Feikin DR, Hammitt LL, Higdon MM, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet. 2019; 394 (10200): 757–79.
7. Bénet T, Picot VS, Messaoudi M, Chou M, Eap T, Wang J, et al. Global Approach to Biological Research, Infectious diseases

and Epidemics in Low-income countries (GABRIEL) Network. Microorganisms Associated With Pneumonia in Children <5 Years of Age in Developing and Emerging Countries: The GABRIEL Pneumonia Multicenter, Prospective, Case-Control Study. Clin Infect Dis. 2017; 65 (4): 604–12.
8. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, et al. British Thoracic Society Standards of Care Committee. 2011. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax. 2011; 66: ii1–ii23.
9. Dean P, Florin TA. Factors Associated With Pneumonia severity in children: a systematic review. J Pediatric Infect Dis Soc. 2018; 7 (4): 323–34.
10. Florin TA, Brokamp C, Mantyla R, DePaoli B, Ruddy R, Shah SS, et al. Validation of the PIDS/IDSA severity criteria in children with community-acquired pneumonia. Clin Infect Dis. 2018; 67 (1): 112–9.
11. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011; 53 (7): e25–76.
12. Williams DJ, Hall M, Auger KA, Tieder JS, Jerardi KE, Queen MA, et al. Association of white blood cell count and C-reactive protein with outcomes in children hospitalized for community-acquired pneumonia. Pediatr Infect Dis J. 2015; 34 (7): 792–3.
13. Araya S, Lovera D, Zarate C, Apodaca S, Acuña J, Sanabria G, et al. Application of a prognostic scale to estimate the mortality of children hospitalized with community-acquired pneumonia. Pediatr Infect Dis J. 2016; 35: 369–73.
14. Fernandes CD, Arriaga MB, Costa MCM, Costa MCM, Costa MHM, Vinhaes CL, et al. Host inflammatory biomarkers of disease severity in pediatric community-acquired pneumonia: a systematic review and meta-analysis. Open Forum Infect Dis. 2019; 6 (12): 520.
15. Barak-Corren Y, Horovits Y, Erlichman M, Picard E. The prognostic value of C-reactive protein for children with pneumonia. Acta Paediatr. 2021; 110 (3): 970–6.
16. Agnello L, Bellia C, Di Gangi M, Lo Sasso B, Calvaruso L, Bivona G., et al. Utility of serum procalcitonin and C-reactive protein in severity assessment of community-acquired pneumonia in children. Clin Biochem. 2016; 49: 47–50
17. Tatochenko VK. Vnebol'nichnye pnevmonii u detej — problemy i reshenija. Rossijskij vestnik perinatologii i pediatrii. 2021; 66 (1): 9–21. Russian.
18. Junkerov VI, Grigorev SG. Matematiko-statisticheskaja obrabotka dannyh medicinskih issledovanij. SPb.: Izd-vo VMedA, 2002; 266 s. Russian.
19. Grigorev SG, Lobzin JuV, Skripchenko NV. Rol' i mesto logisticheskoj regressii i ROC-analiza v reshenii medicinskih diagnosticheskih zadach. Zhurnal infektologii. 2016; 8 (4): 36–45. Russian.
20. Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H; WHO Child Health Epidemiology Reference Group. Global estimate of the incidence of clinical pneumonia among children under five years of age. Bull World Health Organ. 2004; 82 (12): 895–903.
21. Legg J, Rampton C. British Thoracic Society paediatric pneumonia audit 2016/2017 Report. British Thoracic Society [Internet]. 2018 Jan [cited 2023 Jul 08]; 13 p. Available from: https://www.brit-thoracic.org.uk/quality-improvement/clinical-audit/bts-national-audit-reports/.
22. Nascimento-Carvalho CM. Community-acquired pneumonia among children: the latest evidence for an updated management. J Pediatr (Rio J). 2020; 96 (Suppl 1): 29–38.
23. de Benedictis FM, Kerem E, Chang AB, Colin AA, Zar HJ, Bush A. Complicated pneumonia in children. Lancet. 2020; 396 (10253): 786–98.
24. Ledjaev MJa, Shefatova EI, Zhukova JuA, Svetlova LV. Kliniko-anamnesticheskij analiz techenija vnebol'nichnyh pnevmonij u detej v celjah optimizacii lechenija i profilaktiki. Lekarstvennyj vestnik. 2021; 15 (4): 35–41. Russian.
25. Serebrjanaja NB, Shanin SN, Fomicheva EE, Jakuceni PP. Trombocity kak aktivatory i reguljatory vospalitel'nyh i immunnyh reakcij. Chast' 1. Osnovnye harakteristiki trombocitov kak vospalitel'nyh kletok. Medicinskaja immunologija. 2018; 20 (6): 785–96. Russian.

Литература

1. World Health Organization. Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities: Evidence Summaries. Geneva: World Health Organization, 2014; 34 p.
2. World Health Organization. Pneumonia in children [cited 2023 Jul 07]. Available from: https://www.who.int/news-room/fact-sheets/detail/pneumonia.
3. Федеральная служба по надзору в сфере защиты прав потребителей и благополучия человека. О состоянии санитарно-эпидемиологического благополучия населения в Российской Федерации в 2022 году: Государственный доклад. М.: Федеральная служба по надзору в сфере защиты прав потребителей и благополучия человека; 368 с.
4. Горбич О. А. Эпидемиологическая характеристика и профилактика внебольничных пневмоний у детей [диссертация]. Минск, 2018.
5. Нестеренко З. В., Прокопьева Н. Э., Маталыгина О. А., Шестакова М. Д., Полунина А. В. Внебольничная пневмония у детей в период коронавирусной эпидемии. Медицина: теория и практика. 2021; 6 (4): 12–20.
6. O'Brien KL, Baggett HC, Brooks WA, Feikin DR, Hammitt LL, Higdon MM, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet. 2019; 394 (10200): 757–79.
7. Bénet T, Picot VS, Messaoudi M, Chou M, Eap T, Wang J, et al. Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL) Network. Microorganisms Associated With Pneumonia in Children <5 Years of Age in Developing and Emerging Countries: The GABRIEL Pneumonia Multicenter, Prospective, Case-Control Study. Clin Infect Dis. 2017; 65 (4): 604–12.
8. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, et al. British Thoracic Society Standards of Care Committee. 2011. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax. 2011; 66: ii1–ii23.
9. Dean P, Florin TA. Factors Associated With Pneumonia severity in children: a systematic review. J Pediatric Infect Dis Soc. 2018; 7 (4): 323–34.
10. Florin TA, Brokamp C, Mantyla R, DePaoli B, Ruddy R, Shah SS, et al. Validation of the PIDS/IDSA severity criteria in children with community-acquired pneumonia. Clin Infect Dis. 2018; 67 (1): 112–9.
11. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011; 53 (7): e25–76.
12. Williams DJ, Hall M, Auger KA, Tieder JS, Jerardi KE, Queen MA, et al. Association of white blood cell count and C-reactive protein with outcomes in children hospitalized for community-acquired pneumonia. Pediatr Infect Dis J. 2015; 34 (7): 792–3.
13. Araya S, Lovera D, Zarate C, Apodaca S, Acuña J, Sanabria G, et al. Application of a prognostic scale to estimate the mortality of children hospitalized with community-acquired pneumonia. Pediatr Infect Dis J. 2016; 35: 369–73.
14. Fernandes CD, Arriaga MB, Costa MCM, Costa MCM, Costa MHM, Vinhaes CL, et al. Host inflammatory biomarkers of disease severity in pediatric community-acquired pneumonia: a systematic

review and meta-analysis. Open Forum Infect Dis. 2019; 6 (12): 520.
15. Barak-Corren Y, Horovits Y, Erlichman M, Picard E. The prognostic value of C-reactive protein for children with pneumonia. Acta Paediatr. 2021; 110 (3): 970–6.
16. Agnello L, Bellia C, Di Gangi M, Lo Sasso B, Calvaruso L, Bivona G., et al. Utility of serum procalcitonin and C-reactive protein in severity assessment of community-acquired pneumonia in children. Clin Biochem. 2016; 49: 47–50
17. Таточенко В. К. Внебольничные пневмонии у детей — проблемы и решения. Российский вестник перинатологии и педиатрии. 2021; 66 (1): 9–21.
18. Юнкеров В. И., Григорьев С. Г. Математико-статистическая обработка данных медицинских исследований. СПб.: Изд-во ВМедА, 2002; 266 с.
19. Григорьев С. Г., Лобзин Ю.В., Скрипченко Н. В. Роль и место логистической регрессии и ROC-анализа в решении медицинских диагностических задач. Журнал инфектологии. 2016; 8 (4): 36–45.
20. Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H; WHO Child Health Epidemiology Reference Group. Global estimate of the incidence of clinical pneumonia among children under five years of age. Bull World Health Organ. 2004; 82 (12): 895–903.
21. Legg J, Rampton C. British Thoracic Society paediatric pneumonia audit 2016/2017 Report. British Thoracic Society [Internet]. 2018 Jan [cited 2023 Jul 08]; 13 p. Available from: https://www.brit-thoracic.org.uk/quality-improvement/clinical-audit/bts-national-audit-reports/.
22. Nascimento-Carvalho CM. Community-acquired pneumonia among children: the latest evidence for an updated management. J Pediatr (Rio J). 2020; 96 (Suppl 1): 29–38.
23. de Benedictis FM, Kerem E, Chang AB, Colin AA, Zar HJ, Bush A. Complicated pneumonia in children. Lancet. 2020; 396 (10253): 786–98.
24. Ледяев М. Я., Шефатова Е. И., Жукова Ю. А., Светлова Л. В. Клинико-анамнестический анализ течения внебольничных пневмоний у детей в целях оптимизации лечения и профилактики. Лекарственный вестник. 2021; 15 (4): 35–41.
25. Серебряная Н. Б., Шанин С. Н., Фомичева Е. Е., Якуцени П. П. Тромбоциты как активаторы и регуляторы воспалительных и иммунных реакций. Часть 1. Основные характеристики тромбоцитов как воспалительных клеток. Медицинская иммунология. 2018; 20 (6): 785–96.