https://doi.org/10.15360/1813-9779-2024-2-14-28

Prognostic Markers of Acute Suppurative Lung Disease

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For citation: *Dmitry L. Fetlam, Anastasia G. Chumachenko, Maria D. Vyazmina, Victor V. Moroz, Artem N. Kuzovlev, Vladimir M. Pisarev.* Prognostic Markers of Acute Suppurative Lung Disease. *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (2): 14–28. https://doi.org/10.15360/1813-9779-2024-2-14-28 [In Russ. and Engl.]

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Summary

The mortality rate among patients with acute suppurative lung diseases (ASLD) in the ICU reaches 30%. Early, pathogenetically relevant biomarkers are needed to ensure personification and better efficacy of ASLD treatment. Numeric variations in the counts of immune system cells in patient's blood can be viewed as such candidate biomarkers.

The aim of the study. Identification of potential markers predicting ASLD outcome after community-acquired pneumonia and COVID-19.

Materials and methods. The study included 216 in-hospital patients aged 18–87 with ASLD after community-acquired pneumonia with (*N*=81) and without (*N*=135) COVID-19 history.

Results. Patients survival after COVID-19 was linked to lymphocyte count on Day 1 of hospital stay (hazard ratio, HR=5.9 95%CI 0.9–37.4; *P*=0.0188, log-rank test). In patients who had not have COVID-19, a difference in survival was associated with lymphocyte (HR=2.9 95%CI 1.0–8.4; *P*=0.0184, log-rank test; *N*=135), and monocyte counts (HR=2.7 95% CI 0.8–9.5; *P*=0.0196, log-rank test) on Day 1 of hospital stay. Patients' survival after COVID-19 infection depended on SII (systemic immune-inflammation index. HR=9.3 95%CI 1.7–49.8; *P*=0.0124, log-rank test; *N*=81, SIRI (systemic inflammatory response index, HR=7.2 95%CI 1.4–36.6; *P*=0.0339, log-rank test; *N*=81) and NLR (neutrophil-to-lymphocyte ratio, HR=9.6 95%CI 1.8–52.0; *P*=0.0108; log-rank test; *N*=81) values on Day 1 of hospital stay. In patients who did not have COVID-19 SII values had no influence on survival.

Conclusion. The lymphocyte count makes it possible to predict outcomes of pleural empyema, regardless of patient's history of COVID-19, i. e. a decrease in the lymphocyte count below 1.2×10^9 in 1 L is associated with fatal outcome. Monocyte count carries prognostic information for cases of pleural empyema without previous COVID-19 infection. As for the relative indicators, SIRI, SII and NLR values measured on Day 1 in the hospital were predictors of ASLD outcome only in patients after COVID-19 infection, i. e., higher values were associated with increased risk of death, with NLR index being the most informative. Overall severity of illness above 10 scores by CIRS was associated with an unfavorable ASLD outcome, regardless of patient's history of COVID-19.

Keywords: acute suppurative lung diseases; COVID-19; pleural empyema; lung abscess; immune system cells; SIRI; SII; NLR

Conflict of interest. The authors declare no conflict of interest.

Introduction

Suppurative diseases of the lung and pleura (SDLP) are characterized by inflammatory infiltration and subsequent destruction of lung tissue due to activities of infectious agents [1]. Despite improvements in treatment, there has been an increasing trend in morbidity, resulting in high mortality rates of 5–30% [2–4]. Several factors, including age, nutritional status, comorbidities, immunity, timely antibiotic therapy, and supportive care, play an important role in determining the patient's condition [5].

Pleural empyema is a common manifestation of SDLP. It involves the accumulation of pus or fluid with evidence of infection in the pleural cavity, with inflammatory involvement of both the parietal and visceral pleura and secondary compression of lung tissue. The main etiology of pleural empyema (in 60% of cases) is community-acquired pneumonia. Parapneumonic effusion and purulent destructive processes in lung tissue are the main causes of pleural empyema. In some patients, pleural empyema without fistula results from parapneumonic effusion, whereas in other patients with underlying lung destruction, a fistula may develop, worsening the course of SDLP [1, 6]. Bronchopleural fistula is characterized by an abnormal channel lined with bronchial epithelium, forming a persistent connection between the bronchial tree and the pleural cavity. It is a serious complication of SDLP and surgical interventions, leading to persistent lung collapse and chronic inflammation in the pleural cavity [7]. Patients with bronchopleural fistula are at increased risk of sepsis, septic shock and multiple organ failure (MOF), which significantly worsens their prognosis [8]. Although modern diagnostic methods for SDLP are well known, predictors of its course and outcome have not been established.

It seems promising to investigate two groups of indicators for this purpose: 1) cellular biomarkers, such as neutrophils, lymphocytes, and monocytes; and 2) relative indices, including NLR (Neutrophil to Lymphocyte Ratio), SIRI (Systemic Inflammatory Response Index, calculated by multiplying NLR by monocyte count), and SII (Systemic Immune Inflammation Index, calculated by multiplying NLR by platelet count).

Neutrophils are phagocytic leukocytes that constitute the «first line» of the host immune response to invading pathogens through a variety of mechanisms, including chemotaxis, phagocytosis, reactive oxygen species (ROS) and granule release, cytokine production and release, and neutrophil extracellular trap (NET) formation [10, 11]. Neutrophils also play an important regulatory role in adaptive immunity: they recruit, activate and program other immune cells (B cells, NK cells, CD4, CD8 and $\delta\gamma$ T cells) and secrete a variety of pro-inflammatory and immunomodulatory cytokines and chemokines [12, 13]. Lymphocytes are the cells of the immune system that provide adaptive immunity, the main components of which are T and B cells. T cells ensure the full development of cellular and humoral adaptive immunity through intercellular interactions with other cells, while B cells are responsible for the direct production of antibodies, which are essential for humoral immunity [14].

CD4+ and CD8+ T lymphocytes are critical for defense against sepsis [15]. Systemic inflammation results in a marked suppression of cellular immunity, causing a reduction in CD3+ T cells, CD4+ T cells, CD8+ T cells, and NK cells [16, 17]. Monocytes are short-lived circulating cells that participate in inflammation both by direct action, releasing cytokines, and by differentiation into dendritic cells and macrophages [18, 19].

The neutrophil-to-lymphocyte ratio (NLR) is a biomarker that assesses the systemic inflammatory response and predicts outcomes in several diseases, including cerebrovascular events [20], cardiovascular disease [21], bacterial and fungal infections and sepsis, community-acquired pneumonia, SARS-CoV-2 infection [22], metabolic syndrome [23], rheumatoid arthritis [24], several cancers [25, 26], decompensated liver cirrhosis [27], and severe trauma [28]. NLR is calculated by dividing the absolute number of neutrophils by lymphocytes per unit volume [29], and is readily available and convenient for use in clinical practice [30]. The NLR is thought to reflect the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses [31]. SIRI and SII have been used as prognostic markers in cancer, stroke, and cardiovascular disease [32–34].

However, the prognostic value of potential markers in SDLP is not well established. Therefore, the aim of this study was to identify potential markers for the outcome of SDLP in survivors of community-acquired pneumonia and COVID-19.

Since COVID-19 is characterized by a wide range and variability of possible clinical manifestations and can lead to the development of pulmonary complications, including SDLP [35–39], it was of interest to evaluate the prognostic value of potential markers separately in groups of patients with SDLP who had undergone COVID-19 and those who had not.

Materials and Methods

We conducted an uncontrolled, prospective, observational, randomized trial that was approved by the Ethics Committee of the V. A. Negovsky Research Institute of General Reanimatology, protocol No. 2/22/1 dated July 26, 2022. The study recruited participants between November 2021 and August 2023.

Based on our initial data, the mortality rate for pleural empyema is estimated to be approximately 10 percent. We used this information to determine the required sample size. The sample size, calculated using the formula $n=(t2*P*Q)/\triangle 2$, where t is the critical value of Student's criterion (1.96 at a significance level of 0.05), $\triangle$ is the maximum allowable error (5%), P is the proportion of cases in which the studied parameter occurs (90), and Q is the proportion of cases in which the studied parameter does not occur (10), was determined to be 138.

Patients and Treatment. The study included 216 patients with SDLP that developed as a result of community-acquired pneumonia in the previous 30 days, including 81 patients who underwent COVID-19 and 135 who did not undergo COVID (Fig. 1). The total cohort included the group of patients with pleural empyema (PE) without fistula (due to parapneumonic effusion) (*N*=127) and the group of patients with pleural empyema with fistula

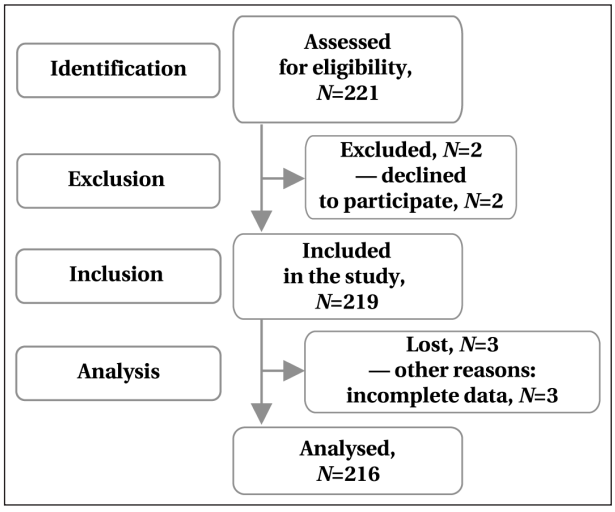

Fig. 1. Study flowchart.

(PEF) due to complicated parapneumonic effusion with bacterial contamination, lung abscess, or destructive pneumonia (*N*=89).

The diagnosis of SDLP was based on the computed tomography findings [40]. The conclusion that the patient was infected with SARS-CoV-2 was based on the results of PCR diagnostics, regardless of the date.

COVID-19 was treated according to the current version of the «Provisional guidelines for the prevention, diagnosis, and treatment of COVID-19». Pleural drainage or videothoracoscopic pleural drainage was performed in all the patients. NLR, SII, and SIRI values were calculated. Data were retrieved from the EMIAS database. Missing or incomplete data were excluded from analysis.

General criteria for inclusion in the study:

— Presence of SDLP (pleural empyema without fistula, pleural empyema with fistula, lung abscess) in a patient who had a community-acquired bacterial or viral lung infection in the previous 30 days or confirmed by COVID-19 PCR data at different times before hospitalization;

— Age 18 years or older;

— Written informed consent to participate in the study;

— The patient's ability to cooperate adequately for an extended period of time during the clinical trial.

Study exclusion criteria were:

— Refusal of further observation by the patient and/or his/her legal representative;

— Evidence of cancer or tuberculosis.

On admission, the presence or absence of diabetes mellitus was noted and the patients were assessed using SOFA, APACHE II, Charlson, CIRS (Cumulative Index Rating Scale), and RAPID scales (Table 1). Blood analysis was performed using a Sysmex XN-1000 automated hematology analyzer.

When comparing patients in the PE and PEF groups, we found that males had a higher incidence of empyema with fistula than females (*P*=0.023, FEM, OR=2.09, 95%CI: 1.12–3.9). There were no differences in age (*P*=0.394), frequency of DM (*P*=0.386), Charlson (*P*=0.694), CIRS (*P*=0.292), SOFA (*P*=0.483), APACHE-2 (*P*=0.173), or RAPID (*P*=0.274) scores on admission.

The normality of distribution of the quantitative variables was assessed using the Shapiro–Wilk test. Parameters with a normal distribution were reported as the arithmetic mean *(Me)*, standard deviation *(SD)*, and 95% confidence intervals (95% CI). Quantitative data with non-normal distribution were reported as median *(Me)* and lower and upper quartiles *(Q1–Q3)*. Variables with a normal distribution were compared between groups using the Student's t-test if the variance was equal. If the distribution pattern differed from normal, the Mann–Whitney *U*-test was used. Categorical data were expressed as absolute values and percentages. Percentages in contingency table analyses were compared using the χ^2 criterion with Yates' correction for sampling continuity and Fisher's exact method (FEM). The odds ratio with 95% confidence interval (95% CI) was used as a quantitative measure of the effect when comparing relative rates. A log-rank test was used for the Kaplan–Meier survival analysis. The results were presented as hazard ratios (HR) with 95% confidence intervals (CI). The ROC curve method was used to predict the probability of an adverse outcome (mortality). Differences were considered statistically significant at $P<0.05$. Statistical analysis was performed using MedCalc version 11.6 and SigmaStat version 3.5.

Results

Age and sex did not affect the outcomes of SDLP (Fig. 2, *b*). When analyzed separately in patients with or without COVID-19, no difference in survival was found based on sex and age (Fig. 2, *d*, *e*, *g*, *h*). An increase in SOFA score on day 1 of hospitalization was associated with a poor outcome in the entire patient cohort (Fig. 2, *c*). In patients who did not have PCR-proven COVID-19, a similar association persisted (Fig. 2, *i*); however, in patients who had COVID-19, no differences in SOFA-dependent survival with a SOFA score on day 1 of hospitalization were revealed (Fig. 2, *f*).

We found an association between comorbidity severity and mortality (Fig. 3). An increase in the CIRS comorbidity scale score above 10 was associated with an adverse outcome both in the entire patient cohort (Fig. 3, *a*) and in patients who survived COVID-19 (Fig. 3 *d*) or did not have COVID-19 (Fig. 3, *g*). A Charlson comorbidity index score

Table 1. Characteristics of patients included in the study.

Parameter	Value
Men, *N* (%)	151 (70)
Women, *N* (%)	65 (30)
Age, *Me (IQR)*	54 (41–66)
SOFA score on admission, *Me (IQR)*	2 (2–2)
APACHE II score on admission, *Me (IQR)*	5 (3–8)
Diabetes mellitus, *N* (%)	33 (15)
Charlson comorbidity index, *Me (IQR)*	2 (1–4)
CIRS comorbidity score, *Me (IQR)*	10 (7–13)
RAPID pleural infection assessment [41], *Me (IQR)*	1 (1–2)

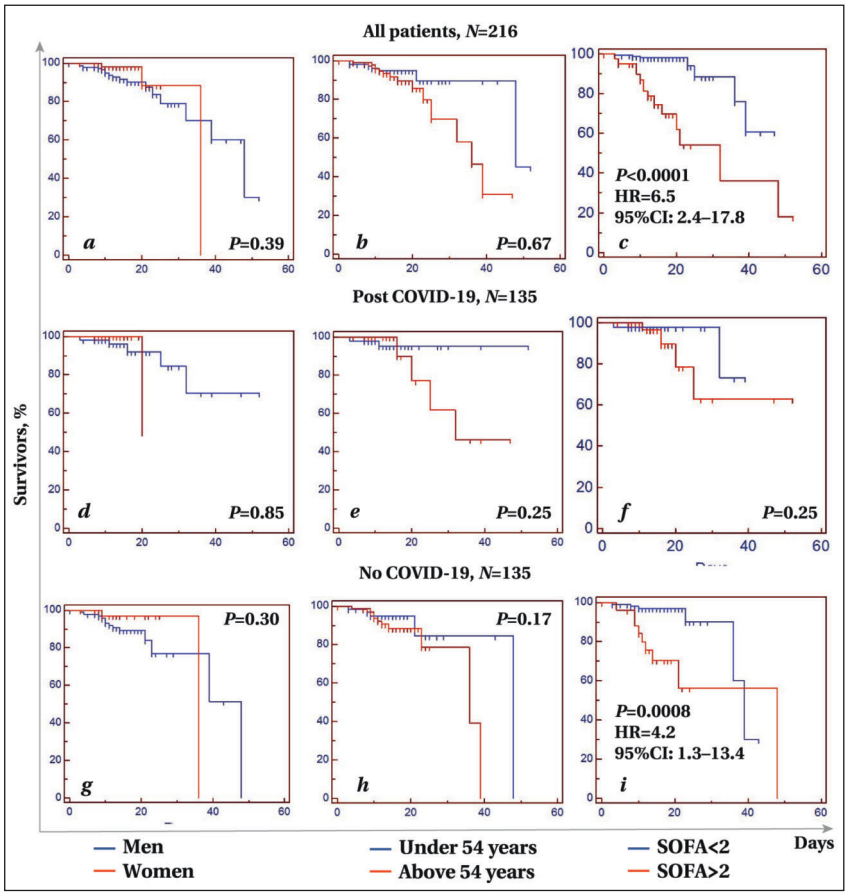

Fig. 2. Prognostic significance of sex, age, and SOFA score on day 1 of hospitalization for outcome in pleural empyema regardless of fistula formation (Log-rank test.).

Total mortality was 21 cases (9.7%). The causes of death included sepsis (14 cases, 66.6%), pulmonary hemorrhage (4 cases, 19.1%), and pulmonary embolism (3 cases, 14.3%). The total length of hospital stay was 14 (11–18) days. The detailed analysis of causes of death and length of hospital stay in the PE and PEF groups with/without COVID-19 history is shown in Table 2.

The results of linear regression analysis of demographics, scores, and cellular parameters of the total patient cohort are presented in Table 3. SOFA, RAPID, and Charlson index scores correlated with patient age. CIRS, RAPID and Charlson index scores correlated with sex. In women, the mean Charlson index score was higher and the CIRS and RAPID scores were lower than in men. Increased SOFA scores correlated with increased CIRS scores, adverse outcomes, increased neutrophil count, and decreased monocyte count. CIRS score predicted outcome. Although the CIRS comorbidity scale and Charlson index scores correlated, the Charlson index score did not influence the outcome of pleural empyema. Increased monocyte counts correlated with increased neutrophil and lymphocyte counts; however, only neutrophil and monocyte counts significantly predicted outcome (Table 3).

greater than 2 also predicted mortality in the entire patient cohort (Fig. 3, *c*), but no such association was found in patients who survived or did not have COVID-19 (Fig. 3 *e*, *h*). The use of the RAPID scale to assess patient functional status also contributed to the prediction of outcome. RAPID index scores >2 represented unfavorable prognostic markers in the total patient cohort (Fig. 3, *c*). However, in patients who had survived COVID-19, the RAPID score had no prognostic significance (Fig. 3, *f*), and in patients who did not have COVID-19, the association of poor survival with increased RAPID score values persisted (Fig. 3, *i*).

The results of linear regression analysis of demographics, scores, and cellular parameters as a function of history of COVID-19 are shown in Table 4. The NLR value correlated with SOFA, CIRS, RAPID scores, Charlson index, and outcome in the entire patient cohort and in patients without a history of COVID-19.

Table 2. Causes of death and length of stay in the PE and PEF groups.

Parameter	Values in groups					
	Pulmonary empyema (PE)			Pulmonary empyema with fistula (PEF)		
	Total cohort	Post COVID-19	No COVID-19 history	Total cohort	Post COVID-19	No COVID-19 history
Mortality, *N* (%)	2 (1.5)	1 (2.0)	1 (1.2)	19 (21.3)	5 (15.6)	14 (24.5)
Causes:						
sepsis	2 (100)	1 (100)	1 (100)	12 (63.2)	4 (80)	8 (57.2)
pulmonary hemorrhage	—	—	—	4 (21)	1 (20)	3 (21.4)
pulmonary embolism	—	—	—	3 (15.8)	—	3 (21.4)
Length of hospital stay, days, *Me (Q1–Q3)*	13 (10–16)	13 (10–16)	13 (10–16)	17 (13–21)	16(14–23)	18(13–21)

In patients with a history of COVID-19, the NLR index only correlated with SOFA score and outcome. In the entire patient cohort, an increase in the SIRI index correlated with an increase in SOFA score. This pattern did not persist when patients with/without a history of COVID-19 were analyzed separately. The SII score correlated with the Charlson Index and RAPID scores in the entire patient cohort and in those without previous COVID-19, and with SOFA scores in COVID-19 survivors. An increase in SII correlated with poor prognosis in the entire cohort and in COVID-19 survivors.

We then analyzed the neutrophil, lymphocyte, and monocyte counts in patients in the PE and PEF groups on the 1st, 3rd, 5th, 7th and last day of hospitalization (Fig. 4).

Neutrophils. As shown in Figure 4, there was a significant difference in neutrophil counts between patients with and without fistula on the 5th, 7th, and last days of hospitalization.

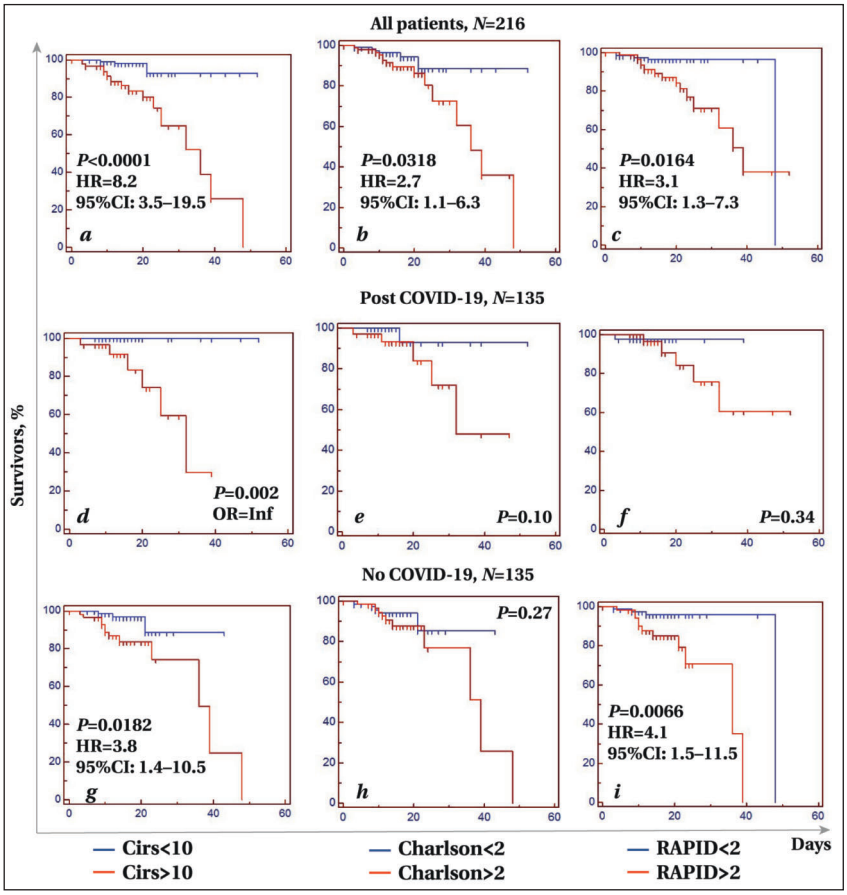

Fig. 3. Prognostic significance of CIRS and RAPID scores, Charlson score for outcome in pleural empyema regardless of fistula formation (Log-rank test).

In both PEF and PE groups, when comparing the circulating neutrophil counts on day 1 of hospitalization between the subgroups of patients with vs without a history of COVID-19, no differences were found (Table 5).

The prognostic value of circulating neutrophils counts for the outcome of SDLP was also analyzed, including those in relation to history of COVID-19 (Fig. 5).

As shown in Figure 5, an elevated neutrophil count was associated with an unfavorable outcome of SDLP in the entire patient cohort (Fig. 5, *a*). However, on separate analysis of patients with/with-

Table 3. Results of linear regression analysis of demographics. scores and cellular parameters.

Parameter	Age	Sex	SOFA	CIRS	Charlson index	RAPID	Lymphocyte count	Neutrophil count	Monocyte count
Age	—	0.13	0.23	0.63	0.77	0.67	–0.12	0.04	–0.18
		0.09	**0.0098**	0.063	<0.0001	**<0.0001**	0.57	0.09	0.35
Sex	0.13	—	–0.02	0.11	0.11	–0.03	0.013	–0.04	–0.07
	0.09		0.67	**0.02**	**0.02**	**0.037**	0.9	0.59	0.34
SOFA	0.23	–0.02	—	0.45	0.40	0.36	–0.26	0.23	–0.20
	0.0098	0.67		**0.02**	0.051	0.16	0.20	**0.0015**	**0.016**
CIRS	0.63	–0.03	0.45	—	0.77	0.58	–0.17	0.09	–0.17
	0.063	**0.015**	**0.02**		**<0.0001**	0.82	0.75	0.9	0.56
Charlson index	0.77	0.11	0.40	0.77	—	0.66	–0.18	0.015	–0.24
	<0.0001	**0.02**	0.051	**<0.0001**		**<0.0001**	0.64	0.58	**0.0498**
RAPID	0.67	–0.03	0.36	0.58	0.66	—	–0.20	0.02	–0.24
	<0.0001	**0.037**	0.16	0.82	**<0.0001**		0.30	0.64	0.07
Neutrophil count	0.04	–0.04	0.23	0.09	0.015	0.02	–0.08	—	0.46
	0.09	0.59	**0.0015**	0.9	0.58	0.64	0.11		**<0.0001**
Monocyte count	–0.18	–0.07	–0.20	–0.17	–0.24	–0.24	0.22	0.46	—
	0.35	0.34	**0.016**	0.56	**0.0498**	0.07	**0.0058**	**<0.0001**	
Outcome	0.16	0.11	0.48	0.38	0.29	0.30	–0.25	0.26	–0.15
	0.08	0.19	**0.0001**	**0.0198**	0.89	0.17	0.17	**0.0005**	**0.0232**

Note. In each column, the upper value corresponds to r values, the lower value corresponds to *P*-values, *N*=216.

Table 4. Results of linear regression analysis of demographics, scores, and cellular parameters in relation to COVID-19 history.

Parameter	Patients														
	Total, *N*=216						History of COVID-19, *N*=81						No history of COVID-19, *N*=135		
	SIRI	SII	NLR	Lym	Nf	Mon	SIRI	SII	NLR	Lym	Nf	Mon	SIRI	SII	NLR
Age	0.03	0.06	0.18	–0.13	0.02	0.02	0.09	0.007	0.07	–0.10	0.05	–0.27	0.0007	0.09	0.22
	0.96	0.53	0.47	0.45	0.98	0.58	0.23	0.18	0.96	0.16	0.36	**0.004**	0.39	**0.019**	**0.02**
Sex	–0.01	0.03	–0.001	–0.05	–0.1	0.07	–0.01	–0.05	–0.02	0.05	–0.004	–0.07	–0.01	0.05	0.005
	0.49	0.29	0.88	0.089	0.31	0.48	0.38	0.58	0.71	0.30	0.94	0.24	0.62	0.35	0.42
SOFA	0.17	0.32	0.47	–0.28	0.37	–0.13	0.17	0.18	0.47	–0.25	0.16	–0.22	0.16	0.38	0.5
	0.0016	0.12	**<0.0001**	0.72	0.47	0.86	0.27	**0.01**	**0.002**	0.54	0.75	0.58	0.23	0.77	**<0.0001**
CIRS	0.06	0.14	0.24	–0.23	0.09	–0.01	0.14	0.07	0.17	–0.13	0.09	–0.25	0.02	0.17	0.27
	0.08	0.26	**0.0002**	0.23	0.70	0.42	0.24	0.13	0.98	0.51	0.28	0.09	0.58	0.31	**0.03**
Charlson	0.03	0.09	0.22	–0.12	0.03	–0.02	0.07	–0.03	0.08	–0.22	0.005	–0.33	0.008	0.12	0.27
index	0.09	**0.03**	**<0.0001**	0.58	0.93	0.54	0.26	0.06	0.73	0.57	0.88	**0.003**	0.31	**0.03**	**0.02**
RAPID	0.11	0.18	0.34	–0.09	0.06	0.05	0.05	0.15	0.12	–0.27	0.07	–0.29	0.11	0.24	0.42
	0.10	**0.01**	**<0.0001**	0.92	0.61	0.55	0.13	0.13	0.60	0.39	0.52	**0.02**	0.39	**0.007**	**<0.0001**
Outcome	0.26	0.18	0.43	–0.29	0.34	–0.14	0.23	0.19	0.46	–0.23	0.22	–0.16	0.16	0.28	0.42
	0.11	**0.012**	**<0.0001**	0.65	0.49	0.12	0.42	**0.002**	**0.023**	0.83	0.12	0.43	0.34	0.14	**0.001**

Note. In each column, the upper value corresponds to the values of *R*, the lower value corresponds to the values of *P*.

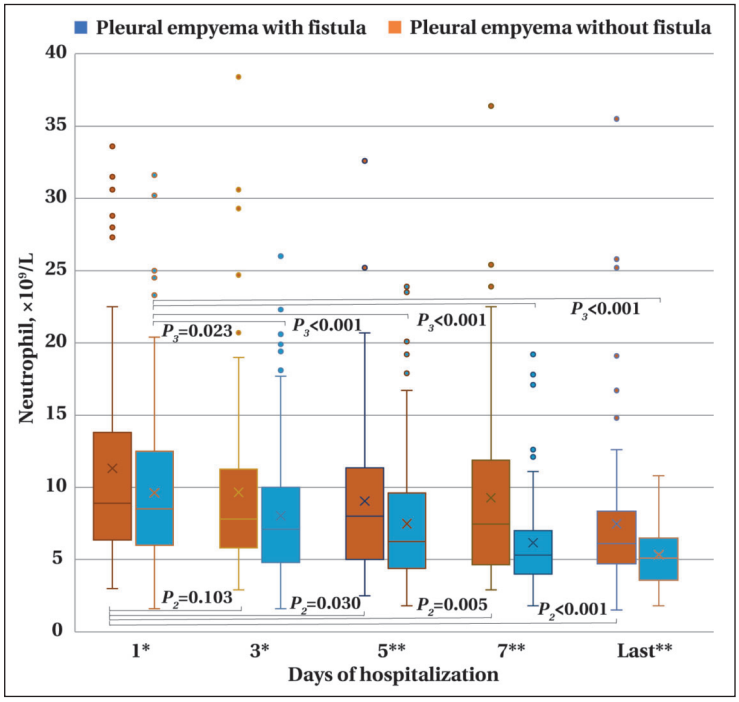

Fig. 4. Neutrophil count in patients with pleural empyema with and without fistula.

Note. ** P_1<0.05; *P_1>0.05. P_1 — significance of differences between neutrophil counts in patients with PE with fistula (blue bars) and without fistula (orange bars) on different days of hospitalization. P_2 — significance of differences between neutrophil counts on different days of hospitalization separately in the PEF group. P_3 — significance of differences between neutrophil counts on different days of hospitalization separately in the PE group.

out COVID-19, we found that an elevated neutrophil count predicted a poor outcome only in patients without a history of COVID-19 (Fig. 5, *c*). For patients with a history of COVID-19, the association was not significant (Fig. 5, *b*).

Lymphocytes. As shown in Table 6, the groups of patients with and without fistula did not differ in lymphocyte counts on days 1, 3, 5, and on the last day of hospitalization. On day 7, patients with pleural empyema with fistula had lower lymphocyte counts than patients with pleural empyema without fistula. Patients with/without a history of COVID-19 in the PEF group had similar lymphocyte counts on days 1, 5, 7, and the last day of hospitalization. However, on day 3 of hospitalization, the lymphocyte count was higher in patients with a history of COVID-19. When comparing the lymphocyte counts in patients in the PE group with/without a history of COVID-19 on the 1st, 3rd, 5th, 7th, and last day of hospitalization, no significant differences were found (Table 6).

We also analyzed the potential contribution of circulating lymphocyte count to the outcome of SDLP (Fig. 5). An increased lymphocyte count was associated with a better prognosis both for the entire patient cohort (Fig. 5, *d*) and for patients with/without a history of COVID-19 (Fig. 5, *e*, *f*). Thus, an increased lymphocyte count during hospitalization may be relevant for a favorable outcome of SDLP, independent of a history of COVID-19.

Monocytes. Monocyte counts in patients with and without fistulas on the 1st, 3rd, 5th, 7th, and last day of hospitalization did not differ (Table 7). There were no differences in monocyte counts between patients with pleural empyema with/without a history of COVID-19.

The associations of neutrophil, lymphocyte, monocyte counts, NLR, SII and SIRI scores with the outcome of SDLP were analyzed using the log-rank test.

The association of patient survival and neutrophil (Fig. 6, *a*), lymphocyte (Fig. 6, *b*) and monocyte (Fig. 6, *c*) counts was found on day 1 of hospitalization.

Table 5. Neutrophil counts in patients with pleural empyema with and without fistula.

Group	History of COVID-19	Values by study days									
		1		3		5		7		Last	
PEF	+	8.9	8.3	7.8	7.6	8.0	7.8	7.0	6.8	6.1	6.1
		(6.3–13.6)	(5.8–11.2)	(5.8–11.2)	(5.7–11.2)	(5–11.2)	(5.2–9.9)	(4.5–11.5)	(5.0–9.8)	(4.7–8.2)	(4.3–7.9)
		N=89	*N*=32	*N*=89	*N*=32	*N*=85	*N*=31	*N*=85	*N*=31	*N*=85	*N*=31
	–		9.7		8		8.4		7.3		6.2
			(6.5–15.9)		(5.8–11.5)		(4.9–11.7)		(4.4–12.5)		(4.7–9.1)
			N=57		*N*=57		*N*=54		*N*=54		*N*=54
PE	+	8.5	8.0	7.2	7.0	6.2	6.6	5.3	5.6	5.1	5.1
		(6–12.4)	(5.5–12)	(4.9–10)	(4.3–9.7)	(4.4–9.6)	(4.2–10.3)	(4.0–7.0)	(3.9–8.0)	(3.6–6.5)	(3.5–6.2)
		N=127	*N*=49	*N*=127	*N*=49	*N*=126	*N*=48	*N*=126	*N*=48	*N*=126	*N*=48
	–		8.6		7.3		6.1		5.2		4.9
			(6.2–12.7)		(5.0–10.1)		(4.5–8.7)		(4.0–7.0)		(3.6–6.6)
			N=78		*N*=78		*N*=78		*N*=78		*N*=78
		P_1=0.179		P_1=0.084		P_1=0.024		P_1≤0.001		P_1=0.001	
		P_2=0.101		P_2=0.489		P_2=0.396		P_2=0.446		P_2=0.565	
		P_3=0.390		P_3=0.482		P_3=0.998		P_3=0.725		P_3=0.947	

Note. For Tables 5–7: reported are *Me (IQR)* and n values for each of the groups (PEF, PE) and subgroups (PEF and a history of COVID-19, PEF without a history of COVID-19; PE and a history of COVID-19; PE without a history of COVID-19) by study day (1st to last). Significance of differences when comparing groups and subgroups: P_1 — PEF vs. PE; P_2 — PEF+ vs. PE+; P_3 — PEF⁻ vs. PE⁻.

Table 6. Lymphocyte counts in patients with pleural empyema with and without fistula.

Group	History of COVID-19	Values by study days									
		1		3		5		7		Last	
PEF	+	1.7	1.9	1.6	1.8	1.5	1.7	1.4	1.5	1.4	1.6
		(1–2.3)	(1.2–2.5)	(1–2)	(1.4–2.2)	(1–1.9)	(1.3–2)	(1–1.9)	(1.1–1.9)	(1–2.1)	(0.9–2.1)
	–		1.6		1.5		1.3		1.2		1.4
			(1–2.3)		(0.9–2)		(1–1.8)		(0.9–1.8)		(1.1–2)
PE	+	1.9	2.1	1.6	1.5	1.6	1.5	1.6	1.5	1.7	1.5
		(1.3–2.3)	(1.1–2.6)	(1.2–2)	(1.2–2.3)	(1.2–2)	(1.1–2.1)	(1.2–2)	(1–2)	(1.2–2.3)	(1.2–2)
	–		1.8		1.7		1.6		1.6		1.8
			(1.3–2.3)		(1.1–2)		(1.2–2)		(1.2–2)		(1.2–2.3)
		P_1=0.292		P_1=0.726		P_1=0.254		P_1=0.010		P_1=0.061	
		P_2=0.479		P_2=0.046		P_2=0.106		P_2=0.126		P_2=0.578	
		P_3=0.561		P_3=0.661		P_3=0.594		P_3=0.598		P_3=0.181	

Increased neutrophil count and decreased lymphocyte and monocyte counts were associated with a poor outcome of SDLP in the entire patient cohort. However, the presence of a prior COVID-19 hospitalization reduced the significance of this association for neutrophil and monocyte counts (Fig. 6, *d*, *f*), but not for lymphocyte counts. The prognostic value of lymphocyte count remained consistent for patients with and without a history of COVID-19 (Fig. 6, *b*, *e*, *h*). In addition, patient survival was significantly associated with lymphocyte count (Fig. 6, *e*, *h*).

In patients without COVID-19, we also found that survival was dependent on the blood monocyte count (Fig. 6, *i*) on day 1 of hospitalization. Thus, a decreased lymphocyte count on day 1 of hospitalization was an adverse prognostic factor regardless of the history of COVID-19, and a decreased monocyte count indicated an unfavorable prognosis only in patients without a history of COVID-19.

Analysis of the relative values of cellular markers of the immune system in all patients of the cohort revealed an association of survival with the values of SII (Fig. 7, *a*), SIRI (Fig. 7, *b*) and NLR (Fig. 7, *c*) on the first day of hospitalization, namely increased values of SII, SIRI and NLR were associated with an unfavorable outcome of SDLP.

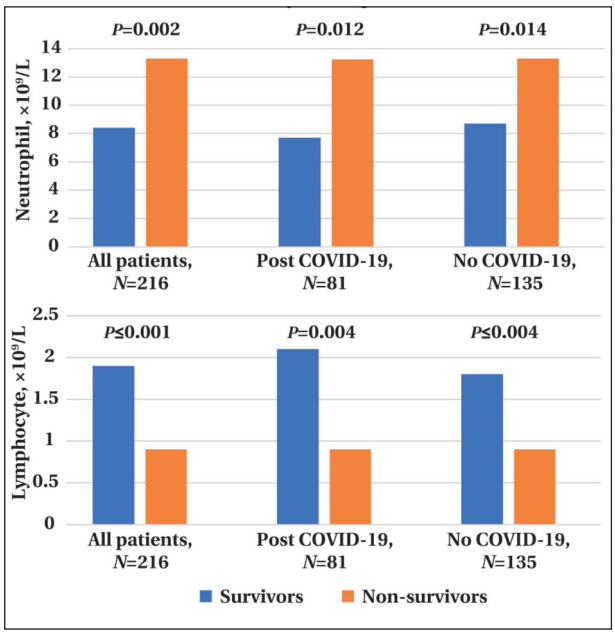

Fig. 5. Outcome of SDLP in relation to neutrophil and lymphocyte count on the 1st day of hospitalization (Mann–Whitney test).

Fig. 7. Prognostic significance of immune cell counts on day 1 of hospitalization.

Group	History of COVID-19	Values by study days									
		1		3		5		7		Last	
PEF	+	0.8	0.7	0.6	0.6	0.5	0.6	0.5	0.5	0.6	0.6
		(0.6–1.2)	(0.6–1.1)	(0.4–0.9)	(0.5–0.8)	(0.4–0.8)	(0.3–0.7)	(0.4–0.7)	(0.4–0.7)	(0.4–0.7)	(0.4–0.8)
	–		0.9		0.6		0.5		0.5		0.6
			(0.5–1.3)		(0.4–1)		(0.4–0.8)		(0.4–0.7)		(0.3–0.7)
PE	+	0.9	0.9	0.7	0.7	0.6	0.6	0.6	0.6	0.5	0.5
		(0.6–1.2)	(0.6–1.1)	(0.5–0.9)	(0.5–0.8)	(0.4–0.8)	(0.4–0.8)	(0.4–0.7)	(0.4–0.8)	(0.4–0.7)	(0.4–0.7)
	–		0.9		0.7		0.6		0.6		0.5
			(0.6–1.2)		(0.5–1)		(0.4–0.7)		(0.5–0.7)		(0.5–0.7)
		P_1=0.480		P_1=0.318		P_1=0.497		P_1=0.624		P_1=0.604	
		P_2=0.541		P_2=0.891		P_2=0.906		P_2=0.916		P_2=0.390	
		P_3=0.634		P_3=0.603		P_3=0.691		P_3=0.794		P_3=0.427	

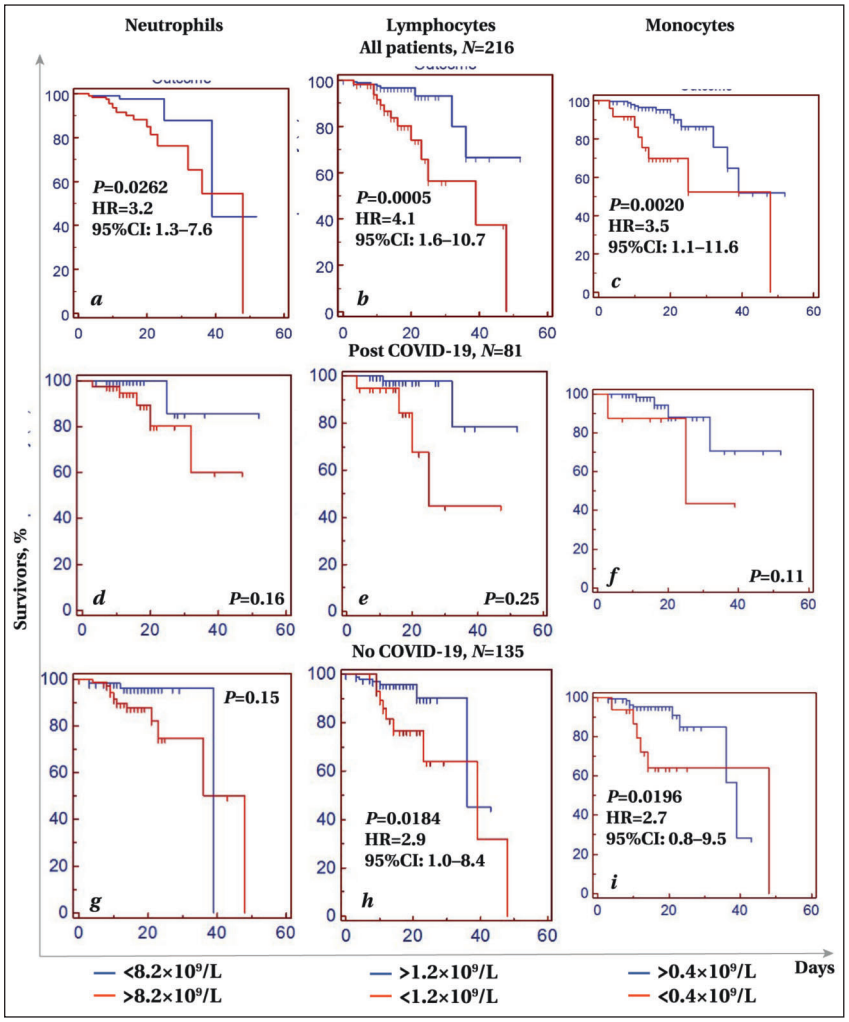

Fig. 6. Prognostic significance of immune cell counts on day 1 of hospitalization.

In patients with a history of COVID-19, there was a significant difference in survival in relation to SII (Fig. 7, *d*), SIRI (Fig. 7, *e*), and NLR (Fig. 7, *f*) on day 1 of hospitalization. No such difference was found in patients without a history of COVID-19 (Fig. 7 *g*, *h*, *i*).

Thus, SIRI, SII, and NLR values were the most informative in predicting the outcome of SDLP in patients with a history of COVID-19 (HR value greater than 7).

The results of the survival analysis based on cell marker levels on day 1 of hospitalization are summarized in Table 8.

Discussion

On the first day of hospitalization, a decrease in lymphocyte count below 1.2×10⁹/L allows predicting an unfavorable outcome of pleural empyema; however, the prognosis does not depend on the patient's history of COVID-19. Another potential marker, monocyte count, could predict the outcome of pleural empyema only in the subset of patients without a history of COVID-19. Increased SIRI (>4), SII (>2500) and NLR (>6), which characterize the severity of the systemic inflammatory response, were associated with the risk of adverse outcomes in patients with SDLP and a history of COVID-19.

The observed significant association of mortality with an increase in NLR on the first day of hospitalization reflects the high prognostic value of both neutrophil and lymphocyte levels (which serve as the basis for calculating NLR values) (Fig. 5, 6). The prognostic value of these markers is understandable given the pathogenetic significance of both cell populations as key components of adaptive defense mechanisms against infection. In response to bacterial infection, neutrophils migrate intensively from the bone marrow and become activated, releasing large amounts of oxygen and nitrogen radicals (ONRs), proteolytic enzymes, and cytokines. Neutrophils undergo netosis, the formation of «neutrophil traps,» which are complexes of positively charged nuclear proteins

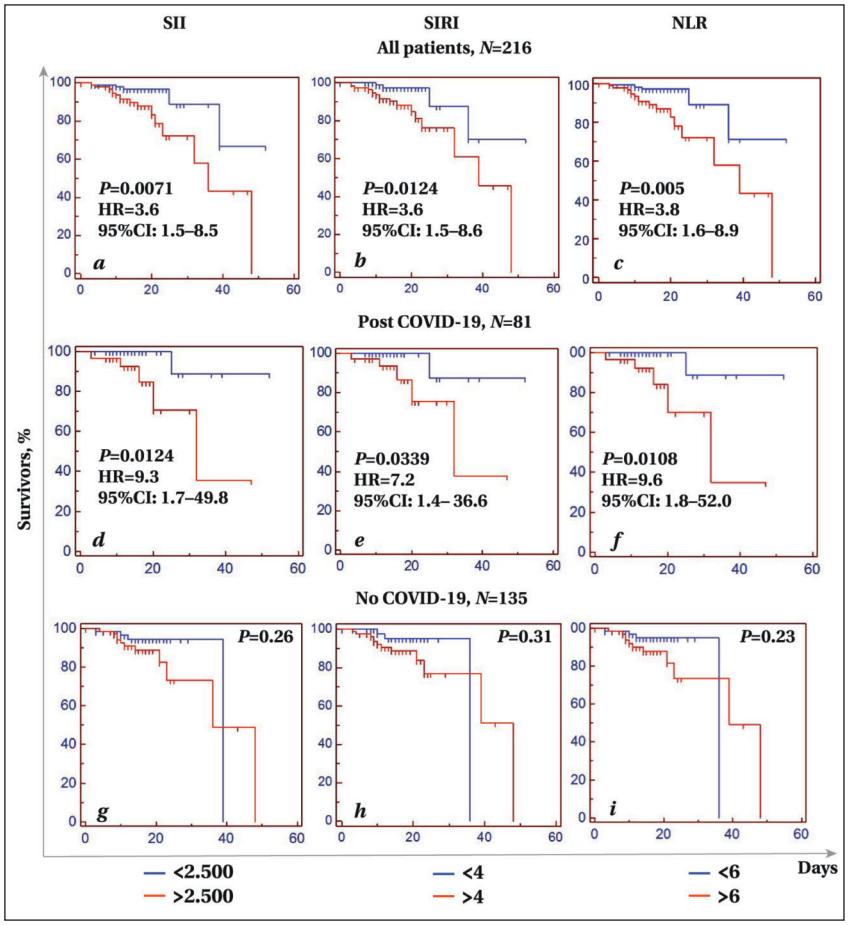

Fig. 7. Values of SII, SIRI, and NLR and the outcome of SDLP.

(HMGB1 and histones) and large fragments of nuclear and mitochondrial DNA. Located on the surface of neutrophils, neutrophil traps bind bacteria, but together with ONRs and the proinflammatory microenvironment, they can cause damage to the vascular endothelium [42]. The latter manifests as degradation of the cell surface glycocalyx and an increase in endothelial permeability due to impaired interactions between endothelial cells. The collapse of endothelial barrier structures consistently leads to increased microvascular permeability, vascular hypotension, edema, decreased tissue perfusion, and the development of life-threatening organ failure typical of septic infectious complications [43]. The associated amplification of procoagulant mechanisms associated with degradation of anticoagulant systems on the surface of endothelial cells and increased expression of tissue factor (TF) may contribute to the severity of the disease [44]. These processes, occurring with underlying progressive endothelial dysfunction, increase the likelihood of thrombotic complications and worsen the prognosis of SDLP.

On the other hand, the decreased lymphocyte count in the blood of patients with SDLP, which is associated with a poor prognosis, indicates a decrease in the immune responses carried out by cells of the adaptive immune system — T and B cells. This increases the risk of an unfavorable outcome due to an increased likelihood of severe infections as a result of decreased immune competence. Lymphopenia and high NLR are recognized as adverse prognostic markers for the progression of pneumonia, including COVID-19-associated pneumonia [45–47]. In contrast, low NLR levels, corresponding to decreased neutrophil counts and increased lymphocyte counts, have been associated with better prognosis in pneumonia [48].

A recent study found that elevated levels of NLR, SII, and SIRI, which are relative biomarkers of systemic inflammatory response, were predictive of COVID-19 outcomes [49]. Patients with SII values above 1835 had a lower oxygenation index and more severe lung changes on CT than those with SII values below 1835.

Neutrophils, the most abundant and diverse circulating granulocytic leukocytes, play an important role in the innate immune system. They serve as the «first line» of immune defense against bacterial and fungal infections, destroying microorganisms by phagocytosis, producing antibacterial peptides

Table 8. Survival analysis in relation to cell marker levels on day 1 of hospitalization using Cox regression.

	All patients			History of COVID-19			No history of COVID-19		
	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**
Lymphocytes	**0.0012**	2.1	1.3–3.2	**0.0026**	0.1	0.01–1.0	**0.0285**	0.4	0.2–1.0
Neutrophils	**0.0199**	1.8	1.0–3.1	**0.0033**	1.2	1.1–1.4	**0.0298**	1.1	1.0–1.2
Monocytes	**0.0071**	2.0	1.2–3.1	0.35			0.14		
SIRI	**0.0091**	1.9	1.1–3.3	0.06			0.057		
SII	**0.0061**	1.9	1.5–3.1	0.08			**0.0096**	1.0	1.0–1.1
NLR	**0.0044**	1.9	**1.2–3.2**	**0.0016**	1.2	1.0–1.3	**0.0009**	1.0	1.0–1.1

and ONRs, and forming NETs. However, their role in viral infections is unclear. Neutrophils in SARS-CoV-infected mice do not appear to be required for virus clearance from lung cells or host survival [50].

Cells with a neutrophil-like phenotype may also have significant immunosuppressive activity [51]. Their increase in circulation is associated with the severity of pneumonia [52]. There are data on the involvement of immunoregulatory cell populations in COVID-19. Here, they perform two opposing functions — they suppress virus-specific T-cell immune response and reduce excessive inflammatory response [53]. However, the prognostic value of detecting this cell population in pneumonia has not yet been established.

The lymphopenia observed in COVID-19 is probably related to the ability of the virus to infect T cells via viral S protein involving angiotensin converting enzyme receptor 2 (ACE2) and possibly CD147 [54]. In COVID-19 disease, a decrease in CD3+, CD4+, and CD8+ T lymphocytes and an increase in regulatory T cells are often observed.

The prognostic significance of a decrease in lymphocyte count on the first day of hospitalization was established in patients without a history of COVID-19 (Fig. 7, *b*, *e*, *h*). This indicates that even a small decrease in lymphocyte count (cut-off point of less than 1.0×10^9/L, not even reaching the lymphopenia limit, i. e., less than 10^9/mL) is of key importance for the course of SDLP. It can be assumed that disturbances of the adaptive T-cell immunity system in COVID-19, possibly caused by «immune exhaustion» after the period of their previous activation, may be of a prolonged nature, being part of the whole complex of various consequences of this disease. It is possible that such patients require immunomodulatory drugs capable of increasing the functional activity of CD4+ and CD8+ T lymphocytes or B cells. However, clinical evidence supporting the use of immunomodulators in the treatment of SDLP is currently lacking, as no large-scale clinical trials of treatment with immunomodulators such as Lycopid©, Immunophan©, Polyoxidonium©, and immunoglobulin-containing preparations have been reported in the literature.

In several diseases, a decrease in CD4+ and CD8+ T lymphocytes is often associated with disease severity and leads to an increase in NLR values. This ratio is considered to be a more sensitive biomarker of clinically significant immune system disorders than neutrophil and lymphocyte counts taken separately [49, 55].

The relative markers NLR, SII, and SIRI seem to reflect systemic inflammation and a wide range of immune responses carried out by innate and adaptive immune cells in an integrated manner. In prolonged or recurrent infections, a sustained inflammatory response can exhaust the immune system, thereby reducing systemic immunity. The reason for the rapid decline in peripheral blood lymphocyte counts in SDLP may be inadequate recovery from COVID-19 or increased susceptibility to immune cell death by apoptosis [56] or pyroptosis characteristic of lung disease [57].

Elevated NLR and CRP levels may predict adverse outcomes in COVID-19 patients [58, 59]. Considering that SARS-CoV-2 can directly infect endothelial cells, an increase in the NLR in COVID-19 may indicate a risk of endothelial dysfunction as a result of the joint damaging effect of the virus and neutrophils on the endothelium, followed by progressive endothelial damage, induction of a proinflammatory cascade with activation of complement factors C3 and C5, increased endothelial permeability, and production of chemokines that increase chemotactic migration of inflammatory cells. It is possible that coronavirus infection preceding SDLP permanently disrupts some components of the innate and adaptive immune systems, predisposing to a greater migratory ability of neutrophils and leading to an increase in the relative indices of innate immunity NLR, SII, SIRI, a decrease in the peripheral blood lymphocyte count, and the ability of the adaptive immune system to resist the increased bacterial load in SDLP [58].

Interestingly, the relative SIRI index, which depends on the increase in neutrophils and monocytes on the one hand and the decrease in lymphocytes on the other, had the potential to predict early death in patients with SDLP and a history of COVID-19 (Fig. 8). This may be due to the marked immunosuppression in these patients, as morphologically granulocytic myeloid-derived suppressor cells (G-MDSC) can belong to the neutrophilic granulocytes and monocytic myeloid-derived suppressor cells (M-MDSC) to the monocytic population [51]. Both subpopulations of immunosuppressive cells are generated during infection, and an association with mortality in septic complications in ICU patients has been found for both G-MDSC [60] and M-MDSC [61].

The ongoing search for pathogenetically significant biomarkers that can aid in the early detection of life-threatening and emergency conditions remains a priority. Researchers hope to find prognostic biomarkers that can stratify patients into risk groups for adverse outcomes of SDLP and allow timely selection of optimal personalized treatment methods. The present study provides simple clinical and laboratory relative cellular biomarkers of SDLP outcomes that are associated with the pathogenesis of lung disease and reflect the levels of immune system cells and may serve as candidate markers for further validation in other studies.

The limitation of our study was its lack of external validity, as it was conducted in a single center.

This highlights the importance of confirming the results in other clinical settings.

Conclusion

In patients with suppurative diseases of lungs and pleura, prior COVID-19 may influence the prognostic value of absolute and relative cellular markers of the immune system. Lymphocyte count on day 1 of hospitalization is a biomarker independent of demographic and clinical variables that can predict the outcome of pleural empyema in patients regardless of prior COVID-19; namely, a decrease in lymphocyte count below 1.2×10^9/mL is associated with mortality.

In patients with pleural empyema and no history of COVID-19, the monocyte count is prognostically significant. Increased levels of the relative cell biomarkers SIRI, SII and NLR on the first day of hospitalization are associated with mortality in patients with COVID-19.

An increase in CIRS comorbidity score above 10 is associated with an unfavorable outcome of SDLP, independent of COVID-19 history.

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Received 08.12.2023
Accepted 15.03.2024