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# Influence of anticoagulant therapy on immune and inflammatory response in patients with community-acquired pneumonia associated with coronavirus infection

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**Keywords:** immune response, pneumonia, COVID-19, anticoagulant therapy, heparin, enoxaparin, interleukin-6, C-reactive protein.

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The publication raises the issue of finding ways to reduce the level of thrombotic complications in patients with community-acquired pneumonia associated with COVID-19.

**Aim.** To determine the effect of anticoagulant therapy on the immune and inflammatory response in patients with community-acquired pneumonia associated with coronavirus infection.

**Material and methods.** An open, prospective, observational study was conducted in the period from January 2021 to February 2022 at the Kherson City Clinical Hospital named after Athanasius and Olga Tropin of the Kherson City Council, 143 patients with community-acquired pneumonia aged 46 to 65 years who tested positive for SARS-CoV-2 were observed. To participate in the study, patients signed a voluntary consent form.

**Results.** Patients with community-acquired pneumonia develop an immune-inflammatory response characterized by increased levels of interleukin-6 and C-reactive protein, with significantly higher values of these biomarkers in combination with COVID-19. Combination therapy is effective in reducing the levels of markers of the immune-inflammatory response Heparin at a dose of 1000 IU/h is more effective in reducing the risk of death in patients with community-acquired pneumonia associated with coronavirus infection than 100 IU anti-Xa/kg (1 mg/kg) twice daily.

**Conclusions.** The results of our study showed that therapy with heparin is more effective than enoxaparin in reducing interleukin-6 levels within 72 hours (by -12.93 % vs -4.75 %, respectively, $p < 0.05$). Multivariate regression analysis determined that changes in the levels of D-dimer, interleukin-6 and INR were independent predictors of adverse disease outcome.

**Ключові слова:** імунозапальна відповідь, негоспітальна пневмонія, COVID-19, антикоагулянтна терапія, гепарин, еноксапарин, інтерлейкін-6, С-реактивний білок.

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## Вплив терапії, що включала антикоагулянти, на показники імунозапальної відповіді у хворих на негоспітальну пневмонію, асоційовану з коронавірусною інфекцією

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Актуальним залишається пошук шляхів зменшення рівня тромботичних ускладнень у хворих на негоспітальну пневмонію, що асоційована з COVID-19.

**Мета роботи –** визначити вплив терапії, що включала антикоагулянти, на показники імунозапальної відповіді у хворих на негоспітальну пневмонію, асоційовану з коронавірусною інфекцією.

**Матеріали і методи.** Здійснили відкрите, проспективне, обсерваційне дослідження в період з січня 2021 до лютого 2022 року на базі КНП «Херсонська міська клінічна лікарня мені Афанасія і Ольги Тропіних» Херсонської міської ради. Під спостереженням перебували 143 хворих на негоспітальну пневмонію віком від 46 до 65 років, які мали позитивний тест до SARS-CoV-2. Для участі в дослідженні пацієнти підписали форму добровільної згоди на участь.

**Результати.** У хворих на негоспітальну пневмонію спостерігали розвиток імунозапальної відповіді, що характеризувалася підвищенням рівнів інтерлейкіну-6 та С-реактивного білка. Значення цих біомаркерів достовірно вищі при поєднанні з COVID-19. Комбінована терапія є ефективною для зниження рівнів маркерів імунозапальної відповіді. Гепарин у дозі 1000 МО/год ефективніше знижує ризик смерті в пацієнтів із негоспітальною пневмонією, що асоційована з коронавірусною інфекцією, ніж 100 МО анти-Ха/кг (1 мг/кг) двічі на добу.

**Висновки.** Результати дослідження показали: терапія, що включала гепарин, ефективніше порівняно з еноксапарином знижує рівні інтерлейкіну-6 протягом 72 годин (на -12,93 % vs -4,75 % відповідно, $p < 0,05$). Згідно з результатами мультиваріантного регресійного аналізу, незалежними предикторами несприятливого перебігу захворювання є зміни рівнів D-димеру, інтерлейкіну-6 і МНВ.

Severe pneumonia caused by COVID-19 has made researchers aware of the seriousness of the medical problem. In addition to the known factors – age and comorbidities – that increase the risk of severe community-acquired pneumonia (CAP) associated with coronavirus infection, additional factors are being sought. At the beginning of the pandemic, doctors around the world observed an increase in blood clots and inflammation among patients with COVID-19, which affected multiple organs and led to complications such as pulmonary insufficiency, heart attack, and stroke [1,2,3].

The rate of thrombotic complications in patients with COVID-19-associated CAP is high and may be associated with a risk of adverse outcomes. A group of researchers by A. S. Manolis et al. reported that the incidence of thrombotic complications in COVID-19 cases occurs in 35 % of patients, which is associated with a risk of adverse outcomes. In addition, pulmonary thrombotic events

can occur even in patients already taking anticoagulant therapy. The conclusion of the study by C. M. Niculae et al. who analyzed 13 cohort studies including 4058 patients concluded that pulmonary thrombotic events in patients with COVID-19 are more likely to be associated with inflammation than with traditional risk factors for thromboembolism, so this aspect should be taken into account in the therapeutic approach [4,5].

The hypothesis of whether full-dose heparin is more beneficial for the treatment of hospitalized adults with COVID-19 compared to the usual lower dose of heparin has been the basis for a number of clinical trials. At the beginning of the pandemic, it was not known whether the use of blood thinners at average therapeutic doses would be sufficient or whether higher doses of anticoagulants, which are regularly administered to hospitalized patients, would be safe and more effective. Currently, researchers are working as quickly as possible to publish the full results of the studies so that clinicians can make informed decisions about the treatment of their patients with COVID-19. Research questions remain on how to improve clinical care for patients with COVID-19 [6,7].

The immune status of the patients currently of particular importance, as more and more data on the immunopathogenesis of COVID-19 are becoming available. Multiorgan damage is triggered by a dysfunctional immune response to the virus, which can persist in a context similar to cytokine release syndrome. Studies have reported elevated plasma levels of various interleukins and chemokines in patients with COVID-19, but it has been difficult to identify a pattern associated with poor prognosis. Among cytokines, elevated levels of interleukin-6 have been consistently reported in patients with COVID-19, which correlates with disease activity [8,9].

Cytokine homeostasis is significantly altered by SARS-CoV-2. COVID-19 patients with hypoxic respiratory failures how signs of systemic hyperinflammation, including the release of proinflammatory cytokines such as interleukin-1 (IL), IL-6, IL-8 and tumor necrosis factor-α (TNF-α), with increased concentrations of the acute phase inflammatory protein C-reactive protein (CRP). There lease of pro-inflammatory cytokines in combination with respiratory failure caused by fibrin synthesis by fibroblasts with subsequent formation of hyaluronic membranes in lung tissues, as well as damage to type 2 alveolocytes, is considered the main pathogenetic mechanism leading to serious disorders of internal organs [10]. According to D. M. Del Valle et al., serum levels of IL-6, IL-8, and TNF-α at the time of hospitalization are strong and independent predictors of survival in this cohort of patients [11].

Patients with severe COVID-19 are at high risk of developing disseminated intravascular coagulation syndrome and venous thromboembolism. The inclusion of anticoagulant therapy, in particular with low-molecular-weight heparin, in the treatment of patients with severe COVID-19 improves the prognosis of such patients. The criterion for prescribing drugs may be cumulative changes in the complete blood count (thrombocytopenia) and coagulation test (increased D-dimer level, prothrombin time). In the absence of contraindications, low-molecular-weight heparins are prescribed [12,13].

Coronavirus COVID-19 is a complex respiratory and systemic disease that can progress to severe inflammation, which can lead to a prothrombotic state. The biomarkers of the immune-inflammatory response in patients with CAP associated with coronavirus infection, both the levels and dynamics of inflammatory markers, are being studied to determine their usefulness in predicting the course of the disease and evaluating the effectiveness of treatment. From the foregoing, it becomes obvious that the assessment of the dynamics of immune-inflammatory response in patients with CAP associated with COVID-19 is relevant not only in a scientific but also in a practical sense, which determined the purpose of this study [14,15].

## Aim

To determine the effect of anticoagulant therapy on the immune and inflammatory response in patients with community-acquired pneumonia associated with coronavirus infection.

## Material and methods

An open, prospective, observational study was conducted in the period from January 2021 to February 2022 at the Kherson City Clinical Hospital named after Athanasius and Olga Tropin of the Kherson City Council, 143 patients with community-acquired pneumonia aged 46 to 65 years who tested positive for SARS-CoV-2 were observed. To participate in the study, patients signed a voluntary consent form.

Exclusion criteria for the study: pregnant women; uncontrolled hypertension; hypertension of the third stage; decompensated diabetes mellitus; congenital and acquired hemodynamically significant heart defects; chronic heart failure of the second and third stages; oncological diseases; alcohol dependence, drug addiction, mental disorders; patient's refusal to participate in the study.

All patients were carefully examined for compliance with the inclusion / exclusion criteria. The diagnosis of community-acquired pneumonia was verified on the basis of the adapted evidence-based clinical practice guideline "Community-acquired pneumonia in adults", 2019. COVID-19 was detected in accordance with Order No. 722 of the Ministry of Health of Ukraine dated 03/28/2020 as amended by Order No. 2122 of the Ministry of Health of Ukraine dated 09/17/2020.

Within the framework of this topic, the author evaluated patients by anthropometric parameters, the state of patients by PSI, CURB-65, quickSOFA scales, and monitored oxygen saturation.

All patients received oxygen support. In both subgroups, oxygen support was provided by high-flow nasal oxygen therapy.

Determination of interleukin-6, interleukin-10, hsCRP was performed in blood plasma by enzyme-linked immunosorbent assay using standard kits: "HF CRP-ELISA-Best", "IL-6-ELISA-Best", "IL-10-ELISA-Best" according to the attached instructions, in the certified laboratory of the Kherson City Clinical Hospital named after Athanasius and Olga Tropin of the Kherson City Council. The ELISA method is based on an immunologic "sandwich" reaction.

The content of IL-6 (IL-10, HF-CRP) in the test sample was determined after interpolation of the actual data to a standard calibration curve. The content of interleukin-6 (interleukin-10) in blood plasma was expressed in pg/mL, the content of hsCRP in blood plasma was expressed in mg/L.

At the inpatient stage of treatment, all patients (n = 143) received oxygen therapy. Systemic corticosteroids were prescribed: dexamethasone 6 mg once daily. Nonsteroidal anti-inflammatory drug ibuprofen: 400 mg twice daily.

After randomization, 71 patients received standard heparin at a dose of 1000 IU/h for 10 days and 72 patients received enoxaparin at a dose of 100 IU anti-Xa/kg (1 mg/kg) twice daily for an additional 10 days at a dose of 1 mg/kg. The calculation of LMWH doses and the timing of administration was carried out in accordance with Order of the Ministry of Health of Ukraine No. 722 of March 28, 2020 "Organization of Medical Care for Patients with Coronavirus Disease (COVID-19)".

The prescribed doses of LMWH were adjusted based on the analysis of the results of INR, PTT, blood fibrinogen, APTT, PI.

Interim study results were assessed on days 3 and 14 after randomization.

Remdesivir was also administered in the hospital: a single dose of 200 mg on the first day and 100 mg intravenously daily on the following days. Remdesivir was administered to 31 patients in the first subgroup and 32 patients in the second subgroup. Remdesivir was administered within the first 5 days of disease onset. The average treatment duration was 5 days.

The effectiveness of treatment was determined by clinical evaluation, laboratory tests and functional tests. The observation period was 30 days, and the endpoint of the study was 30-day survival.

Statistical processing of the data obtained during the study began with descriptive statistics, including the calculation of the median and interquartile range (Me [Q25; Q75]), and the size of the analyzed subgroup (n). The data distribution was determined using the Shapiro–Wilk test, and the data obtained are presented as Me [Q25; Q75], since most of them had a distribution that differs from the normal one. When testing statistical hypotheses, the null hypothesis was rejected at a statistical significance level of $p < 0.05$, which corresponds to the values accepted in biomedical research. All statistical procedures were performed using the Apache OpenOffice (version 4.1.0, Apache Software Foundation, U.S.A. Apache License 2.0.) and PSPP (version 1.2.0, Free Software Foundation, U.S.A., GNU GPL license) application packages.

## Results

Using the adaptive randomization method, patients were divided into two groups depending on the anticoagulant prescribed. The groups of subjects were comparable in terms of age and social status, as well as BMI, $SpO_2$ level, duration of illness at the time of inclusion in the study, and frequency of oxygen support, $p > 0.05$ *(Table 1)*.

The coagulation parameters in patients of the first subgroup (with heparin) and the second subgroup (with enoxaparin) were evaluated at screening and after 72 hours of treatment. The results are presented in *Table 2*.

During the screening, the PTT was compared between the first and second observation subgroups. No significant differences in this indicator between the observation subgroups were found after 72 hours ($p > 0.05$).

At the beginning of treatment, the level of INR was comparable between both subgroups. A statistically significant difference in INR levels between the subgroups was found after 72 hours of treatment.

There were no statistically significant differences between the subgroups in total fibrinogen levels at screening. There were no statistically significant differences between the subgroups in the level of total fibrinogen after 72 hours of observation ($p > 0.05$).

During screening, the value of APTT was comparable between the first and second subgroups. There were no significant differences in APTT between the follow-up subgroups after 72 hours ($p > 0.05$).

The dynamics of markers of the immune-inflammatory response was determined after 72 hours. The results are shown in *Table 3*.

At the beginning of treatment, there were no significant differences in such an indicator as hsCRP between the observation subgroups. There were no statistically significant differences in this indicator between the subgroups after 72 hours ($p > 0.05$).

Both treatment subgroups had comparable values of IL-6 at screening. The values of IL-6 after 72 hours significantly differed between the first and second.

At baseline, the level of IL-10 (pg/mL) was comparable between both subgroups. There were no statistically significant differences in this indicator after 72 hours between the two observation subgroups ($p > 0.05$).

During the screening of patients, there were no statistically significant differences between the subgroups in the level of IL-6/IL-10 ratio. There was a statistically significant difference in the levels of IL-6/IL-10 ratio between the subgroups after 72 hours.

We selected 4 indicators, assuming that they, regardless of the magnitude of their variance, could be predictors of the unfavorable course of severe APB. In order to assess the significance of each of the selected factors, the method of univariate logistic regression with Wald's test ($\chi^2$) was used.

Two datasets were used: the first one included patients with severe COP, those who survived (n = 119) and the second (n = 24) included those who died. During the entire observation period, 24 patients died (15 died of thrombotic complications, 9 died of respiratory failure). In the first group there were 6 deaths, in the second group there were 18 (8.5 % vs 25.0 %, $\chi^2$, $p = 0.01$). There were 10 deaths within 14 days (all patients died of thrombotic complications).

The results of the logistic regression analysis are shown in *Table 4*.

When analyzing the univariate logistic regression model, it was found that such an indicator as AST was not valuable in relation to the unfavorable course of severe CAP. Only such indicators as the dynamic change of Δ3 days – INR, IL-6, D-dimer can have a predictive value according to the univariate logistic regression model.

**Table 1.** Comparison of the main characteristics of patient groups, Me [Q25; Q75], n = 143

| Indicator, units of measurement | Observation subgroups | | p-level |
|---|---|---|---|
| | Group I, n = 71 | Group II, n = 72 | |
| Age of patients, years | 57.00 [53.00; 61.00] | 59.00 [54.00; 63.00] | 0.11 |
| BMI, kg/m$^2$ | 24.69 [23.38; 25.88] | 25.22 [23.38; 25.99] | 0.23 |
| $SpO_2$, % | 92.00 [89.00; 94.00] | 90.00 [87.50; 94.00] | 0.24 |
| Time from disease onset to hospitalization, days | 5.00 [4.00; 6.00] | 5.00 [3.00; 6.00] | 0.69 |

**Table 2.** Dynamics of coagulogram parameters after 72 hours, Me [Q25; Q75], n = 143

| Indicator, units of measurement | Observation subgroups | | | | p-level |
|---|---|---|---|---|---|
| | Group I, n = 71 | | Group II, n = 72 | | |
| | At screening | In 72 hours | At screening | In 72 hours | |
| Prothrombin time, s | 10.90 [9.60; 11.60] | 12.00 [11.00; 13.00] | 11.15 [9.30; 11.80] | 11.30 [10.00; 12.30] | $p_{1-3} = 0.640$<br>$p_{1-2} = 0.001$<br>$p_{3-4} = 0.001$<br>$p_{2-4} < 0.001$ |
| | $\Delta_1$% = 12.50 [7.50; 17.27] | | $\Delta_2$% = 6.03 [2.38; 8.81] | | |
| Prothrombin index, U | 1.30 [1.20; 1.30] | 1.30 [1.20; 1.40] | 1.20 [1.15; 1.30] | 1.30 [1.20; 1.40] | $p_{1-3} = 0.820$<br>$p_{1-2} = 0.001$<br>$p_{3-4} = 0.001$<br>$p_{2-4} = 0.560$ |
| | $\Delta_1$% = 0.0 [0.0; 8.33] | | $\Delta_2$% = 3.33 [0.0; 8.33] | | |
| INR, U | 0.90 [0.80; 1.00] | 1.20 [1.10; 1.30] | 0.90 [0.80; 1.00] | 1.10 [1.00; 1.30] | $p_{1-3} = 0.910$<br>$p_{1-2} = 0.001$<br>$p_{3-4} = 0.005$<br>$p_{2-4} = 0.040$ |
| | $\Delta_1$% = 25.00 [16.67; 30.77] | | $\Delta_2$% = 19.09 [10.06; 27.27] | | |
| Total fibrinogen, g/l | 4.80 [4.50; 5.40] | 4.80 [4,60; 5,50] | 4.85 [4.65; 5.50] | 4.90 [4.65; 5.60] | $p_{1-3} = 0.130$<br>$p_{1-2} = 0.030$<br>$p_{3-4} = 0.004$<br>$p_{2-4} = 0.160$ |
| | $\Delta_1$% = 1.82 [0.00; 2.27] | | $\Delta_2$% = 1.82 [0.00; 3.93] | | |
| Activated partial thromboplastin time, seconds | 26.70 [26.40; 27.90] | 31.00 [29.00; 33.00] | 26.80 [26.40; 28.40] | 30.00 [28.00; 33.00] | $p_{1-3} = 0.570$<br>$p_{1-2} = 0.001$<br>$p_{3-4} = 0.001$<br>$p_{2-4} = 0.350$ |
| | $\Delta_1$% = 11.82 [6.79; 16.77] | | $\Delta_2$% = 10.64 [2.17; 16.62] | | |

**Table 3.** Dynamics of markers of the immune-inflammatory response after 72 hours, Me [Q25; Q75], n = 143

| Indicator, units of measurement | Monitoring subgroups | | | | p-level |
|---|---|---|---|---|---|
| | Group 1, n = 71 | | Group 2, n = 72 | | |
| | At screening | In 72 hours | At screening | In 72 hours | |
| hsCRP, mg/l | 19.10 [14.10; 20.00] | 19.45 [15.50; 21.44] | 18.10 [13.05; 19.85] | 18.47 [15.77; 20.69] | $p_{1-3} = 0.220$<br>$p_{1-2} = 0.001$<br>$p_{3-4} = 0.001$<br>$p_{2-4} = 0.350$ |
| | $\Delta_1$% = 5.66 [1.82; 11.82] | | $\Delta_2$% = 6.91 [0.62; 16.32] | | |
| IL-6, pg/ml | 9.12 [8.12; 10.12] | 8.01 [7.07; 9.00] | 9.05 [8.00; 10.17] | 8.72 [7.36; 9.55] | $p_{1-3} = 0.880$<br>$p_{1-2} = 0.001$<br>$p_{3-4} = 0.001$<br>$p_{2-4} = 0.020$ |
| | $\Delta_1$% = -12.93 [-16.50; -5.20] | | $\Delta_2$% = -4.75 [-7.32; -2.37] | | |
| IL-10, pg/ml | 4.66 [4.24; 5.14] | 5.02 [4.56; 5.47] | 4.83 [4.28; 5.29] | 4.97 [4.53; 5.46] | $p_{1-3} = 0.140$<br>$p_{1-2} = 0.001$<br>$p_{3-4} = 0.001$<br>$p_{2-4} = 0.830$ |
| | $\Delta_1$% = 5.12 [2.16; 9.32] | | $\Delta_2$% = 1.94 [0.74; 5.25] | | |
| IL-6/IL-10 | 1.91 [1.70; 2.16] | 1.58 [1.40; 1.78] | 1.87 [1.63; 2.15] | 1.70 [1.49; 1.97] | $p_{1-3} = 0.240$<br>$p_{1-2} = 0.001$<br>$p_{3-4} = 0.001$<br>$p_{2-4} = 0.030$ |
| | $\Delta_1$% = -18.96 [-26.96; -11.44] | | $\Delta_2$% = -8.00 [-11.51; -4.77] | | |

**Table 4.** Values of variants for the unfavorable course of severe COP according to the results of univariate regression

| Indicator, units of measurement | Univariate model | | Multivariate model | | |
|---|---|---|---|---|---|
| | $\chi^2$ Wald | p-level | Coefficient | Std. error | p-level |
| AST Δ3 days, % | 8.92 | 0.350 | – | – | – |
| INRΔ3 days, % | 18.47 | 0.020 | 0.15 | 0.045 | 0.001 |
| IL-6Δ3 days, % | 29.00 | <0.001 | 0.49 | 0.155 | 0.002 |
| D-dimerΔ3 days, % | 21.23 | 0.007 | -0.21 | 0.068 | 0.002 |

Only these indicators reliably demonstrated the value of the unfavorable course of severe AP and were subsequently included in the multivariate logistic regression model. dynamic changes in Δ3-day indicators – INR, IL-6, D-dimer according to the results of the multivariate logistic regression model were independent predictors of the unfavorable course of severe AP.

## Discussion

Heparin therapy suppresses reactions that lead to blood clotting and fibrin thrombus formation. In addition to affecting the coagulation cascade, heparin has many benefits, including anti-inflammatory properties and endothelial protection. In addition, heparin has many benefits and may potentially have antiviral properties. According to the results of scientific studies, heparin dramatically reduces the amount of inflammatory mediators due to the "cytokine storm", reduces inflammation in the lungs, and prevents coagulopathy and thrombotic complications. Given the increased risk of coagulopathy, inflammatory markers, and mortality associated with COVID-19, as well as the noted benefits of heparin, its use in the treatment of patients with moderate COVID-19 has become an important topic of discussion in the current literature [16,17,18,19,20].

There are differences between the relative inhibition of low fractionated heparin and low molecular weight heparins of thrombin (factor IIa) and factor Xa. Due to their shorter chain length and molecular weight (4500–5000 Daltons), LMWH have relatively higher activity against factor Xa and less inhibition of thrombin. It is unclear whether the proposed benefits of heparin are also present with low-molecular-weight heparins, but LMWHs have a lower incidence of complications, so enoxaparin is the most commonly used drug in studies of coronavirus infection. When used once or twice daily, it has a more predictable anticoagulant effect than heparin, which reduces the need for regular laboratory monitoring [21,22,23].

Our results coincide with the data of C. Shi et al. Statistical analysis of the levels of inflammatory cytokines in the two groups of patients showed that IL-6 significantly decreased in the heparin group compared to the control group, while changes in other inflammatory factors were not statistically significant [24]. Reducing IL-6 levels can prevent the cytokine storm syndrome caused by the virus, thereby improving the condition of patients with COVID-19, which is consistent with the above data [24,25].

Thus, the results of our study showed that heparin significantly reduces 30-day mortality in patients with NSTEMI with COVID-19 and significantly reduces levels of inflammatory mediators. Our analysis shows that heparin can improve the prognosis of patients. Although the study has limitations, as it includes a small number of patients and no patients with comorbidity, it is reasonable to recommend the use of heparin for patients at low risk of bleeding, while others use enoxaparin to prevent thrombotic complications. In addition, our analysis further identifies the need for future well-designed, high-quality randomized controlled trials to provide additional guidance on the role of anticoagulation in the treatment of COVID-19.

## Conclusions

1. Combination therapy is effective in reducing the levels of markers of the immune-inflammatory response.

2. Combination therapy, including heparin, was more effective in reducing IL-6 levels after 72 hours.

3. Dynamic changes in Δ3 days of INR, IL-6, D-dimer according to the results of a multivariate logistic regression model are independent predictors of the unfavorable course of severe CAP associated with coronavirus infection.

**Prospects for further research.** The study of the role of the immune-inflammatory response in patients with community-acquired pneumonia associated with coronavirus infection remains the subject of further research. Determining the levels of inflammatory biomarkers that would indicate the progression and adverse course of the disease requires further research, which will help optimize patient treatment.

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