https://doi.org/10.15360/1813-9779-2026-1-2617

Polymorphism of *OLR1* Gene Encoding Oxidized LDL Receptor LOX-1 Modifies the Course of Necrotizing Pulmonary Infection

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For citation: *Dmitry L. Fetlam, Anastasia G. Chumachenko, Alexander V. Ilyichev, Vladimir M. Pisarev.* Polymorphism of *OLR1* Gene Encoding Oxidized LDL Receptor LOX-1 Modifies the Course of Necrotizing Pulmonary Infection. *Obshchaya Reanimatologiya = General Reanimatology.* 2026; 22 (1): 14–25. https://doi.org/10.15360/1813-9779-2026-1-2617 [In Russ. and Engl.]

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Summary

Necrotizing pulmonary infections (NPI) emerge as severe complications of community-acquired pneumonia (CAP), and immune system cells are involved in their pathogenesis. Highly informative biomarkers are required to determine high-risk patients to prevent life-threatening complications of NPI. Previously, we have shown that variations in immune cell numbers can be employed as prognostic biomarkers in NPI. We proposed that genetic variants encoding receptors detected on the surface of neutrophils, monocytes, and macrophages migrating to lung tissues during inflammation may predict the unfavorable course of NPI. One of these candidate genes could be the *OLR1* gene, which encodes LOX-1 receptors that bind oxidized low-density lipoproteins oxLDL on the surface of immune and other cells.

The aim of the study. To find out the *OLR1* gene single nucleotide polymorphism contribution to the clinical course of NPIs (pleural empyema) and variability in the number of immune cells in patients with post-CAP NPI.

Materials and methods. The study included patients of the Moscow City Hospital (aged 18–87 years, $n=216$) with NPIs developed after CAP. Categorical data were described by indicating absolute values, which were compared using four-field contingency tables and the χ^2 test with Yates' correction for sample continuity and Fisher's exact test (FET).

Results. NPIs were the most common complication of CAP. In patients with NPI and the minor allele G *OLR1* rs11053646, which encodes the LOX-1 167N variant, the course of the disease was less likely to be complicated by a fistula ($p=0.0015$; exact Fisher test (EFT); OR = 3.55, 95% CI: 1.55–8.13; RR = 2.37, 95% CI: 1.24–4.50; $n=216$). However, the significance of this association was influenced by previous COVID-19 documented in patient's medical history based on PCR test results. For patients who had been infected with COVID-19, this association persisted ($p=0.0058$; EFT; OR = 7.27, 95% CI: 1.54–34.3; RR = 4.28, 95% CI:1.31–16.23; $n=81$), whereas in patients with no PCR test confirmed COVID-19, this association was not statistically significant ($p=0.1065$, EFT, $n=135$). Thus, only post-COVID-19 carriers of the minor allele G *OLR1* rs11053646 were protected from a severe course of NPIs complicated with fistula development. A study in a limited subgroup of patients showed a trend for a fistula development to associate with increased OxLDL plasma concentration of more than 100 ng/ml ($p=0.045$; $n=19$).

Conclusion. Post-COVID-19 carriers of major *OLR1* rs11053646 CC genotype exhibit increased risk for the unfavorable course of NPI (pleural empyema) complicated with fistula. The presence of alternative G allele of *OLR1* rs11053646 in patient genotype associates with favorable course of NPIs.

Keywords: necrotizing pulmonary infections; OLR1 genetic polymorphism; LOX-1 receptor; oxidized low-density lipoproteins; OxLDL; community-acquired pneumonia; COVID-19; lung abscess; lung gangrene; pleural empyema

Conflict of interest. The authors declare that there is no conflict of interest.

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Introduction

Necrotizng pulmonary infections (NPIs) are severe pathological conditions characterized by inflammatory infiltration and subsequent destruction of lung tissue as a result of exposure to infectious agents [1]. Currently, there is a trend toward an increase in the incidence of NPIs. Despite improvements in treatment methods, mortality remains high, ranging from 5% to 30% and reaching 70% in cases of lung gangrene [2, 3]. Up to 15% of such patients seeking medical care require support for vital body functions [4]. At the same time age, nutritional status, concomitant diseases, the state of the immune system, and the timeliness of targeted antibacterial

and supportive therapy are essential for patient's condition [5].

Pleural empyema (PlE) is one of the most common entity among NPIs manifesting as accumulation of pus or fluid in the pleural cavity with biological signs of infection, involving the parietal and visceral pleura in the inflammatory process and causing secondary compression of the lung tissue. About 60% of PlE cases are associated with some primary pulmonary process emerging as an outcome of community-acquired pneumonia (CAP). Parapneumonic effusion and purulent- destructive processes complicating CAP are the main causes of pleural empyema. In some patients parapneumonic effusion results in PlE without fistula, while in others the outcome is less favorable and complicated by fistula formation, which worsens the course of the disease and prognosis [1, 6].

Early prediction of complicated NPI and its outcome is hampered by the lack of reliable and highly informative biomarkers that are pathogenetically substantive for the development of complications and are associated with immune disorders. Immune system cells are widely represented in the respiratory tract, and their migration and accumulation in the lungs significantly depends on receptor expression and chemokinesis. LOX-1 receptors, known as class E scavenger receptors, are common on the surface of neutrophils, monocytes, and macrophages [7], and their ligands are oxidized low-density lipoprotein molecules (OxLDL). Expression of these scavenger receptors on the cell surface increases when the *OLR1* receptor gene is activated in response to pro- inflammatory or proatherogenic factors [8]. The gene products — LOX-1 molecules, are involved in the pathogenesis of arterial hypertension, diabetes mellitus, hyperlipidemia, and ischemia/reperfusion [7, 9, 10, 11]. There is evidence of LOX-1 accumulation in the lungs of patients with acute respiratory distress syndrome and in mice with pneumonia [12]. LOX-1 contributes to the control of inflammatory responses in a wide range of ways: from stimulating the activity of innate immune cells [13] to activating myeloid-derived suppressor cells (MDSC) [14,15].

It is now known that ORL1 gene translation leads to expression of a wide range of protein isoforms, the composition and quantitative representation of which depends on alternative splicing and single nucleotide polymorphisms (SNPs) [16].

Alternative splicing of ORL1 results in three variants of LOX-1 mRNA: transcript 1 (ORL1 NM 002543), transcript 2 (ORL1D4 NM 001172632), and transcript 3 (LOXIN NM 001172633) [16]. Transcript variant 1 contains all 6 exons and leads to the transcription of a full-length LOX-1 with full binding activity to OxLDL. Transcript 2 lacks exon 4, so the encoded protein is shorter [17]. In transcript variant 3, the absence of exon 5 as a result of splicing leads to formation of the LOXIN protein, which lacks two-thirds of the LOX-1 lectin-like domain, a region important for OxLDL binding. The latter isoform plays a protective role in cardiovascular diseases associated with increased LOX-1 expression [16].

Another source of quantitative and structural diversity of *OLR1* gene products is single nucleotide polymorphism. Mutant variants of the *OLR1* gene are associated with the risk of acute myocardial infarction [18], carotid artery atherosclerosis [19, 20], ischemic stroke [21, 22], atherosclerotic lesions of the femoral and popliteal arteries [23], arterial hypertension [24], and vascular complications of diabetes mellitus [11].

The most studied are the associative links between various polymorphic variants of the *OLR1* gene and the development of cardiovascular diseases [8, 9, 17, 18]. One of the transversions, c.501 G > C (rs11053646) in exon 4, leads to the amino acid substitution of lysine for asparagine at 167 (p.K167N) position. The presence of this *OLR1* rs11053646 allele was shown to alter the binding and utilization of OxLDL, which increases the risk of acute myocardial infarction, ischemic stroke, and hypertension in its carriers [25, 21, 26, 27].

The significance of *OLR1* polymorphism in lung diseases, including NPIs, has not been studied, although the pathogenetic link between NPI, inflammation and immune system cells suggests the likelihood of such a connection [28]. Nowdays, the search for molecular predictors of the course and outcome of life-threatening lung conditions remains a challenge in critical care medicine [29, 28, 30. The results of our study show the potential contribution of the *OLR1* gene single nucleotide polymorphism to clinical course of NPIs that presumably may affect variations in innate and acquired immunity cells activity/counts in post-community-acquired pneumonia patients.

Materials and Methods

Study characteristics. A prospective observational study was conducted at the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (FRCC ICMR). Data collection was carried out at the I. V. Davydovsky City clinical hospital from July 2022 to August 2023 in the departments of thoracic surgery, pulmonology, resuscitation and intensive care, and the department of anesthesiology and resuscitation.

The study was approved by the Ethics Committee of the FRCC ICMR (protocol No. 2/22/1 dated July 26, 2022).

Development of fistula was the primary endpoint of the study.

An increase in immune cells counts was the secondary endpoint.

Characteristics of the study population.

- Criteria for inclusion of patients in the study:

— presence of CAP or NPI (lung abscess without sequestration, lung abscess with sequestration, lung gangrene, pleural empyema without fistula/fenestration, pleural empyema with fistula/fenestration) in a patient who had had a community-acquired bacterial infection in the previous 30 days;

— age 18 years or older;

— written informed consent to participate in the study;

— patient's ability to adequately cooperate in the clinical study for an extended period of time.

• Criteria for exclusion of patients from the study:

— patients' and/or their legal representatives' refusal to continue treatment;

— establishing the diagnosis of cancer or tuberculosis.

According to our preliminary data, the mortality rate for NPI averaged around 16%; taking this into account, we calculated the sample size [28]. Using the formula for calculating the sample size $n = (t^2 \times P \times Q) / \triangle^2$, where t is the critical value of Student's t-test (at a significance level of 0.05, it is 1.96); $\triangle$ is the maximum permissible error (5%); P is the proportion of cases in which the studied feature occurs (84%); Q is the proportion of cases in which the studied feature does not occur (16%); the resulting n was 206. To obtain statistically significant differences, the calculated sample size was increased by 5% to 216 patients.

The study included 216 patients with NPIs developed after CAP within the previous 30 days. The NPI cohort included patients from two groups: NPIs as the outcome of parapneumonic effusion not complicated by fistula (NPInF, $n=127$) and NPI complicated by fistula (NPIwF, $n=89$) as the outcome of lung abscess without sequestration, lung abscess with sequestration, and lung gangrene. The NPI diagnosis was established based on CT images on admission to the hospital.

The conclusion about previous SARS-CoV-2 infection was based on documented PCR test results, regardless of the date. Treatment of COVID-19 was previously guided by «temporary methodological recommendations for the prevention, diagnosis, and treatment of COVID-19» as they were updated.

The selection of patients with NPIs for the study is presented in Fig. 1.

Assessment upon admission to the hospital (Table 1) included patients' demographic characteristics, assessment by comorbidity scales: CCI (Charlson Comorbidity Index) [31] and CIRS (Cumulative Illness Rating Scale) [32], assessments by the SOFA (Sequential Organ Failure Assessment) and APACHE II (Acute Physiology and Chronic Health Evaluation II) scales, and for presence of diabetes mellitus. The severity of pleural infection was assessed using the specialized RAPID scale (Renal, Age, fluid Purulence, Infection source, Dietary — taking into account kidney function parameters (urea), age, presence of pus in fluids, source of infection, albumin content — as a factor related to nutrition) [33]. This scale is important for stratifying the risk of adverse outcomes in patients with pleural empyema.

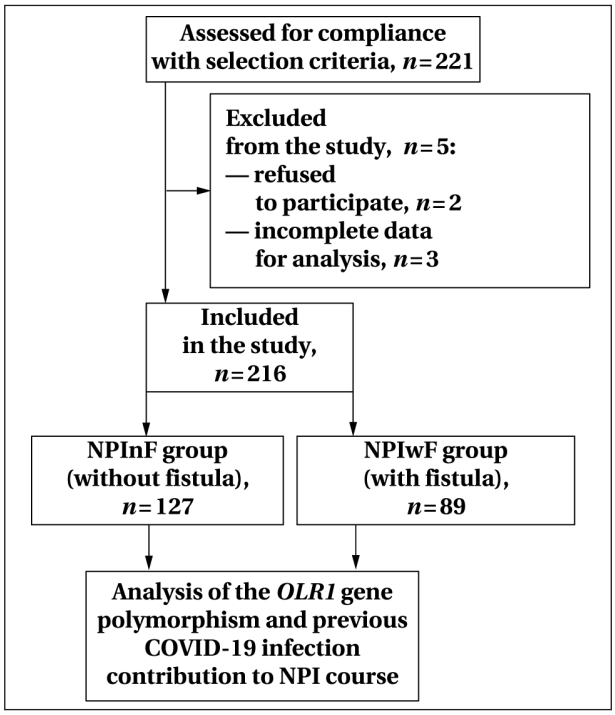

Fig. 1. Flowchart of patient selection for the study.
Note. NPI — necrotizing pulmonary infection

The incidence of empyema with fistula was higher in men than in women ($p=0.0235$; FET; OR = 2.09, 95% CI: 1.12–3.9; OR = 1.586; 95% CI: 1.047–2.4039). There were no differences based on age ($p=0.394$), presence of diabetes mellitus ($p=1$), scores on Charlson ($p=0.694$), CIRS ($p=0.292$), SOFA ($p=0.483$), APACHE II ($p=0.173$), and RAPID ($p=0.218$) scales.

In further analysis, patients with NPIs were divided into two subgroups: those who had previous COVID-19 ($n=81$) and those who had not ($n=135$).

The control group of «conditionally» healthy individuals included 155 people without HIV or viral hepatitis.

The CAP group included 101 patients. Patients' mean age, *Me* (IQR) was 66 (47–81) years, the SOFA score on admission, *Me* (IQR) was 2 (1–4), and the CIRS score, Me (IQR) was 11 (6–16). Women accounted for 49.5% of the cohort.

Laboratory assessments and instrumental examinations.

a) Clinical and laboratory parameters:

• Complete blood count:

— frequency: 1–3–5–7–last day of hospitalization;

— tubes: EDTA K3E/2.7 ml;

— device: ADVIA 2120i.

• Genetically polymorphic markers:

— frequency: 1st day of hospital stay;

— DNA for genotyping was extracted from 200 µl of whole blood using Diatom DNA Prep 200 kits, according to the instructions provided

Allele variants of *OLR1* rs11053646 were determined using a tetraprimer polymerase chain reaction followed by electrophoretic separation and identification of stained

Table 1. Demographic characteristics, morbidity and comorbidities in patients with NPIs.

Parameters	Values in cohorts				
	All patients	With fistula, NPIwF	Without fistula, NPInF	With previous COVID-19	With no history of COVID-19
Age, years, *M (IQR)*	54 (40.7–66)	54 (40–63)	56 (41–66)	52 (40–64)	56 (41–67)
Men, *n* (%)	151 (70)	70 (79)	81 (64)	57 (70)	94 (70)
Women, *n* (%)	65 (30)	19 (21)	46 (36)	24 (3)	41 (30)
CCI comorbidity index value, score, *M (IQR)*	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–3)	2 (1–4)
CIRS comorbidity score, score, *M (IQR)*	10 (7–13)	10 (8–13)	10 (7–13)	10 (7–13)	10 (7–13)
DM, *n* (%)	33 (15)	14 (16)	19 (15)	8 (10)	25 (19)
SOFA score on admission, points, *M (IQR)*	2 (2–2)	2 (2–3)	2 (2–2)	2 (2–2)	2 (2–2)
APACHE II score on admission, *M (IQR)*	5 (3–8)	5 (3–8)	5 (3–7)	5 (3–8)	5 (3–8)
Assessment of pleural infection using the RAPID scale, points, *M (IQR)*	2 (1–3)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)

products in a gel. Using the Primer-BLAST program (https://www.ncbi.nlm.nih.gov/tools/primer-blast/), the following primers were selected and synthesized at Eurogen LLC.

OLR1 1for 5`TACAGAGCCTGTCCGTCCA-3`

OLR1 2for 5`-GACAAGCACTTCTCTTGGCTC-3`

OLR1 2rev 5`-GGCTCATTTAACTGGGAAAAC-3`

OLR1 1rev 5`-ATGCACGTGAGAGAACTAAGG-3`

The amount of oxidized low-density lipoproteins (OxLDL) in blood plasma was measured by enzyme-linked immunosorbent assay using ELISA Oxidized Low Density Lipoprotein kits (Cloud clone Corp, PRC). The median OxLDL content in patients plasma, M(IQR) was 88 (80–95) ng/ml.

b) Instrumental examination:

- Chest CT:

— frequency: 1st day of hospital stay;

— Equipment: Siemens SOMATOM Perspective 64 computerized tomography scanner, Germany.

The diagnosis of CAP was established within the first 48 hours after admission based on CT scans, and the diagnosis of NPI was made based on CT scans at hospital admission.

Patient management protocol. Within 2 hours upon admission to the hospital, pleural cavity drainage was implemented using G. Bülau technique. After drainage was established, pleural empyema without fistula (PlEnF, NPInF) and pleural empyema with fistula (PlEwF, NPIwF) were differentiated. The presence of air discharge through the drain indicated PlEwF. In the thoracic department or ICU, patients were managed with corrective i/v fluids, antimicrobial therapy according to current antibiotic stewardship strategy, therapy for prevention of thromboembolic complications (anticoagulants + elastic compression of lower legs for VTE/DVT control), stress ulcers therapy, adequate pain relief, symptomatic therapy, and respiratory support if necessary. Laboratory tests included complete blood count, full biochemistry profile, coagulogram, ABB. Further tactics were determined based on the results of initial therapy after 48–72 hours. When indicated, video-assisted thoracoscopic surgery (VATS) was implemented to drain fluid out of the pleural cavity. VATS was performed under general anesthesia with separate intubation of the bronchi using a double-lumen tube. Single-lung ventilation was necessary for complete lung collapse to create free space, which allowed for a thorough and complete examination of the chest cavity. Effectiveness of antibiotic therapy was assessed 72 hours after its initiation.

In patients with pleural empyema and fistula with continued air leak, a decision was made to temporarily occlude the bronchi (bronchial blocker placement) in order to close the bronchopleural fistula. Subsequently, the bronchial blocker was removed and air leak was assessed.

In the absence of purulent discharge and air leak, the degree of lung tissue expansion confirming the absence of pneumothorax, was assessed after clamping the drainage tube using chest X-ray. When clinical and laboratory parameters and lung tissue aeration normalized, the drain was removed and the patient was discharged from the clinic.

Statistical analysis of the obtained results. The Shapiro-Wilk test was used to assess if quantitative dataset follows a normal distribution. Variables with normal distribution were described using arithmetic means (*M*) and standard deviations (*SD*), as well as 95% confidence intervals (95% CI). In the case of abnormal distribution of quantitative data, they were described using the median (*Me*) and lower and upper quartiles (*Q1–Q3*). Variables with normal distribution were compared in groups using the Student's *t*-test, provided that the variances were equal. If the distribution differed from normal, the Mann–Whitney *U* test was used.

Categorical data were described using absolute values, which were compared using four-field contingency tables and the χ^2 test with Yates' correction for continuity of the sample and Fisher's exact test (FET). As a quantitative measure of the effect when comparing relative indicators, odds ratios (*OR*) and relative risk (*RR*) with 95% confidence intervals (*CI*) were used. Differences were considered significant at $p < 0.05$. The Bonferroni correction was used for multiple comparisons.

SPSS Statistics software (IBM SPSS Statistics for Windows, Version 27.0.1, IBM Corp., Armonk, NY) was used for statistical data processing. Microsoft Office Excel 2019 software platform was used to create graphs, scatter plots, and tables. OR was calculated using MedCalc software, version 11.6.

Results

A study of the genetic diversity in groups of patients with CAP and NPIs, as well as conditionally healthy individuals, based on the distribution of single nucleotide polymorphic variants rs11053646

of the *OLR1* gene revealed the following genotype frequencies: *OLR1* CC — 81%, *OLR1* CG — 17.6%, *OLR1* GG — 1.4% $n=216$, which was consistent with Hardy-Weinberg law ($\chi^2=0.319$, $p=0.572$) and did not differ statistically significantly from the distribution in the group of patients with CAP (CC — 88.1%, CG — 11.9%, GG — 0%, $\chi^2=0.403$, $p=0.526$, $n=101$, and the group of conditionally healthy individuals (CC — 87.8%, CG — 10.9%, GG — 1.3%, $\chi=2.7$, $p=0.10$, $n=155$ (Fig. 2).

In patients with NPIs and the minor G allele of *OLR1* rs11053646 polymorphism (genotypes CG, GG), encoding the 167N *OLR1* variant, the course of the disease was less frequently complicated by fistula ($p=0.0015$; FET; OR=3.55, 95% CI: 0.12–0.64; OR=2.37, 95% CI: 1.24–4.50; $n=216$; Fig. 3, *a*). For patients who had recovered from COVID-19, this association remained ($p=0.0058$; FET; OR=7.27, 95% CI: 1.54–34.3; RR=4.28, 95% CI: 1.31–16.23; $n=81$; Fig. 3, *b*). Among patients who had not had COVID-19, the pattern was not significant ($p=0.1065$; FET; $n=135$; Fig. 3, *c*). Thus, the minor G allele of *OLR1* rs11053646 protects against more severe NPI course in patients who have had COVID-19.

The frequency of minor *OLR1* CG and GG genotypes was also higher in patients with NPIs without fistula compared to the cohort of patients with community-acquired pneumonia ($p=0.0114$, FET, OR=2.6, 95% CI: 1.3–5.4).

We have previously shown that decreased lymphocyte counts and increased neutrophil counts and the neutrophil-to-lymphocyte ratio (NLR) values are significantly associated with NPIs outcome [28]. It was interesting to find out whether the two predictors — the *OLR1* genotype and immune cell counts in the circulation — were interrelated in patients with NPIs. Taking into account the potential influence of previous COVID-19 on manifestation of this association, for further analysis the participants were divided into two groups based on presence or absence of previous COVID-19 infection (COVID-19 confirmed by PCR results). We compared neutrophil, lymphocyte, and monocyte counts in patients with NPIs with and without fistulas and different *OLR1* rs11053646 genotypes on the 1st, 3rd, 5th, 7th, and last days of hospital stay in these two groups.

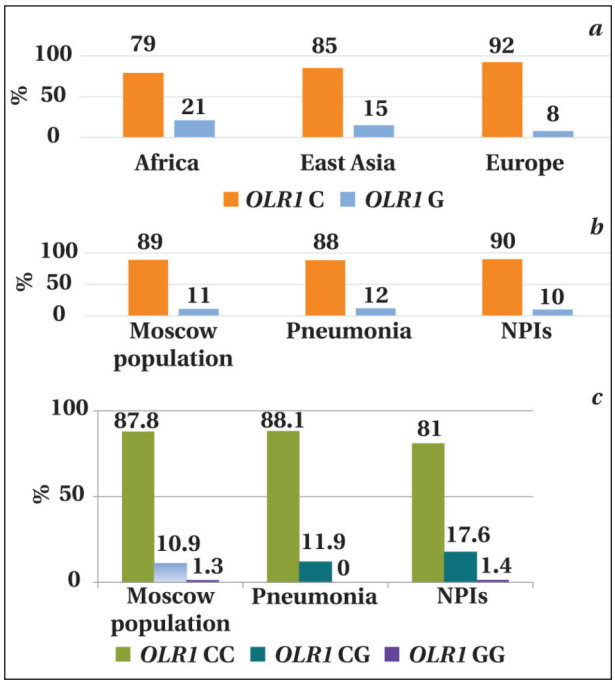

Fig. 2. Distribution of *OLR1* rs11053646 allele and genotype frequencies.
Note. Allele frequencies: *a* — literature data; *b* — conditionally healthy individuals (Moscow population) and patients with CAP and NPIs. Genotype frequencies: *c* — conditionally healthy individuals (Moscow population) and patients with CAP and NPIs.

Neutrophils. For subgroups of patients with NPIs with and without fistulas and different *OLR1* rs11053646 genotypes, no differences in circulating

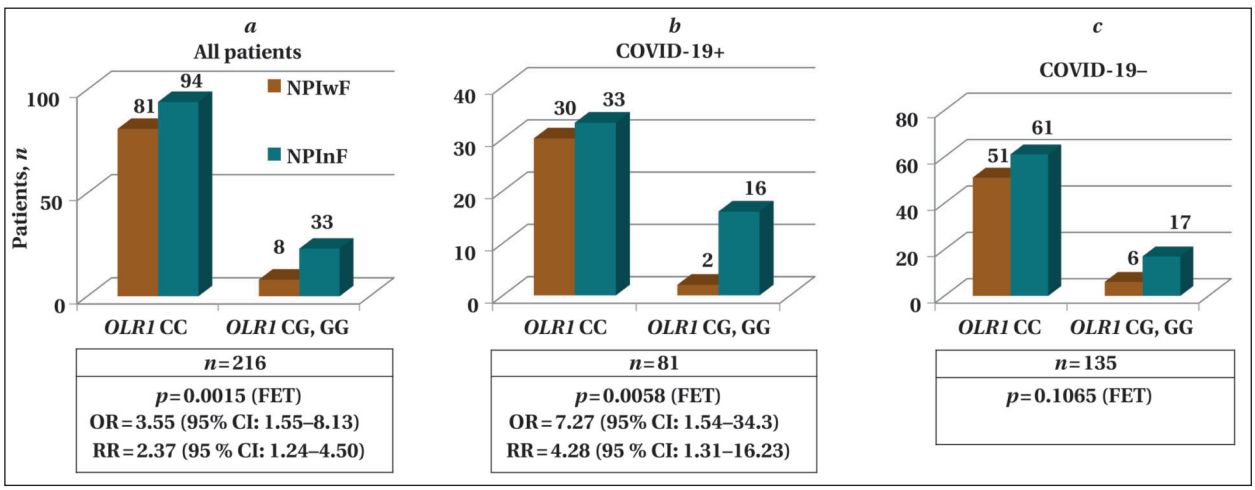

Fig 3. Development of fistula depending on the *OLR1* rs11053646 allele.
Note. *a* — incidence of fistula in all patients; *b* — incidence of fistula in patients with history of COVID-19; *c* — incidence of fistula in patients who did not have COVID-19.

neutrophil counts were found on the 1st, 3rd, 5th, 7th, and last days, regardless of whether they had had COVID-19 (Table 2).

Lymphocytes. No differences in lymphocyte counts were found between subgroups of patients with NPIs with fistula and different *OLR1* rs11053646 genotypes on the 1st, 7th, and last days of hospital stay. Differences in this group were found only on the 3rd and 5th days of hospital stay: patients with minor *OLR1* CG and GG genotypes had higher counts of circulating lymphocytes (Table 3).

In cases complicated with fistula and no previous COVID-19 infection, a difference in counts of circulating lymphocytes was found only on the 5th day. Thus, for patients who had not had COVID-19, the lymphocyte counts in carriers of the minor *OLR1* G allele was higher than in patients with the major *OLR1* CC genotype. In post-COVID-19 patients developing fistula the calculation was skipped given the small number of the minor *OLR1* G allele carriers. When using the Bonferroni correction (assessment based on neutrophil, lymphocyte, and monocyte counts), the significance of the differences was not preserved.

For subgroups of patients with NPI without fistula and different *OLR1* rs11053646 genotypes, lymphocyte counts did not differ on any day of hospital stay, regardless previous COVID-19 infection status (Table 3).

Monocytes. The monocyte counts in the subgroup of NPInF patients who had had COVID-19 and various *OLR1* rs11053646 genotypes, were the same on the 1st, 3rd, 7th, and last days of hospital stay. On the 5th day of hospital stay, patients with minor *OLR1* CG and GG genotypes had significantly higher monocyte counts.

In the subgroup of patients developing fistula and no history of COVID-19 infection, no difference in monocyte counts was found on the 3rd, 7th, and last days of hospital stay. On days 1 and 5, the difference in monocyte counts was linked with different genotypes: in patients with minor *OLR1* CG and GG genotypes, monocyte counts were significantly higher than in carriers of the CC genotype.

Next, we compared the monocyte counts in the subgroup of post-COVID-19 NPInF patients with different *OLR1* rs11053646 genotypes. There was no difference in monocyte counts on the 1st, 5th, 7th, and last days of hospital stay. However, on the 3rd day, the monocyte counts were significantly lower in carriers of the minor *OLR1* G allele compared to the major *OLR1* CC carriers. When using the Bonferroni correction (assessment based on neutrophil, lymphocyte, and monocyte counts), the significance remained for the 1st ($p=0.03$) and 5th days ($p=0.027$) of hospital stay in patients with NPIwF and no previous COVID-19.

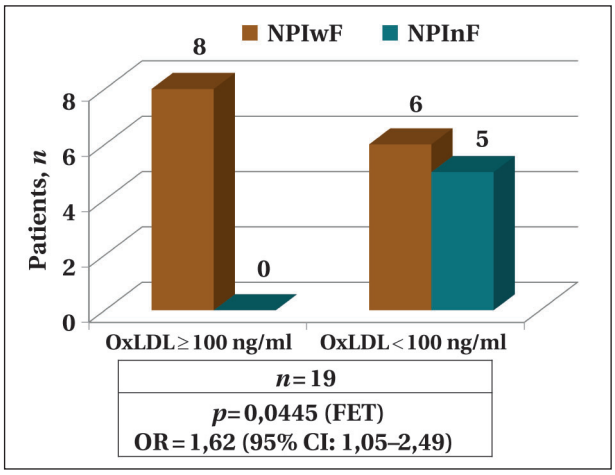

Fig. 4. OxLDL content in the plasma of patients with NPIs depending on the presence of fistula.

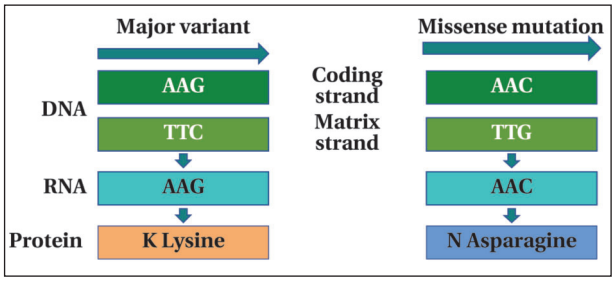

Fig. 5. Single nucleotide substitution *OLR1* rs11053646 (author's drawing).

In patients who had not had COVID-19, the monocyte count did not differ (Table 4).

Keeping in mind the *OLR1* gene potential role in inducing complications of pneumonia, OxLDL levels were measured in a limited number of plasma samples ($n=19$) from COVID-19-expirienced patients. Relatively high OxLDL levels (over 100 ng/mL) were associated with development of fistula ($p=0.0445$; FET; OR = Infinity; RR = 1.62, 95% CI = 1.05–2.49; $n=19$, Fig. 4).

Discussion

We examined genetic markers that predict the NPI course. We showed that the minor allele *OLR1* G (rs11053646) «protects» against development of fistula in patients with NPIs. Since the distribution of *OLR1* genotype frequencies in the cohort did not differ from that in healthy population and among patients with community-acquired pneumonia, the *OLR1* G rs11053646 allele is involved in controlling the course of NPIs, namely preventing development of pneumonia complications such as fistula.

The contribution of the *OLR1* rs11053646 single nucleotide substitution was also investigated, in which the c.501 G > C transversion in exon 4 of the coding strand of the gene leads to the replacement of the amino acid lysine with asparagine at position 167 (p.K167N, Fig. 5) of the LOX-1 receptor. A few

Table 2. Counts of neutrophils in the circulation in patients with NPIs with and without fistulas (×10⁹/L).

NPIs	Genotype *OLR1*	Post-COVID-19	Days			
			1		3	
NPIwF; *M* (IQR)	CC	+	9.2 (6.37–13.6); 89	—	7.8 (5.75–11.1); 89	—
		—		10.5 (6.87–16.05); 57		8.4(5.85–11.1); 57
	CG/GG	+	8.45 (5.8–20.05); 89	—	9.65 (5.85–21.1); 89	—
		—		7.3 (5.2–8.7; 57		6.2 (5.8–12.8); 57
NPInF; *M* (IQR)	CC	+	8.3 (6–13); 127	8.6 (5.82–12.77); 49	7.3 (4.8–10.4); 127	7 (4.3–9.77); 49
		—		8.2 (6.07–13.3); 78		7.5 (5–10.67); 78
	CG/GG	+	9 (6.05–10.3); 127	6.6 (4.85–9.55); 49	7 (4.87–9.12); 127	6.7 (4.35–9.15); 49
		—		9.3 (6.87–12.5); 78		7.2 (5–8.95); 78
			$p_1 = 0.920$		$p_1 = 0.491$	
			$p_2 = 0.411$		$p_2 = 0.638$	
			$p_3 = $ ND		$p_3 = $ ND	
			$p_4 = 0.185$		$p_4 = 0.649$	
			$p_5 = 0.193$		$p_5 = 0.779$	
			$p_6 = 0.837$		$p_6 = 0.799$	

Table 3. Lymphocyte count in patients with NPIs with and without fistula (×10⁹/L).

NPIs	Genotype *OLR1*	Post-COVID-19	Days			
			1		3	
NPIwF; *M* (IQR)	CC	+	1.7 (1.07–2.22); 89	—	1.5 (1–2); 89	—
		—		1.5 (1–2.15); 57		1.4 (0.9–1.97); 57
	CG/GG	+	2.4 (1.25–2.9); 89	—	2.35 (1.85–2.65); 89	—
		—		2.4 (1.6–2.7); 57		2.2 (1.7–2.6); 57
NPInF; *M* (IQR)	CC	+	1.9 (1.2–2.3); 127	1.9 (1.1–2.52); 49	1.7 (1.2–2); 127	1.5 (1.2–2.05); 49
		—		1.9 (1.3–2.3); 78		1.7 (1.17–2); 78
	CG/GG	+	1.8 (1.4–2.22); 127	2.25 (1.45–2.75); 49	1.6 (1.175–2.3); 127	1.75 (1.35–2.9); 49
		—		1.6 (1.37–2); 78		1.4 (1.1–1.8); 78
			$p_1 = 0.239$		$p_1 = 0.031$	
			$p_2 = 0.991$		$p_2 = 0.971$	
			$p_3 = $ ND		$p_3 = $ ND	
			$p_4 = 0.164$		$p_4 = 0.116$	
			$p_5 = 0.169$		$p_5 = 0.208$	
			$p_6 = 0.123$		$p_6 = 0.238$	

Table 4. Monocyte counts in patients with NPIs with and without fistula (×10⁹/L).

NPIs	Genotype *OLR1*	Post-COVID-19	Days			
			1		3	
NPIwF; *M* (IQR)	CC	+	0.8 (0.6–1.1); 89	—	0.6 (0.4–0.9); 89	—
		—		0.8 (0.5–1.17); 57		0.6 (0.4–0.97); 57
	CG/GG	+	1.3 (0.65–1.45); 89	—	0.85 (0.4–1); 89	—
		—		1.3 (1.3–1.6); 57		0.95 (0.8–1); 57
NPInF; *M* (IQR)	CC	+	0.9 (0.7–1.2); 127	0.9 (0.7–1.2); 49	0.7 (0.5–1); 127	0.7 (0.5–0.92); 49
		—		0.9 (0.6–1.3); 78		0.7 (0.5–1); 78
	CG/GG	+	0.8 (0.6–1.02); 127	0.8 (0.55–0.95); 49	0.6 (0.5–0.7); 127	0.55 (0.45–0.7); 49
		—		0.9 (0.67–1.1); 78		0.6 (0.5–0.92); 78
			$p_1 = 0.194$		$p_1 = 0.469$	
			$p_2 = 0.195$		$p_2 = 0.043$	
			$p_3 = $ ND		$p_3 = $ ND	
			$p_4 = 0.010$		$p_4 = 0.172$	
			$p_5 = 0.075$		$p_5 = 0.036$	
			$p_6 = 0.823$		$p_6 = 0.380$	

Note. Tables 2–4 are located on pages 20–21 in a two-page format for easier following the dynamics.

studies indicate an increased risk of atherosclerosis, AMI, ischemic stroke, and hypertension for carriers of minor *OLR1* (rs11053646) genotypes [22, 26, 27].

As can be seen in Fig. 2, there is a tendency for the minor allele G *OLR1* rs11053646 frequency to increase in the African population compared to the European population: in the European population, carriers of the major genotype account for 92%, while in the African population, they account for 78% [34]. The incidence of infectious diseases in Africa is higher [35]. It can be assumed that higher prevalence of the minor *OLR1* G allele in the African population is adaptive in nature due to higher rate of infectious diseases. Perhaps the presence of the minor *OLR1* mutation and, accordingly, the carriage of the CG and GG genotypes, provided better protection against infections due to more effective immune mechanisms that prevent the development of life-threatening purulent complications and other infections that can be fatal in circumstances of medications scarcity or untimely treatment. These may be the selection factors contributing to the accumulation of the «protective» minor allele in the population. The price paid for this evolutionary advantage could be an increased risk of cardiovascular disease, which is characteristic of these geno-

Days					
5		7		The last day	
8 (5.1–11.17); 85	—	7 (4.65–11.72); 85	—	6.1 (4.7–7.9); 85	—
	8.5 (5.02–11.82); 54		7.4 (4.55–12.62); 54		6.4 (4.7–8.425); 54
7.8 (4.9–11.5); 85	—	6.7 (3.1–10.5); 85	—	7.55 (4.8–16.7); 85	—
	7.4 (4.8–13.8); 54		7.3 (3.07–13.85); 54		5.6 (4.67–21.4); 54
6.6 (4.47–9.7); 126	7.45 (4.1–11.5); 48	5.8 (4.25–7); 126	7 (4.05–8.2); 48	5.5 (3.75–6.82); 126	5.3 (3.7–6.45); 48
	6.6 (4.72–9.60); 78		5.5 (4.25–7); 78		5.6 (3.75–7); 78
6 (4.17–8.22); 126	5.45 (4.3–8.7); 48	5 (3.9–6.32); 126	5.05 (3.75–6.05); 48	4.5 (3.2–5.9); 126	5.1 (3.35–5.95); 48
	6 (4.07–8.22); 78		5 (3.9–7); 78		4 (3.175–5.9); 78
$p_1 = 0.884$		$p_1 = 0.738$		$p_1 = 0.372$	
$p_2 = 0.457$		$p_2 = 0.208$		$p_2 = 0.074$	
$p_3 = ND$		$p_3 = ND$		$p_3 = ND$	
$p_4 = 0.831$		$p_4 = 0.654$		$p_4 = 0.676$	
$p_5 = 0.432$		$p_5 = 0.177$		$p_5 = 0.634$	
$p_6 = 0.611$		$p_6 = 0.521$		$p_6 = 0.055$	

Days					
5		7		The last day	
1.4 (1–1.87); 85	—	1.4 (1–1.87); 85	—	1.4 (1.02–2.1); 85	—
	1.3 (0.97–1.8); 54		1.2 (0.8–1.72); 54		1.4 (1.07–2); 54
1.95 (1.6–3.2); 85	—	1.4 (1.1–2.0); 85	—	1.45 (1.2–1.8); 85	—
	2 (1.57–3.35); 54		1.5 (1.07–2.5); 54		1.5 (1.3–2.5); 54
1.5 (1.2–2); 126	1.4 (0.95–1.9); 48	1.5 (1.07–2); 126	1.5 (1–2); 48	1.7 (1.17–2.3); 126	1.5 (1.2–1.9); 48
	1.6 (1.27–2.02); 78		1.7 (1.27–2); 78		1.8 (1.1–2.4); 78
1.6 (1.17–2.2); 126	1.6 (1.15–2.45); 48	1.8 (1.37–2.02); 126	1.8 (1.5–2.25); 48	2 (1.3–2.32); 126	2 (1.2–2.55); 48
	1.6 (1.17–2); 78		1.6 (1.2–2.02); 78		2 (1.37–2.22); 78
$p_1 = 0.027$		$p_1 = 0.520$		$p_1 = 0.771$	
$p_2 = 0.472$		$p_2 = 0.262$		$p_2 = 0.376$	
$p_3 = ND$		$p_3 = ND$		$p_3 = ND$	
$p_4 = 0.019$		$p_4 = 0.270$		$p_4 = 0.456$	
$p_5 = 0.135$		$p_5 = 0.084$		$p_5 = 0.114$	
$p_6 = 0.861$		$p_6 = 0.947$		$p_6 = 0.973$	

Days					
5		7		The last day	
0.5 (0.4–0.8); 85	—	0.5 (0.4–0.7); 85	—	0.6 (0.4–0.7); 85	—
	0.5 (0.4–0.62); 54		0.5 (0.4–0.7); 54		0.6 (0.37–0.7); 54
0.95 (0.6–1.1); 85	—	0.5 (0.5–0.8); 85	—	0.8 (0.3–0.9); 85	—
	1 (0.82–1.1); 54		0.5 (0.5–0.85); 54		0.8 (0.27–0.97); 54
0.6 (0.4–0.8); 126	0.6 (0.4–0.85); 48	0.6 (0.5–0.8); 126	0.6 (0.4–0.8); 48	0.6 (0.475–0.7); 126	0.6 (0.4–0.7); 48
	0.6 (0.4–0.7); 78		0.6 (0.5–0.72); 78		0.6 (0.5–0.8); 78
0.6 (0.37–0.7); 126	0.6 (0.4–0.7); 48	0.5 (0.4–0.62); 126	0.55 (0.45–0.6); 48	0.5 (0.3–0.6); 126	0.5 (0.35–0.55); 48
	0.6 (0.37–0.72); 78		0.5 (0.3–0.7); 78		0.5 (0.3–0.6); 78
$p_1 = 0.010$		$p_1 = 0.668$		$p_1 = 0.332$	
$p_2 = 0.775$		$p_2 = 0.090$		$p_2 = 0.030$	
$p_3 = ND$		$p_3 = ND$		$p_3 = ND$	
$p_4 = 0.009$		$p_4 = 0.502$		$p_4 = 0.483$	
$p_5 = 0.599$		$p_5 = 0.743$		$p_5 = 0.238$	
$p_6 = 0.908$		$p_6 = 0.068$		$p_6 = 0089$	

types. Available data confirm that in human macrophages, the presence of the minor G mutation, which promotes the replacement of Lys167Asn, led to a decrease in the binding of the LOX-1 receptor ligand OxLDL and inhibition of the ERK1/2 kinases activated by this ligand [36] — the final molecules of the pro-inflammatory RAS-ERK1/2 signaling pathway in the cytoplasm, which activate transcription factors of genes (including NFkB) in the nucleus that control inflammatory processes. Thus, the pathogenesis of a less severe purulent complication of pneumonia (without fistula formation) associated with a minor variant of *OLR1* with Lys167Asn replacement may be associated with a predisposition to development of a less intense inflammatory reaction in the lungs, which does not result in structural and morphological alterations and a prolonged purulent process with an increased likelihood of a life-threatening condition — sepsis, including septic shock.

It is worth noting that myeloid-derived suppressor cells (MDSCs), which play a key role in the course and outcome of infectious complications of critical conditions, including sepsis, may contribute to NPI pathogenesis depending on the *OLR1* genotype [27, 14, 15, 37]. MDSC generation occurs as a

result of persistent stimulation of myeloid cell precursors in the bone marrow due to prolonged or chronic infection, chronic inflammation, or cancer. Relatively weak but constant signals induce persistent myelopoesis with the release of immature myeloid cells into the bloodstream, followed by their maturation into MDSCs [38, 39]. The main functional characteristic of such cells is their powerful ability to suppress various types of immune responses through different mechanisms [14, 40–42].

There are at least two subpopulations: granulocytic or polymorphonuclear MDSCs (G-MDSCs or PMN-MDSCs, respectively) and monocytic MDSCs (M-MDSCs). Although MDSCs are involved in suppressing the activity of various immune system cells, the main targets of MDSCs are T cells. M-MDSCs and PMN-MDSCs use different mechanisms of immunosuppression. M-MDSC suppress T cell responses in both antigen-specific and non-specific ways, using mechanisms related to the production of NO and cytokines. PMN-MDSCs are capable of suppressing the functional activity of interacting immune system cells predominantly in an antigen-specific manner, causing T cell tolerance due to the modification of their cell receptors when interacting with MDSCs that produce peroxynitrite radicals, as well as arginase and prostaglandins [43, 44].

It has been established that the LOX-1 receptor plays a role in the generation of PMN-MDSC [45], and ERK1/2-dependent signaling mechanisms ensure the accumulation of this subpopulation in the body [46]. A potential association with NPI pathogenesis is supported by evidence of MDSC accumulation in pleural effusion preceding the development of pleural empyema [47]. It is possible that the expected reduced activity of MDSC in carriers of the minor variant of *OLR1* will lead to less immunosuppression and greater effectiveness of the innate and adaptive immune systems, which will manifest in conditions of high probability of developing healthcare-associated infections (HAIs). The role of PMN-MDSC in the development of HAI and the contribution of MDSC to suppression of T-cell immunity against the life-threatening HAI pathogen, hypervirulent *K.pneumoniae*, was demonstrated in the works of F. Uhel et al. [48] and Q. Xu et al. [49], respectively.

It should be noted that in patients with the major CC genotype, the lymphocyte count was lower than in carriers of the minor allele, although the statistical significance was marginal and was detected only on the 5th day of hospital stay. It can be assumed that carriers of the major CC genotype might have reduced ability to develop cellular and humoral adaptive immune responses, including post-COVID-19 cases [50, 51]. These results suggest that patients who carry the minor G *OLR1* mutation have a greater potential for developing effective anti-infective immunity due to higher lymphocyte counts in the blood and reduced risk of developing persistent or chronic inflammatory reactions, predisposing to a more severe course of infection. It is possible that it is precisely the more intense ERK-dependent signaling mechanisms initiated in carriers of the major variant of the *OLR1*-CC gene by the interaction of circulating OxLDL with the LOX-1 receptor that determine the high risk of fistula development.

It's worth noting that the association of the major CC variant with development of fistula in pleural empyema was significant only in the subgroup of COVID-19-experienced patients. It is possible that the increased risk of developing fistula after COVID-19 is associated with both the increased content of the OxLDL ligand and the presence of allele variant of the *OLR1* gene, which provides more frequent ligand-receptor interaction, combined with impaired lung and immune system function as a consequence of COVID-19.

A limited sample showed that increased Ox-LDL content is associated with the development of fistula. The use of PCSK9 inhibitors in patients with NPIs may have potential.

Despite the small size of the group and the marginal statistical significance, the results revealed a tendency toward an association between high plasma OxLDL levels and the actual development of fistulas. This warrants the continuation of the studies determining the value of plasma LOX-1 ligand levels as predictors for patients with NPIs.

It is possible that complementary markers — the *OLR1* genetic variant and high concentration of the gene product ligand LOX-1 receptor — in combination may become the most informative predictors of the risk of adverse pleural empyema progression and be used to select optimal personalized treatment methods.

A limitation of our study is the absence of a registered study protocol and a small number of patients.

Conclusion

Carriage of the C allele of the *OLR1* rs11053646 gene in a homozygous form (CC genotype) is an unfavorable marker of NPI course for patients who have had COVID-19. The presence of the minor G allele of *OLR1* rs11053646 (CG, GG genotypes), on the contrary, protects against the development of fistula. An OxLDL content of $\geqslant$100 ng/ml has the potential to be a predictive marker of a more severe NPI course with development of fistula.

Note. Based on the results of accumulated data, a Russian Federation patent was obtained for «Method for predicting fistula development in necrotizing pulmonary infections» No. 2 845 356 C1, reg. 18.08.2025, priority 19.12.2024 (authors: Pisarev V. M., Chumachenko A. G., Fetlam D. L., Grechko A. V.)

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Received 01.09.2025
Accepted 14.01.2026
Online First 30.01.2026