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Genetic factors contributing to a severe course of pneumonia: a systematic review

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ABSTRACT

The article presents a systematic review of publications devoted to the study of genetic markers of severe pneumonia.

The **aim** of the study was to compile a list of genetic markers that contribute to a severe course of pneumonia on the basis of the published data.

In the current study, we searched for and analyzed articles published between January 2000 and April 2021. Following the search for and subsequent selection of articles, a list of 10 publications was compiled, which demonstrated a clear association of certain gene variants with severe and complicated pneumonia. Finally, we made a list of genetic markers of severe pneumonia consisting of 16 polymorphisms in 12 genes (*CD86, IL6, IL10, PAI1, TNFα, HMGB1, ATG16L1, AGTR1, GCLC, CAT, IFNγ, FCGR2A*).

These genetic markers of severe and complicated pneumonia are responsible for various innate immune responses. The odds ratio for complicated pneumonia with a risk allele in the polymorphisms in the mentioned genes ranges from 1.39 to 4.28. To understand molecular and genetic mechanisms of severe pneumonia, further investigation of the effect of these genetic factors on the outcomes of pneumonia in different groups of patients with a simultaneous assessment of the cumulative effect of genetic variants and genetic interactions is required.

Keywords: pneumonia, genes, polymorphism, innate immunity, severity criteria, cytokines, secreted proteins

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Генетические факторы риска тяжелого течения пневмонии: систематический обзор

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РЕЗЮМЕ

Представлен систематический обзор публикаций, посвященных поиску генетических маркеров тяжелого течения пневмонии.

Цель исследования: на основании опубликованных данных сформировать перечень генетических маркеров, способствующих тяжелому течению пневмонии.

В ходе исследования выполнен поиск и анализ статей, опубликованных в период с января 2000 г. по апрель 2021 г. В результате проведенного поиска и последующего отбора статей сформирован список из 10 публикаций, в которых продемонстрирована четкая ассоциативная связь определенных генных вариантов с тяжелым и осложненным течением пневмонии, и список генетических маркеров тяжелого течения пневмонии, состоящий из 16 полиморфизмов в 12 генах (*CD86, IL6, IL10, PAI1, TNFα, HMGB1, ATG16L1, AGTR1, GCLC, CAT, IFNγ, FCGR2A*).

Приведенные генетические маркеры тяжелого и осложненного течения пневмонии отвечают за разнообразные реакции врожденного иммунитета. Отношение шансов при наличии рискового аллеля по соответствующим полиморфным локусам этих генов колеблется от 1,39 до 4,28. Необходимо дальнейшее изучение влияния данных генетических факторов на исходы пневмонии в группах пациентов различных популяций с одновременной оценкой совокупного влияния генетических вариантов и взаимодействия генов между собой.

Ключевые слова: пневмония, гены, полиморфизм, врожденный иммунитет, критерии тяжести, цитокины, секретируемые белки

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Pneumonia is a form of acute respiratory infection characterized by focal parenchymal lung lesions with intra-alveolar exudate [1]. In 2019, pneumonia and other lower respiratory infections were ranked fourth among the leading causes of death as the deadliest group of infectious diseases [2]. According to the World Health Organization, pneumonia is currently one of the three main causes of death in the world, and among respiratory diseases, pneumonia accounts for 41.5% of deaths [3]. The incidence of community-acquired pneumonia in Russia in 2019 was 410 per 100,000 population according to the data of official statistics of the Russian Federation [4].

Pneumonia is a typical multifactorial disease as it can be caused by a wide range of bacteria, viruses, and fungi. Its course and prognosis are determined by human genetic characteristics, environmental factors, and the features of the pathogen. Numerous multicenter clinical trials discovered a large number of risk factors for a severe course of pneumonia and development of its complications in order to optimize treatment regimens and prevent the incidence of pneumonia. However, additional risk factors remained undetected in a significant proportion of patients [5]. In this regard, identifying reliable predictors of severe and complicated pneumonia is an urgent issue in modern medicine.

Researchers have made repeated attempts to solve this issue by identifying candidate genes and their variants associated with susceptibility to pneumonia and the course and clinical outcomes of the disease. Currently, a large number of studies devoted to this problem have been published. Particularly, in a systematic review, A.T. Kloek et al. (2019) analyzed 1,219 studies published from 2000 to 2018 [5]. When conducting a meta-analysis, the authors found a statistically significant association between the alleles in the *MBL2* and *CD14* genes and the risk of developing pneumococcal pneumonia. As it was noted in the research, there were contradictory results in the literature on the role of gene polymorphisms in susceptibility to pneumonia and the course and outcome of the disease. This fact can be explained by methodological flaws and poor reproducibility of the studies [5].

In this article, we provided a systematic analysis of the effect of genetic factors on the severity of pneumonia, compiled a list of genetic markers contributing to its severe course, and discussed possible directions for further research in this field.

The aim of the study was to compile a list of genetic markers that contribute to a severe course of pneumonia based on the published data on genetic aspects that determine the features of the course of this disease.

MATERIALS AND METHODS

In this study, we searched for and analyzed articles from the database of medical and biological articles PubMed (https://pubmed.ncbi.nlm.nih.gov/) which were published from January 2000 to April 2021 and then analyzed the publications found. The search query contained the words “pneumonia” and derivatives, “gene” and derivatives, “polymorphism” and derivatives. To narrow down the search, articles containing the words “children” and “covid” with their variations were excluded. So, the search algorithm looked like this: (“pneumonia”[MeSH Terms] OR “pneumonia”[All Fields] OR “pneumoniae”[All Fields] OR “pneumonias”[All Fields] OR “pneumoniae s”[All Fields]) AND (“genes”[MeSH Terms] OR “genes”[All Fields] OR “gene”[All Fields]) AND (“polymorphic”[All Fields] OR “polymorphics”[All Fields] OR “polymorphism s”[All Fields] OR “polymorphism, genetic”[MeSH Terms] OR (“polymorphism”[All Fields] AND “genetic”[All Fields]) OR “genetic polymorphism”[All Fields] OR “polymorphism”[All Fields] OR “polymorphisms”[All Fields])) NOT (“child”[MeSH Terms] OR “child”[All Fields] OR “children”[All Fields] OR “child s”[All Fields] OR “children s”[All Fields] OR “childrens”[All Fields] OR “childs”[All Fields])) NOT (“sars cov 2”[MeSH Terms] OR “sars cov 2”[All Fields] OR “covid”[All Fields] OR “covid 19”[MeSH Terms] OR “covid 19”[All Fields])) AND (2000:2021[pdat]). When applying the presented search algorithm, we initially found 795 articles. After further investigation, 761 articles were excluded because they did not fully meet the aim of this study as they were devoted to genetic characteristics of microorganisms causing bronchopulmonary diseases or studied the odds for the disease, but not its course. Therefore, the list was reduced to 34 articles.

After a thorough analysis of these publications, several articles were additionally excluded from the study, as they examined groups of patients unsuitable for our study or did not contain data relevant to the aim of this study. Particularly, several excluded works studied patients under the age of 18, and other publications did not analyze the association

of genetic markers with the severity of pneumonia, but with predisposition to pneumonia. In addition, studies that demonstrated a statistically insignificant ($p > 0.05$) association of a gene polymorphism with a severe course of pneumonia were eliminated from the list.

Thus, at the last stage of the detailed evaluation, 24 publications were excluded from 34 articles. As a result, we formed a list of 10 publications, which demonstrated a clear association of certain gene variants with a severe and complicated course of pneumonia (Figure).

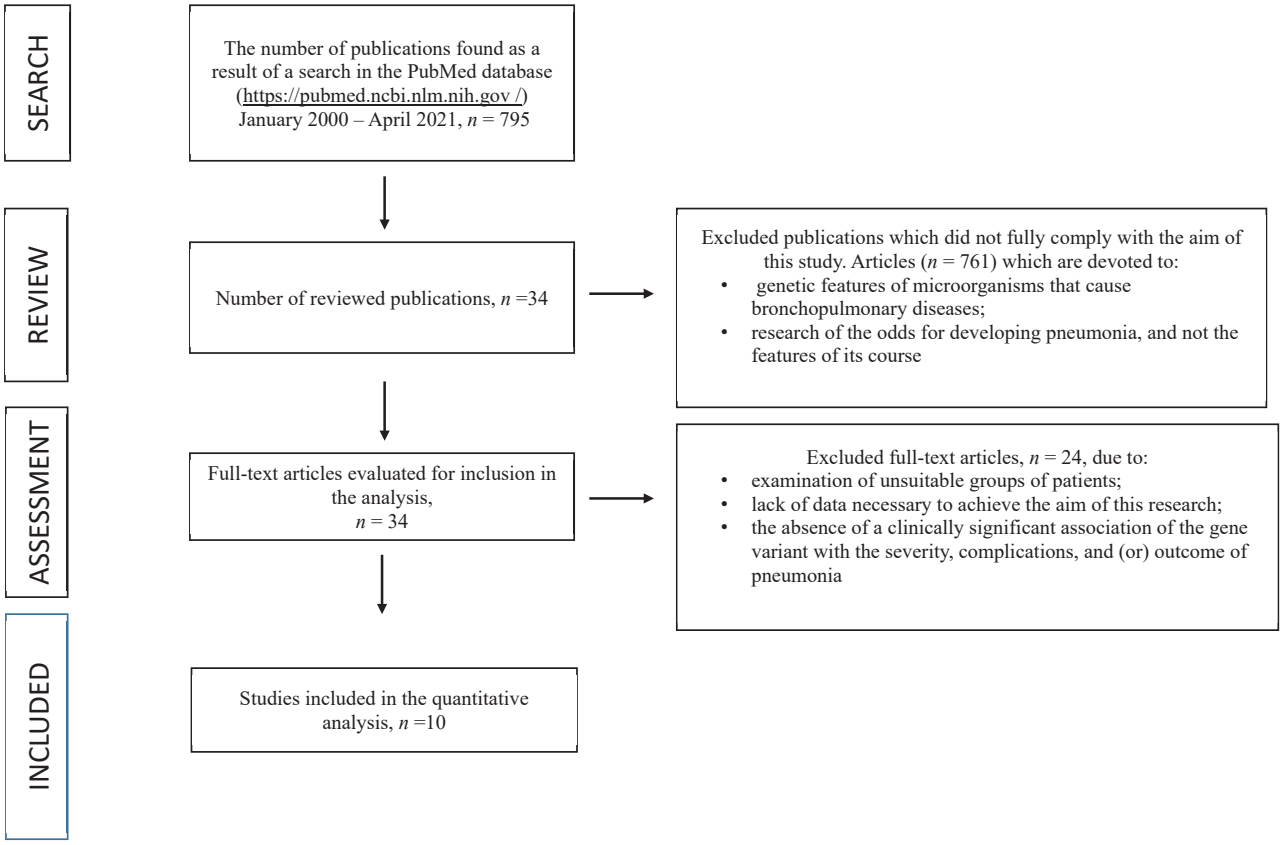

Figure. Schematic representation of the selection of publications devoted to the identification of genetic markers associated with severe pneumonia in accordance with PRISMA guidelines

The contribution of various polymorphisms to the development of the disease was determined using the odds ratio (OR), which is a traditional parameter for such studies. The results obtained were interpreted as follows: if the OR was equal to 1, then there was no correlation between a gene polymorphism and clinical and laboratory features of the course of pneumonia; if the OR was > 1, then there was an increased risk of severe pneumonia; if the OR was < 1, then there was a protective marker against the complicated course of pneumonia. Associations with $p < 0.05$ were considered statistically significant.

Furthermore, genetic databases and genomic browsers dbSNP (https://www.ncbi.nlm.nih.gov/snp/), Ensembl (https://www.ensembl.org/index), SNPedia (https://www.snpedia.com/), and OMIM (https://www.omim.org/) were analyzed to assess the results of the identified genetic associations, clarify the frequency characteristics of gene polymorphisms, and determine their biological role in the processes responsible for innate immune responses.

According to the Russian clinical guidelines for the diagnosis, management, and prevention of severe pneumonia in adults, it is advisable to use the IDSA / ATS criteria, containing two major and nine minor criteria, to determine the severity of the disease (Table 1) [6]. The presence of one major and three minor criteria in a patient indicates a severe course of pneumonia [7].

Table 1

IDSA / ATS criteria for the severity of pneumonia

Major criteria	Severe respiratory failure requiring MV
	Septic shock requiring vasopressors
Minor criteria	RR ≥ 30 per min
	PaO_2 / FiO_2 ≤ 250
	Multilobar infiltration
	Impaired consciousness
	Uremia (blood urea nitrogen ≥ 20 mg / dl)
	Leukopenia (leukocytes < 4×10^9 / l)
	Thrombocytopenia (platelets < 100×10^9 /l)
	Hypothermia (< 36 °C)
	Hypotension requiring aggressive fluid resuscitation

Note: IDSA – Infectious Diseases Society of America; ATS – American Thoracic Society; MV – mechanical ventilation; RR – respiratory rate; PaO_2 / FiO_2 – partial pressure of arterial oxygen / fraction of inspired oxygen; WBC – white blood cells.

RESULTS

As a result of a systematic literature review, we have formed a list of genetic markers of severe pneumonia, consisting of 16 polymorphisms in 12 genes (Table 2).

These genetic markers of a severe and complicated course of pneumonia are responsible for various innate immune responses. In general, the selected genes can be grouped according to the functional principle: extracellular cytosolic opsonizing proteins (proinflammatory cytokines) (*IFNG, IL6, IL10, TNFα*), secreted proteins (genes of the complement system and Fc receptors) (*FCGR2A*) and genes encoding synthesis of other proteins (*CAT, GCLC, AGTR1, PAI1 (SERPINE1)*).

Table 2

Genetic factors associated with the risk of severe and complicated pneumonia

Gene	Polymorphism	OR for allele and / or genotype (complication of pneumonia)	Features of the sample under study	Source (PubMed ID), population features
CB86	rs17281995 G/C	Allele C – 1.75 (95% CI; 1.04–2.95). Genotype GC – 1.85 (95% CI; 1.07–3.20) (sepsis)	Chinese population, 192 patients with pneumonia and sepsis and 201 healthy individuals	25129060 [8]
	rs2332096 T/G	Allele G – 1.65 (95% CI; 1.21–2.24). Genotype GG – 2.75 (95% CI; 1.46–5.16) (sepsis)	Chinese population, 186 patients with pneumonia and sepsis and 196 healthy individuals	25912130 [9]
IL6	rs1800795 G/C	Allele C – 2.83 (95% CI; 2.1–3.78). Genotype CC – 4.45 (95% CI; 2.69–5.37) (sepsis)	Chinese population, 188 patients with pneumonia and sepsis, 162 patients with pneumonia, and 200 healthy individuals	27388228 [10]
	rs1800795 G/C	Allele C – 2.42 (95% CI; 1.08–5.45) (septic shock)	Chinese population. The group of 277 patients was divided into two subgroups depending on the severity of sepsis and its outcome	26025100 [11]
IL10	rs1800896 A/G	Allele A – 2.08 (95% CI; 1.15–2.80) (sepsis)	Chinese population, 188 patients with pneumonia and sepsis, 162 patients with pneumonia, and 200 healthy individuals	27388228 [10]
PAI1 (SERPINE1)	rs1799768 4G/5G and 4G/4G	4G/5G and 4G/4G genotypes – 2.74 (95% CI; 1.34–5.60) (multiple organ dysfunction syndrome), 2.57 (95% CI; 1.18–5.62) (septic shock)	208 Caucasian patients with pneumonia and sepsis. Patients were stratified depending on the presence of multiple organ dysfunction syndrome, septic shock or death	20429897 [12]
TNFα	rs1800629 G/A	Allele A – 4.28 (95% CI; 2.24–8.18) (septic shock)	Chinese population.The group of 277 patients was divided into two subgroups depending on the severity of sepsis and its outcome	26025100 [11]
HMGB1	rs1412125 T/C	Genotype TC – 1.74 (95% CI; 1.025–2.958) (severe course). Genotype CC – 4.73 (95% CI; 2.24–10.08) (severe course)	Chinese population, 328 patients with community-acquired pneumonia (depending on the severity of the condition, patients were divided into severe (125) and non-severe community-acquired pneumonia (203) groups) and 317 healthy individuals	30562142 [13]
	rs2249825 C/G	Genotype CG – 1.75 (95% CI; 1.02–3.01) (severe course). Genotype GG – 3.87 (95% CI; 1.58–9.58) (severe course)		
ATG16L1	rs2241880 G/A	Allele A – 2.4 (95% CI; 1.06–5.60) (septic shock and failure of at least one organ in patients with ventilator-associated pneumonia)	Greek population, 155 patients with ventilator-associated pneumonia	24791954 [14]

Table 2 (continued)

Gene	Polymorphism	OR for allele and / or genotype (complication of pneumonia)	Features of the sample under study	Source (PubMed ID), population features
AGTR1	rs5186 A/C	Allele C – 1.86 (95% CI; 1.31–2.64) (complications of pneumonia)	Russian population, 350 patients with ventilator-associated pneumonia, 432 healthy individuals	24068433 [15]
GCLC	rs17883901 C/T	Allele T – 1.90 (95% CI; 1.15–3.15) (complications of pneumonia)		
CAT	rs17880664 T/A	Genotype AA – 1.85 (95% CI; 1.06–3.25) (complications of pneumonia)		
IFNγ	rs2069705 T/C	Allele T – 1.39 (95% CI; 1.03–1.89) (sepsis). Genotype TT – 1.22 (95% CI; 0.58–2.57) TC + TT – 1.84 (95% CI; 1.24–2.73) (sepsis)	Chinese population, 196 patients with sepsis and pneumonia, 213 healthy individuals	24475220 [16]
	rs2430561 A/T	Allele A – 1.49 (95% CI; 1.05–2.12) (sepsis). Genotype AA – 1.70 (95% CI; 0.61–2.12) TA + AA – 1.68 (95% CI; 1.11–2.54)		
FCGR2A	rs1801274 T/C	Allele C – 1.57 (95% CI; 1.00–2.45) Genotype CC – 2.55 (95% CI; 1.30–5.00) (sepsis)	Netherlands, 200 patients with ventilator-associated pneumonia and sepsis, 313 healthy individuals	19494086 [17]

Note: SNV – single nucleotide variant; OR – odds ratio; 95% CI – 95% confidence interval.

According to Table 1, the OR in the presence of a risk allele for the presented polymorphic loci ranges from 1.39 to 4.28.

Here we would like to provide more detailed information on the genetic associations found in the literature. The *CD86* gene is located on the long arm of chromosome 3 (3q13.33) and encodes a membrane protein of the immunoglobulin superfamily expressed by antigen-presenting cells. CD86 protein acts as a co-stimulatory signal for the activation and survival of T lymphocytes [18]. A study by H. Song et al. (2015) which included 192 patients with pneumonia-induced sepsis showed that the frequency of the rs17281995 G/C gene variant in these patients was significantly higher than in the control group. The OR for allele C and genotype GC was 1.75 and 1.85, respectively. In the study by C. Wang et al. (2015), where 186 patients with pneumonia-induced sepsis were examined, a correlation was found between the rs2332096 T/G gene variant and the severe course of the disease. The OR for allele G and genotype GG was 1.65 and 2.75, respectively [8, 9].

The *IL6* gene is located on the short arm of chromosome 7 (7p15.3) and encodes interleukin (IL)-6. IL-6 is a proinflammatory cytokine and one of the most important mediators of the acute-phase response. It stimulates synthesis of acute-phase proteins, proliferation and differentiation of B and T cells and leukopoiesis, and is involved in the development of oxidative stress. IL-6 is secreted by macrophages, fibroblasts, vascular endothelial cells, T cells, glial cells, and epithelial and skin keratinocytes after their activation by pathogen-associated molecules mediated by toll-like receptors [10]. The study by Z.-R. Mao et al. (2017), which included 188 patients with pneumonia-induced sepsis and 162 patients with pneumonia, showed that the rs1800795 G/C variant increases the risk of sepsis. The OR for allele C and genotype CC was 2.83 and 4.45, respectively. B. Feng et al. studied 277 patients with pneumonia-induced sepsis and found a correlation between the rs1800795 G/C gene variant and the development of septic shock. The OR for allele C was 2.42 [11].

The *IL-10* gene is located on the long arm of chromosome 1 (1q32.1) and encodes IL-10. IL-10 has multiple pleiotropic effects on immunoregulation and inflammation. It reduces the expression of Th1 cytokines, MHC class II antigens, and co-stimulatory molecules on macrophages, increases the survival of B cells, their proliferation and antibody production, blocks NF-κB activity, and regulates the JAK-STAT signaling pathway [20]. The study by Z.-R.Mao et al. (2017) which examined 188 patients with pneumonia-induced sepsis and 162 patients with pneumonia showed an increased risk of severe pneumonia in the rs1800896 A/G variant. The OR for allele A was 1.58 [10].

The *PAI1* gene (*SERPINE1*) is located on the long arm of chromosome 7 (7q22.1) and encodes plasminogen activator inhibitor 1 involved in

fibrinolysis. Polymorphisms in this gene are usually considered as risk factors for the development of cardiovascular diseases [21]. K. Madách et al. conducted a study involving 208 patients with pneumonia-induced sepsis and demonstrated the relationship between the genotypes 4G/5G and 5G/5G of the *PAI1* gene (*SERPINE1*) and the development of multiple organ dysfunction syndrome and septic shock. The OR for these two genotypes was 2.74 and 2.57, respectively [12].

The *TNFα* (*TNF*) gene is located on the long arm of chromosome 7 (*6p21.33*) and encodes tumor necrosis factor alpha. This extracellular protein is a multifunctional proinflammatory cytokine synthesized mainly by monocytes and macrophages. TNFα affects lipid metabolism, coagulation, insulin resistance, endothelial function, stimulates the production of IL-1, IL-6, IL-8, interferon gamma, activates leukocytes, and plays a pivotal role in the protection against intracellular parasites and viruses [22]. In the article by B. Feng et al., which studied 277 patients with pneumonia-induced sepsis, a correlation was found between the rs1800629 G/A gene variant and the development of septic shock. The OR for allele A was 4.28 [11].

The *HMGB1* gene is located on the long arm of chromosome 13 (13q12.3) and encodes the HMGB1 protein (amphoterin), which is secreted by activated macrophages and monocytes as a cytokine mediator. In addition, as a nuclear protein, HMGB1 can be released during cell and tissue necrosis. In the extracellular compartment, it can bind to the innate immune receptor TLR4, activating cytokine secretion by macrophages and a subsequent inflammatory response. The HMGB1 protein is highly toxic when released in large amounts, so it is considered as one of the possible therapeutic targets for sepsis [23]. In the study by W. Song et al. which involved 328 patients with pneumonia, a relationship was found between the rs1412125 T/C and rs2249825 C/G gene variants and the severity of pneumonia. When OR for genotype TC was equal to 1.740, OR for genotype TT was 4.728 (rs1412125 T/C). When OR for genotype CG was 1.754, OR for genotype GG was 3.869 (rs2249825 C/G) [13].

The *ATG16L1* gene is located on the long arm of chromosome 2 (2q37.1) and is responsible for synthesis of an intracellular protein involved in the autophagy process which interacts with other proteins of this complex [24]. The research by A. Savva et al. examined 200 patients with sepsis caused by ventilator-associated pneumonia and showed that the rs2241880 G/A gene variant affects the severity of ventilator-associated pneumonia. The OR for allele A was 2.4 [14].

The *AGTR1* gene is located on the long arm of chromosome 3 (*3q24)* and *encodes* production of angiotensin II type 1B receptor, which mediates the main cardiovascular effects of angiotensin II [25]. L. Salnikova et al. studied 350 patients (Slavs, including Russians) with pneumonia and found a relationship of the rs5186 A/C gene variant with complications of pneumonia, as well as with the development of acute respiratory failure (ARF). The risk of complicated pneumonia in the presence of allele C is quite high; OR is 1.862 [15].

The *GCLC* gene is located on the short arm of chromosome 6 (6p12.1) and encodes glutamate-cysteine ligase catalytic subunit, which is involved in synthesis of glutathione from L-cysteine and L-glutamate [26]. In the previously discussed study by L. Salnikova et al., where 350 patients (Slavs, including Russians) with pneumonia were examined, a relationship was found of the rs17883901 C/T variant with complications of pneumonia, as well as with the development of ARF. OR for complicated pneumonia for allele T was 3.36, and OR for ARF was 1.33 [15].

The *CAT* gene is located on the short arm of chromosome 11 (11p13) and encodes catalase, an enzyme involved in cellular respiration and in converting reactive oxygen species hydrogen peroxide into water and molecular oxygen [27]. L. Salnikova et al. (2013) studied a population of 350 patients (Slavs, including Russians) with pneumonia and described a relationship between the rs17880664 T/A variant and pneumonia complications. OR for genotype AA was 1.85 [15].

The *IFNG* gene is located on the long arm of chromosome 12 (12q15) and encodes a soluble cytokine. It is a member of the interferon type II class. It is secreted by cells of both adaptive and innate immunity. In its active form, this protein binds to the interferon gamma receptor and activates the cellular response to viral or bacterial infection [28]. The study by D. Wang et al. (2014), which involved 196 patients with pneumonia-induced sepsis, showed that the rs2069705 T/C and rs2430561 A/T gene variants are associated with the development of sepsis in patients with pneumonia. For a single-nucleotide substitution rs2069705 T/C, OR for TC, TT, and TC + TT genotypes was 1.99, 1.22, and 1.84, respectively. OR for T allele was 1.39. For a single-nucleotide

substitution rs2430561 A/T, OR for TA, AA, and TA+AA genotypes was 1.68, 1.70, and 1.68, respectively. OR for A allele was 1.49 [16].

The *FCGR2A* gene is located on the long arm of chromosome 1 (*1q23.3*), encodes the low-affinity immunoglobulin Fc receptor IIa (CD32A), and participates in the activation of the cellular response [29]. H. Endeman et al. (2009) examined 201 patients with pneumonia and pneumonia-induced sepsis and found a correlation between the rs1801274 T/C gene variant and the development of severe sepsis. OR for CC genotype was 2.55 [17].

DISCUSSION

According to the analyzed studies, the severity of pneumonia and its outcome are determined by the development of complications through a systemic inflammatory response [8–17]. Systemic inflammatory response syndrome, acute respiratory distress syndrome, multiple organ failure syndrome, as well as pleurisy, empyema, and the development of necrotizing pneumonia are the most significant complications in terms of the most unfavorable prognosis and outcome [30].

As it was shown in our systematic review, at least 12 genes and polymorphisms in them were proven to be associated with a severe course of pneumonia. These genes mostly include the ones responsible for various innate immune responses.

Despite the rigorous selection of genes, which polymorphisms are associated with a risk of severe pneumonia, it is worth noting that the selected genes included the ones responsible for synthesis of multifunctional, often nonspecific factors, such as proteins regulating vascular homeostasis (*PAI1* and *AGTR1*). This fact significantly reduces the significance of the interpretation of the role of these polymorphisms as predictors of clinical features of pneumonia and requires further in-depth study.

In addition, each of the presented gene variants does not act in isolation, but contributes to the risk of developing the disease in the context of the overall genetic constitution of the patient. Several years ago, a number of researchers put forward a hypothesis that a combination of two or more risk alleles in candidate genes is of greater importance for assessing the prognosis and the course of pneumonia. So, J.N. Siebert et al. (2018) demonstrated that a combination of nucleotide polymorphisms in *TLR1* or *TLR6* and *TIRAP* was associated with decreased release of IL-6 and predisposition to pneumonia [31].

In this regard, special attention should be paid to studying genetic interactions and the role of the combination of polymorphisms in receptor genes and opsonizing proteins involved in innate immune responses. Therefore, approaches to determining the presence of genetic associations should include a variety of genetic markers.

In this review we deliberately did not discuss human genetic characteristics that contribute to the development of an infectious process associated with certain types of microorganisms; this issue requires in-depth research. Currently, studies have described more than 100 microorganisms that can cause pneumonia under certain conditions. In most cases, these include *S. pneumoniae, M. pneumoniae, C. pneumoniae, H. influenzae*, respiratory viruses, enterobacteriaceae (*K. pneumoniae and E. coli*), and *S. aureus* [30].

The question of the influence of genetic factors on the course of pneumonia, depending on the causative agent, requires a detailed review and analysis of the available data from the literature.

CONCLUSION

We analyzed data published from 2000 to 2021 and identified a list of 16 polymorphisms in 12 human genes that can affect the severity of pneumonia. The OR for severe pneumonia in the presence of these risk alleles is 1.4–4.3. There is a need for further research of the influence of these genetic factors on the outcomes of pneumonia in groups of patients from different populations with a simultaneous assessment of the cumulative effect of genetic variants and genetic interactions. Therefore, molecular marker systems for the detection of relevant genetic variations should be developed.

In addition, in order to understand the genetic predisposition to severe pneumonia in Russia, it is essential to analyze allele frequencies of the related polymorphisms in Russian populations. The next step in studying the influence of gene polymorphisms on the development of respiratory diseases should be investigation of their molecular effects in combination with large-scale clinical trials involving patients with pneumonia.

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Karnaushkina M.A. – conception and design, drafting of the manuscript, final approval of the manuscript, responsibility for the integrity of all parts of the manuscript. Litvinova M.M. – conception and design, editing, statistical processing of the results, and drafting of the manuscript. Korchagin V.I., Salamaikina S.A., Vasilyeva I.S., Sviridov F.S., Vatsik – Gorodetskaya M.V. – search and review of the literature, processing of the obtained results.

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