SPECIFIC FEATURES OF THE IMMUNE STATUS OF PATIENTS WITH BRONCHIAL ASTHMA AND COVID-19
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Aim: to study the specific features of changes in the immune status of patients with bronchial asthma and COVID-19.

Materials and methods. Study date: 08.2021-04.22. Study design: a review. A literature review was conducted in the PubMed, Scopus, Web of Science, MEDLINE, EMBASE, Cochrane Library databases, as well as a manual search for suitable articles. We analyzed immunological differences that may influence the pathophysiological process in patients with COVID-19 and asthma, including immunoglobulins, interferons, and local immune cells.

Results. Through a study of 39 studies, including retrospective analyses, it was found that it is still unknown whether the asthma phenotype contributes to some protection of patients from COVID-19. Several immune differences have been found between COVID-19 patients with and without comorbid asthma: decreased levels of pro-inflammatory cytokines (e.g., IL-1β, TNF-α, IL-6, and IL-12), impaired production of type I and III interferons (IFN-α, IFN-β, IFN-λ), which is a priority produced to fight the COVID-19 virus.

Conclusions. Several of the research that have been reported so far are retrospective and do not differentiate between asthma phenotypes. Extensive therapeutic and immunological markers are severely lacking. To obtain a better knowledge of the immunological and metabolic link between COVID-19 and asthma, comprehensive endotyping of individuals with COVID-19 and asthma would be necessary. Furthermore, further information on the transcriptional and translational level of receptors modulation is needed at the level of virus-host contacts in relation to the virus's cellular entrance process. Furthermore, longterm prospective investigations are lacking. Additional knowledge on COVID-19 in asthmatic and allergy individuals is fast becoming available. Recent asthma treatment guidelines in the framework of COVID-19 should not be modified, according to current thinking. If indicated, patients will receive pharmacological therapy based on guidelines, including ICSs and biological treatments.

Keywords: SARS-CoV-2, COVID-19, bronchial asthma.
Цель: изучить особенности изменения иммунного статуса у пациентов с бронхиальной астмой и COVID-19.

Материалы и методы. Дата исследования: 08.2021-04.22. Дизайн исследования: обзор. Был проведен обзор литературы в базах данных PubMed, Scopus, Web of Science, MEDLINE, EMBASE, Cochrane Library и других, а также ручным поиском подходящих статей. Были проанализированы иммунологические различия, которые могут влиять на патофизиологический процесс у пациентов с COVID-19 и бронхиальной астмой, включая иммуноглобулины, интерфероны и локальные иммунные клетки.

Результаты исследования. Посредством изучения 39 исследований, включая ретроспективные, было установлено, что до сих пор неизвестно, способствует ли фенотип астмы определенной защите пациентов от COVID-19. Было обнаружено несколько иммунных различий между пациентами с COVID-19 с сопутствующей астмой и без нее: снижается концентрация провоспалительных цитокинов (например, IL-1β, TNF-α, IL-6 и IL-12), нарушается продукция интерферонов I и III типов (IFN-α, IFN-β, IFN-λ), что приоритетно вырабатывается для борьбы с вирусом COVID-19.

Заключение. Многие из опубликованных к настоящему времени исследований являются ретроспективными и не различают фенотипы астмы. Существует значительный недостаток дополнительных клинических и иммунологических параметров. Для лучшего понимания иммунологической и метаболической связи между этими двумя состояниями потребуется глубокое эндотипирование пациентов с COVID-19 и астмой. Кроме того, на уровне взаимодействия вирус-хозяйн необходимы дополнительные данные о транскрипционном и трансляционном уровне регуляции рецепторов. Кроме того, отсутствуют лонгитюдные проспективные исследования. Дополнительные знания о COVID-19 у людей, страдающих астмой и аллергией, быстро становятся доступными. Согласно современным представлениям, последние рекомендации по лечению астмы в рамках COVID-19 изменять не следует.

Ключевые слова: SARS-CoV-2, COVID-19, бронхиальная астма.
Introduction

A pandemic crisis has been caused by the recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]). Certain comorbidities are now widely accepted as defining high-risk individuals. Hypertension, diabetes, and coronary artery disease are among them. The situation with bronchial asthma, on the other hand, is contentious and exhibits significant geographical variances. Because asthma is the most common chronic inflammatory lung illness in the world, and SARS-CoV-2 mostly affects the upper and lower airways, causing significant inflammation, the issue of a clinical and pathophysiological link between asthma and SARS-CoV-2/COVID-19 emerges.

In COVID-19, bronchial asthma has not been fully examined. Respiratory allergies is linked to a decrease in the expression of the angiotensin-converting enzyme 2 receptor, which is COVID-19's entrance receptor.

We look at the worldwide asthma epidemiology among COVID-19 patients and offer the idea that individuals with distinct asthma endotypes (type 2 asthma vs non–type 2 asthma) have a different risk profile for SARS-CoV-2 infection, COVID-19 formation, and progression to severe COVID-19 outcomes. This approach might have significant consequences for the development of COVID-19 diagnostics and immune-based therapies in the future.

In the Republic of Kazakhstan for 2020, one can notice a high upward trend in bronchial asthma, where changes from 2019 (102.8) to 2020 (126.1) amounted to 23.3 per 100,000 people of the population. Also, in the urban population, this nosology is more pronounced than in the rural population, which is 156.3 and 82.8 for 2020, respectively (pic 1-3) [1].

The incidence of COVID-19 in Kazakhstan for 2021 is 1,394,778 cases, which corresponds to 0.26% of the total number of cases worldwide (pic 4, 5). These data raise the question of the need to study the relationship of these diseases from an immunological point of view and substantiate their changes in order to improve diagnostic and treatment tactics [2].
**Pic. 1** - Incidence of bronchial asthma by years (per 100,000 population).

**Pic. 2** - Incidence of bronchial asthma by age (per 100,000 population).

**Pic. 3** - The incidence of bronchial asthma by age for 2016-2020 (per 100,000 population).
Materials and methods
Study date: 08.2021-04.22. Study design: a review. A literature review was conducted in the PubMed, Scopus, Web of Science, MEDLINE, EMBASE, Cochrane Library databases, as well as a manual search for suitable articles. We analyzed immunological differences that may influence the pathophysiological process in patients with COVID-19 and asthma, including immunoglobulins, interferons, and local immune cells.

Results
Through a study of 39 studies, including retrospective analyses, it was found that it is still unknown whether the asthma phenotype contributes to some protection of patients from COVID-19. Several immune differences have been found between COVID-19 patients with and without comorbid asthma: decreased levels of pro-inflammatory cytokines (e.g., IL-1β, TNF-α, IL-6, and IL-12), impaired production of type I and III interferons (IFN-α, IFN-β, IFN-λ), which is a priority produced to fight the COVID-19 virus.

Discussions
Asthmatic individuals' vulnerability to COVID-19
A total of 548 COVID-19 patients admitted to Tongji Hospital were retrospectively examined, with 5 of them having asthma (0.9%) [3]. The Zhongnan Hospital of Wuhan
University conducted a retrospective analysis of 140 COVID-19-infected hospitalized patients and determined that allergy illness or asthma is not a risk factor for SARS-CoV-2 infection [4]. They evaluated 290 hospitalized patients with COVID-19 over the course of three months and found just one patient with asthma. Asthma prevalence varied across Europe, with Swedish and Italian cohort studies revealing relatively low rates of asthma, 1.8 percent and 2.6 percent (Sweden) and 1.96 percent and 1.92 percent (Italy) respectively [6,7]. Patients with asthma were not mentioned in another retrospective case analysis of 1591 patients hospitalized with laboratory-confirmed COVID-19 in the Lombardy area of Italy [8]. In Spain, Catalonia, and Ireland, however, the frequency of asthma among COVID-19 patients was greater (5.2 percent, 6.8 percent, and 8.8 percent, respectively) [9]. Asthma prevalence in the general population is 6.0 percent, 5.0 percent, and 7.0 percent in Italy, Spain, and Ireland, respectively [10,11]. COVID-19 individuals have decreased incidences of asthma, according to studies from Russia, Saudi Arabia, and Brazil (1.8 percent, 2.7 percent, and 1.5 percent respectively) [10,12,13]. In comparison to Brazil, the prevalence of asthma among COVID-19 patients in Mexico (3.6%), which is also in Latin America, was rather high (3.6%). In a retrospective Indian epidemiological investigation, asthma was not listed among COVID-19's comorbidities [14]. As we see, the frequency of COVID-19 in people with asthma varies greatly among places and nations, with some reporting low rates of COVID-19 with asthma, most likely due to a combination of variables including strict self-protection awareness and a low number of non-type 2 phenotypes.

**COVID-19 severity in asthma patients**

Aside from the vulnerability of asthma patients to COVID-19, another significant question is whether there is a difference in severity and mortality among COVID-19 patients with asthma vs those without. There were 5 asthmatics among the 548 COVID-19 patients admitted to Tongji Hospital, including 2 of 279 with nonsevere asthma (0.7 percent) and 3 of 269 with severe asthma (1.1 percent). There was no statistically significant difference in asthma prevalence between COVID-19 severe and nonsevere individuals [3]. According to Saudi Arabia, the prevalence of asthma in individuals with mild, moderate, and severe COVID-19 was 3 (2.9 percent), 0 (0 percent), and 1 (7.7 percent), respectively [13]. As a result, we tentatively infer that asthma is not related with an increased risk of death in COVID-19 individuals with a history of asthma. There is no strong evidence that people with asthma are more likely to become infected with SARS-CoV-2 or to become critically sick.

**Patients with type 2 asthma may be less likely to develop COVID-19**

High amounts of IL-4, IL-5, and IL-13 secretion, blood and airway eosinophilia, and (in the context of allergic asthma) greater rates of overall and allergen-specific IgE antibodies linked with mast cell activation define type 2 asthma. Lymphopenia, especially due to a decrease in T cells, is such a well indicator for COVID-19 intensity, and also because sick people with COVID-19 asthma have greater amounts and initiation T cells and have a less severe course of disease, it is assumed that both CD4+ and CD8+ T cells decrease SARS-destructive CoV-2's power. SARS-CoV-2 uses the angiotensin-converting enzyme-2 (ACE-2) receptor to infiltrate host cells through its morphological spike glycoprotein. The nasal epithelium, lung, heart, kidney, and intestines are the most common sites for ACE-2 expression, while immune cells are seldom affected [16]. Allergic patients have significantly lower levels of ACE-2 transcripts in nasal and bronchial epithelial cells, which has been linked to exposure to the allergen, allergen hypersensitivity, and rising IgE levels, also with lowest rates found in sick people with both elevated amounts of immune disorders and asthma [17]. Nonatopic asthma, on the other hand, was not linked to lower ACE-2 expression [17]. This is seen in asthmatic children and adults alike. However, information on the protein expression is currently scarce [17]. Additionally, although IL-13 lowers ACE-2 expression of genes in both the nasal and bronchial mucosa, ACE-2 gene increased expression link negatively with type 2 biomarkers, indicating a
functional role of these cytokines [18]. ICSs, a first anti-inflammatory therapy for type 2 asthma, also reduce ACE-2 gene transcription in the sputum [19].

Eosinophilia in the blood is a well-known indicator for type 2 inflammation, and eosinophils have antiviral characteristics [20,21]. Single-stranded RNA, which activates eosinophils via Toll-like receptor-7/myeloid development main reaction 88-dependent pathways, and eosinophil-derived neurotoxic, which acts as a restriction endonuclease, are examples [22,23]. In patients with serious COVID-19, eosinopenia has been reported, and blood cell numbers recover after lopinavir therapy, suggesting that they could serve as a signal for improvement [4,24,25]. Maximum blood eosinophil levels were below 0.02 109/L in 85.7 percent of asthma patients in a Russian retrospective review, and also no person had blood eosinophilia [12]. COVID-19 sensitivity was shown to be negatively correlated with blood eosinophil counts in our investigation. Blood eosinophilia is a sign of type 2 inflammation, while eosinopenia is a biomarker of acute COVID-19. Eosinophil-derived neurotoxic and TLR-7/MyD88-dependent pathways can trigger single-stranded RNA viruses, eliciting antiviral defense in eosinophils.

**Allergic-induced cross-reactive T-cell responses to SARS-CoV-2 may have a role in asthmatic individuals**

Heterologous immunity (HI) was first recognized as a result of prior infections altering the immune reaction to a future infection with such a distinct pathogen [26]. This process can occur among antigens that are strongly related or entirely unrelated. Based on cross identification and immunological defense, or the production of immunopathology, HI can eventually influence the outcome of infections [27]. T-cell receptor cross-reactivity, which recognizes similar but different antigens, or cytokine-induced indiscriminate activation of T cells can both cause cellular-mediated HI [28].

T-cell responses to SARS-CoV-2 are first evident around a week after symptoms appear and last until recuperation, with the amount of virus-specific T cells correlated with neutralizing antibody levels [29]. Individuals who survived from SARS-CoV illness exhibited long-lived virus-specific T memory cells, which could be detected for up to two years after the illness was resolved [30].

**COVID-19 development in individuals with type 2 asthma**

It can be assumed that if SARS-CoV-2 establishes clinical symptoms in individuals with allergic asthma, the risk of disease development is expected to be greater than in patients with nonallergic asthma who are infected with COVID-19. This might happen for a variety of purposes: (1) TH2 inflammation counterbalances TH1 immunity and restrictions the expression of proinflammatory cytokines (e.g., IL-1, TNF-α, IL-6, and IL-12), which also are needed to fight infectious diseases; (2) impeded generation of type I and type III interferons (IFN-α, IFN-β, IFN-λ) by respiratory system epithelium has indeed been characterized in patients with asthma in reaction to viral diseases [31-34]; and (3) IgE suppresses IFN-α production by inhibiting TLR signaling in plasmocytoid dendritic cells, which are the major source of IFN-α to protect against viral infections [35,36].

**COVID-19 in non–type 2 asthma individuals**

Patients with non–type 2 asthma are at a greater risk of developing acute COVID-19, according to corroborating evidence. Those with asthma who have a various inflammatory phenotype, such as TH1- or TH17-dominated inflammation, as well as people with chronic obstructive pulmonary disease (COPD), are classified as non–type 2. According to a newly published statewide South Korean research, individuals with asthma, especially nonallergic asthma, had a higher chance of SARS-CoV-2 infection and poor COVID-19 clinical consequences [37]. Older asthma patients have a greater risk of morbidity and death than younger asthma patients. The immune response is non–type 2-mediated in most of these people, and type 1 and/or type 17 T-cell reactions dominate the inflammatory endotype [38].
Inflammasome-associated and metabolic/mitochondrial pathways define a molecular phenotype [39]. As part of the insulin resistance, many of these asthma patients have complications such as overweight, type 2 diabetes, and hypertensive [40]. This endotype is notably common amongst African Americans and inner-city individuals [41].

Conclusions

Several of the research that have been reported so far are retrospective and do not differentiate between asthma phenotypes. Extensive therapeutic and immunological markers are severely lacking. To obtain a better knowledge of the immunological and metabolic link between COVID-19 and asthma, comprehensive endotyping of individuals with COVID-19 and asthma would be necessary. Furthermore, further information on the transcriptional and translational level of receptors modulation is needed at the level of virus-host contacts in relation to the virus's cellular entrance process. Furthermore, longterm prospective investigations are lacking. Additional knowledge on COVID-19 in asthmatic and allergy individuals is fast becoming available. Recent asthma treatment guidelines in the framework of COVID-19 should not be modified, according to current thinking. If indicated, patients will receive pharmacological therapy based on guidelines, including ICSSs and biological treatments.

Bibliography


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