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Asthma and prognosis of coronavirus disease 2019

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ABSTRACT

It is well-known that asthma patients show compromised production of antiviral interferons and lower expression of ACE-2, most likely owing to ACE-2 expression is inversely correlated with type 2 (Th2: T helper 2) cytokine levels of asthmatics. However, COVID-19 patients with poor outcomes show early vigorous type I interferon expression. This does not match with the pathophysiology of worse COVID-19 disease development in asthma patients. Actually, why asthma might protect against poor outcomes in COVID-19 is explained in detail in recent reviews. Some new data even show decreased mortality in asthma patients. There were no flawless data that asthma patients are at a greater risk of becoming severely ill with SARS-CoV-2 infection, although current reports from the United States and the United Kingdom indicate that asthma is much more common in children and adults with COVID-19 than was formerly described from Asia as well as from central Europe.

Keywords: Asthma, Comorbidity, Prognosis, COVID-19, SARS-CoV-2

DEAR EDITOR,

I have read the article entitled "Association of asthma comorbidity with poor prognosis of coronavirus disease 2019" by Kim et al with great interest.[1] Contrasting with most of the studies in the literature, they advocated that asthma morbidity leads to poor prognosis of coronavirus disease 2019 (COVID-19). Additionally, their study shows that recent asthma exacerbation could be a risk factor for severe/worse consequences of COVID-19 disease.[1]

The results of this study revealed conflicting conclusions. I also think that the authors could not give enough clarification for this conclusion. As mentioned in the article,[1] it is well-known that asthma patients show impaired production of antiviral interferons and lower expression of ACE-2, probably due to ACE-2 expression was inversely correlated with type 2 (Th2: T helper 2) cytokine levels of asthmatics. However, COVID-19 patients with poor outcomes show early vigorous type I interferon expression. This does not match with the pathophysiology of worse COVID-19 disease development in asthma patients.[2] Actually, why asthma might protect against poor outcomes in COVID-19 is explained in detail in a recent review.[3] Therefore, their study's conclusion makes me think of several alternative explanations and/or concerns of their study result.

The first: The result of this study[1] is still contrasting with other new systematic evaluations. Some new data even show decreased mortality in asthma patients. There were no flawless data that asthma patients are at a greater risk of becoming severely ill with SARS-CoV-2 infection, although current reports from the United States and the

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United Kingdom indicate that asthma is much more common in children and adults with COVID-19 than was formerly described in Asia and central Europe. Also in the United Kingdom asthma was demonstrated in 14.0% and 17.9% of hospitalized COVID-19 cases but with no bigger risk of death.[4] Another recent systematic review and meta-analysis of 5 key study databases with a control (non-asthma) group was performed on the effect of asthma morbidity on COVID-19 disease. There were no statistically significant differences in hospitalization, intensive care unit (ICU) admission, and ventilator use between groups.[5] Similarly, the results of the meta-analysis of 150 global studies by Terry et al do not give a net data of augmented risk of COVID-19 diagnosis, hospitalization, severity, or fatality due to asthma.[6] Asthma patients were found to have a lower risk of mortality compared with cases without asthma.[7] The whole conclusion of another recent meta-analysis (587 280 patients) indicate that asthma patients have comparable clinical outcomes.[8] Moreover, a significant (18%) reduction in fatality risk in asthma patients with COVID-19 disease compared to non-asthmatics was reported.[3]

The second is the study's population age (the mean age was 45.9 years) and their patients' multiple co-morbidities. As mentioned in the manuscript,[1] patients with any type of comorbidity defined in the Charlson Comorbidity Index (CCI) other than asthma were 49.5%. All major comorbidities in older asthma patients are at higher rate than non-asthma patients as shown in table 1. One or more ($\geq$1) comorbidity index was 66.1%.[1] Indeed, it would be very helpful and clarifying to compare the data between children (<20 years) and adults (>20 years) for the reader to understand the role of major comorbidities on this poor prognosis of COVID-19.

Consistently, in a recent literature review, older age and underlying comorbidities, such as cardiovascular disorders (hypertension, etc) and metabolic diseases (diabetes, etc), have been recognized as important risk elements for COVID-19 morbidity and fatality. However, asthma may not be a common comorbidity.[4] Izquierdo et al evaluated clinical data consisting 71 182 asthma cases by utilizing big data analytics and artificial intelligence through the SAVANA Manager® clinical platform. The presentation of asthmatics in this clinical population was not mostly serious,

with a low rate of hospital admissions. The amplified risk for hospitalization due to COVID-19 in asthma patients was generally related with age and comorbidities.[9] Additionally, in a new French study, among 768 hospitalized cases worse outcomes were seen mainly in 37 (4.8%) asthmatics with major comorbidities.[3] It is also very clarifying to know that expression of ACE-2, the co-receptor for SARSCoV-2, varies with age.[10]

The third: The description of asthma is not a clear-cut definition in this study.[1] In the text, asthma is described as a simultaneous prescription of any asthma-related medication at least twice a year or having asthma symptoms in 3 years in another paragraph. Definition of asthma should have been made according to the international guidelines such as The Global Initiative for Asthma (GINA). In various study populations in literature, the overall prevalence of asthma is very different, according to definitions of studies. Even the authors said that they included a wider range of subjects with asthma who had a history of asthma symptoms and medication in the last 3 years.[1]

The fourth: The authors should clarify how an exacerbation in 1 year in asthma cases makes the patient inclined to have serious/poorer prognosis of COVD-19. This clarification could be very explanatory and supportive for their study. An exacerbation in asthma patients in 1 year hardly makes these patients uncontrolled. Accordingly, the authors said that the uncontrolled asthma was not an independent risk factor in their multivariate analysis.[1] When looking at the association of asthma control with severity/mortality of COVID-19 in table 4, if the data adjusted, there was no association among uncontrolled asthma, Grade 2/3 of COVID-19 and mortality. Even in crude data, there was no association among uncontrolled asthma and Grade 2 of COVID-19 disease. Therefore, how an exacerbation could result in worse/poorer outcome of COVID-19 disease is not clear. As another point, the existing evidence on use of oral steroid in asthma exacerbations, though a few reported cases in mild asthmatics, is consistent with data from earlier coronavirus outbreaks, showing that systemic steroids can be related with a greater load of SARS-CoV-2. The UK data suggest an increased death risk in patients with asthma, especially in those who recently received systemic steroids.[4] Were their exacerbated patients always

using systemic steroids to recover from exacerbation?

The fifth: When compared between asthma patients and the controls, the survival curve for COVID-19 hospital death according to asthma morbidity and recent exacerbation of asthma looked significantly different up to 60 days in figure 1A.[1] However, it is very interesting that the survival curve for non-asthma patients sharply decreased after 60 days, compared to asthma patient, in figure 1A. How do the authors explain this perplexing data demonstrating a sharp decrease in non-asthma patients? Do they think that is it related to comorbidities?

The sixth: Although the effect of non-allergic vs allergic asthma on the course of COVID-19 is discussed in detail, the authors did not give their ratio or prevalence of non-allergic vs allergic asthma in the study population.[1] It is reported that cases with common allergic diseases (such as rhinitis, eczema, etc) do not progress into severe courses, which may indicate a positive balance of Th2-type immune regulation in COVID-19 pathogenesis.[4] Furthermore, the older population has mostly non-allergic type of asthma such as in this study.[1] A study from the United Kingdom examined the association between different phenotypes of asthma and COVID-19 infection. Interestingly, the morbidity and mortality risk was mostly related to non-allergic asthma.[3]

CONCLUSION

It is well-known that non-type Th2 (non-allergic) asthma is more common in the older population[11] and manifests with an altered risk profile regarding comorbidities, SARS-CoV-2 infection, COVID-19 development, and progression to poor COVID-19 prognosis.[12] Because Th2 type-2 asthma patients tend to be younger than those with other comorbidities, the age factor probably elucidates why asthma cases may not be at a greater risk.[3,13] As a result, this article[1] should not give any confusing messages to the physicians taking care of asthmatics.

Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019, GINA: global initiative for asthma, ACE-2: angiotensin-converting enzyme 2, Th2: T helper 2.

Author contributions
Ö. Özdemir done all the work.

Ethics approval
Not applicable.

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