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Risk Factors for Severe COVID-19 in a Large Medical Records Linkage System in the United States

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More than a year after the first cluster of patients was reported, coronavirus disease 2019 (COVID-19) remains a serious public health threat. During the pandemic, epidemiologic studies have been playing an important role in the response to COVID-19 by providing health care professionals and policymakers with necessary data. Identification of risk factors is one of the fundamental cores of epidemiologic studies because such knowledge is essential to understand disease characteristics, to prioritize resources for vulnerable populations, and to campaign for raising the awareness.

In this issue of *Mayo Clinic Proceedings*, St. Sauver and colleagues add quality evidence to the epidemiology of COVID-19.¹ The authors explored risk factors associated with severe COVID-19 among patients who tested positive for COVID-19 using data from the Rochester Epidemiology Project, an integrated medical records linkage system that covers approximately 1.7 million individuals (or 61% of the population) in southern Minnesota and western Wisconsin in the United States.²

WHAT DID THEY FIND?

Between March 2020 and September 2020, the authors identified 9,928 individuals with a positive COVID-19 test result. Of those, 4.8% (n = 474) developed severe COVID-19, as defined by hospitalization or death due to COVID-19. In a multivariable Cox regression model, significant risk factors of severe COVID-19 were older age (≥ 65 years vs 20 to 44 years), men (vs women), Hispanic ethnicity (vs non-Hispanic ethnicity), Black or Asian race (vs White race), obesity (vs normal weight), and increasing number of chronic conditions.

Among chronic conditions classified according to the Clinical Classifications Software, a scheme developed by the US Healthcare Cost and Utilization Project to systematically categorize *International Classification of Diseases* codes,³ the authors identified 36 major chronic conditions associated with the risk of severe COVID-19. Finally, the authors found that the associations of chronic conditions with the risk of severe COVID-19 were stronger for younger adults than for older adults. Among younger adults, particularly strong associations were observed for developmental disorders, personality disorders, affective disorders, schizophrenia, and other psychoses.

SO, WHAT DO THESE FINDINGS TELL US?

First, older age was a strong risk factor for severe COVID-19. Although this may sound obvious, a markedly high hazard ratio for 65 years or older is noteworthy. In this study, adults aged 65 years or older accounted for 46% of those with severe COVID-19 while composing only 9% of those at risk, resulting in an unadjusted hazard ratio of 17.5 compared with those aged 20 to 44 years. After the adjustment, those aged 65 years or older still had a 6.4-fold higher risk. The attenuated association after adjustment for confounders suggests that crude analysis may overestimate the contribution of age, but also a substantial proportion of older adults had other risk factors for severe COVID-19 (eg, chronic conditions), which multiplicatively increased the risk. Thus, this study reiterates that older adults should be a primary target for infection prevention programs and supports current public health campaigns, such as promoting vaccination and increasing public awareness for older adults.⁴

Second, the associations for race and ethnicity were inconsistent before and after adjustment for confounders. For example, Black individuals appeared to have a low risk of severe COVID-19 in the crude model but had a 50% higher risk compared with White individuals once confounders were accounted for. For Asian individuals and individuals of Hispanic ethnicity, the hazard ratios compared with the reference category became higher in multivariable models. These data are generally consistent with the existing literature⁵ and suggest that patients' characteristics were not homogeneous across races and ethnicities. One plausible explanation is that White individuals or individuals of non-Hispanic ethnicity were more likely to get a COVID-19 test regardless of symptoms, increasing the overall denominator in the sample. However, there is also mounting evidence on disparities by race and ethnicity in the access to health care and quality of care,⁶ which should be further explored in future studies.

Third, the authors identified 36 chronic conditions associated with the risk of severe COVID-19. Some conditions, such as diabetes, obstructive pulmonary disease, heart failure, neurologic disorders, and chronic kidney disease, are well-known risk factors.⁷ However, other conditions were prevalent and posed a high risk of severe COVID-19. For example, anxiety, depression, and bipolar disorders were seen in 24% of COVID-19 patients and associated with a 76% higher risk of severe COVID-19. Although previous studies have reported similar findings,⁸ these conditions may be relatively underrecognized. Thus, this study has implications on the need for paying attention to a wide range of chronic conditions as potential risk factors for severe COVID-19, although the use of *International Classification of Diseases* codes to identify chronic conditions may be susceptible to misclassification and detection bias.

Fourth, the association of major chronic conditions with the risk of severe COVID-19 was modified by age. The stronger association for the risk of infection in younger adults has been reported previously.⁹ In general, when the absolute risk is low (eg, younger

adults), the relative risk tends to be higher when an excess risk is added to the baseline risk. However, it is also possible that younger adults are less likely to seek medical care until they develop a severe form of COVID-19, delaying a timing of receiving appropriate care. In any way, these findings indicate that the risk of severe COVID-19 should not be underestimated for younger adults, particularly for those with underlying conditions such as developmental and personality disorders.

WHAT ARE LIMITATIONS AND STRENGTHS OF THE STUDY?

A few limitations should be noted when we interpret the results. First, the study was conducted before the era of COVID-19 vaccination and emerging threat of COVID-19 variants. Vaccination status and types of vaccine received in combination with dominant circulating variants are likely to modify some associations for the risk factors. Second, hospitalization due to COVID-19 may not be completely objective. For example, physicians may tend to be optimistic about the clinical course for younger adults, thereby elevating the bar for decision for hospitalization. Health care providers may have limited capacity to accept patients or to provide necessary care when hospital beds are overwhelmed. Finally, some factors, such as socioeconomic status, were not well captured in this study. Evidence suggests that social disparity and inequitable health care access are associated with worse outcomes of COVID-19.¹⁰

Nonetheless, the study has a number of strengths. This is one of the largest studies that have used a large medical records linkage system covering a near-representative population in a US region. The study cohort captured detailed characteristics of patients, including information before development of COVID-19 (eg, past medical history, body mass index, smoking status). The authors applied rigorous study design and statistical approach, increasing the interval validity. Finally, their comprehensive analysis allowed them to compare the relative strength of association across health status and chronic conditions.

CONCLUSION

It is increasingly evident that the impact of COVID-19 will last for years. As our fight against COVID-19 continues until we overcome the pandemic, epidemiologic studies continue to take a major part in the COVID-19 response. To that end, the work by St. Sauver and colleagues is a welcome contribution to the science and has implications on future research and public health policymaking.

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