Hypertension and Excess Risk for Severe COVID-19 Illness Despite Booster Vaccination

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Rapid development of vaccines against SARS-CoV-2 led to substantial reductions in morbidity and mortality early in the pandemic. Concerns regarding waning immunity and the risk of emerging new variants, including Omicron, prompted recommendations for a third booster vaccine dose after completion of a 2-dose mRNA vaccine regimen, given its efficacy at further reducing risk for severe illness by up to 70%. However, a proportion of individuals who received 3 mRNA vaccine doses still required hospitalization for COVID-19 during the Omicron surge. We sought to understand the characteristics associated with severe Omicron infection, necessitating hospitalization, despite having completed a full 3-dose mRNA vaccine regimen.

We conducted a retrospective cohort study of adults who received at least 3 mRNA vaccine doses but were subsequently treated for confirmed COVID-19 infection in our academic health care system during the Omicron surge onset in our region and had at least 2 outpatient visits within the preceding 2 years. All laboratory testing for COVID-19 was performed using reverse transcription-polymerase chain reaction (rtPCR) of extracted RNA from nasopharyngeal swabs. We obtained demographic (age, sex, and race/ethnicity), clinical, and outcomes data from the electronic health record and manually confirmed the validity of key variables. We used the International Classification of Diseases, Tenth Revision, diagnoses to identify specific clinical characteristics previously associated with COVID-19 severity, including diabetes, chronic kidney disease (CKD), prior myocardial infarction (MI) or heart failure (HF), and prior chronic obstructive pulmonary disease or asthma. Hypertension was defined by the International Classification of Diseases, Tenth Revision, code or the prescription of antihypertensive pharmacotherapy. Obesity was defined as a calculated body mass index of ≥30 kg/m². Patients with missing data on key variables were excluded. We also curated electronic health record data on ACE (angiotensin-converting enzyme) inhibitor, angiotensin receptor blocker, and statin use and days from the most recent SARS-CoV-2 vaccine dose to confirmed infection. In statistical analyses, we used multivariable logistic regression to assess for associations between each of the characteristics listed above and risk of hospitalization. To minimize confounding by indication for ACE inhibitor/angiotensin receptor blocker use, we performed 2 separate sensitivity analyses: first, we removed ACE inhibitor/angiotensin receptor blocker from the multivariable analyses; second, we excluded individuals with a history of CKD, MI, or HF. All analyses were conducted using R v4.0.2, with a 2-tailed 𝑃<0.05 considered significant.

Overall, we identified a total of 912 individuals who received ≥3 mRNA vaccine doses and were subsequently diagnosed with COVID-19 during the Omicron surge, of whom 145 (15.9%) required hospitalization. Demographic and clinical characteristics of the cohort are shown in the Figure. In multivariable analyses, factors significantly associated with risk of hospitalization for Omicron infection included older age, hypertension, CKD, and MI or HF, as well as longer duration between the last vaccination and infection (Figure).

Key Words: COVID-19 ◼ humans ◼ hypertension ◼ morbidity ◼ pandemics
Notably, the presence of hypertension was associated with the greatest magnitude of risk, which remained significant in sensitivity analyses excluding patients with a history of CKD, MI, or HF. Results were similar when ACE inhibitor/angiotensin receptor blocker use was removed from the model.

Our findings reveal a persistent and marked association between hypertension and risk for severe COVID-19 illness, even among a fully vaccinated patient population. The Omicron variant of SARS-CoV-2 has led to overall less severe COVID-19 illness in most affected individuals when compared with prior variants—with morbidity and mortality even further reduced by receiving 3 doses of vaccine. Age estimates shown are per 10 years of age. Time from vaccine to infection represents the interval (per 10 days) between the date of the last vaccine dose received (ie, booster) and the date of COVID-19 infection diagnosed during the Omicron surge period. ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and COPD, chronic obstructive pulmonary disease.

**ETHICS APPROVAL**

This study was approved by the Cedars-Sinai Institutional Review Board (study 00000603), with a waiver for informed consent.

**AVAILABILITY OF DATA AND MATERIALS**

Due to the sensitive nature of the data collected for this study, requests to access the data set from qualified
researchers trained in protocols on the protection of human subjects may be sent to the Cedars-Sinai Medical Center at biodatacore@cshs.org.

ARTICLE INFORMATION

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Author Contributions
J. Ebinger contributed to conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, and visualization. S. Joung and T. Tran contributed to methodology, validation, formal analysis, writing—review and editing, and visualization. M. Wu, P. Botting, J. Navarrette, and N. Sun contributed to methodology, validation, formal analysis, and writing—review and editing. S. Cheng contributed to conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision, project administration, and funding acquisition.

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Disclosures
None.

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