



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

Joseph E. Ebinger<sup>1</sup>, Matthew Driver<sup>1</sup>, Sandy Joung<sup>1</sup>, Teresa Tran, Denisse Barajas, Min Wu, Patrick G. Botting<sup>1</sup>, Jesse Navarrette, Nancy Sun<sup>1</sup>, Susan Cheng<sup>1</sup>

**R**apid 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%.<sup>1</sup> 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  $\geq 30$  kg/m<sup>2</sup>. Patients with missing data on key variables were excluded. We also curated electronic health record data on ACE (angiotensin-converting enzyme) inhibitor, angiotensive 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/angiotensive receptor blocker use, we performed 2 separate sensitivity analyses: first, we removed ACE inhibitor/angiotensive 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.

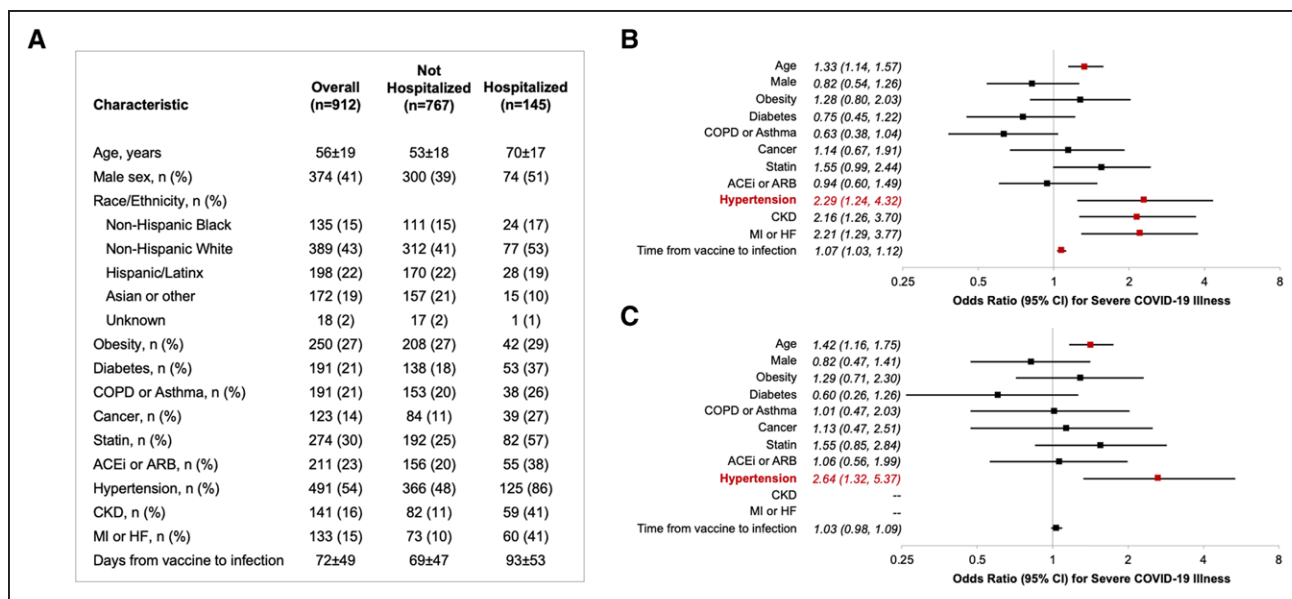
Overall, we identified a total of 912 individuals who received  $\geq 3$  mRNA vaccine doses and were subsequently diagnosed with COVID-19 during the Omicron surge, of whom 145 (15.9%) required hospitalization. Demographic and clinical characteristics of the cohort are shown in the Figure. In multivariable 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

Correspondence to: Joseph E. Ebinger, Department of Cardiology, Smidt Heart Institute, Cedars Sinai Medical Center, Los Angeles, CA. Email joseph.ebinger@csmc.edu  
For Sources of Funding and Disclosures, see page e134.

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**Figure. Risk factors for Omicron infection requiring hospitalization, despite receiving prior booster vaccination.**

**A**, Demographic and clinical characteristics. **B**, Multivariable-adjusted risk factors for hospitalization in the total cohort. **C**, Risk factors for hospitalization in the cohort without chronic kidney disease (CKD), myocardial infarction (MI), or heart failure (HF). All multivariable analyses are adjusted for the covariates displayed in addition to race/ethnicity. 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.

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. Our findings were consistent with prior studies demonstrating greater hospitalization risk with advanced age and time since the last vaccine dose.<sup>2</sup> Even when controlling for these and other clinical variables, the risk of hospitalization related to breakthrough Omicron infection was more than doubled by the presence of hypertension. Recognizing that hypertension is quite prevalent in the setting of high-risk conditions such as CKD, MI, and HF, we repeated our analyses excluding patients with these diagnoses and found still substantial and significant risks associated with hypertension. Our findings extend from prior reports of equivocal or potentially confounded associations of hypertension with COVID-19 illness severity that were based on analyzing early pandemic and particularly pre-Omicron outcomes data.<sup>3</sup> In the context of shifts in the risk factors associated with more

severe forms of COVID-19 during the course of the pandemic,<sup>4</sup> our results indicate persistence and even accentuation of hypertension-related risk in the setting of a more transmissible albeit generally less virulent strain of SARS-CoV-2 and in the era of multidose vaccination. Although the mechanism for hypertension-associated COVID-19 risk remains unclear, prior studies have identified delayed SARS-CoV-2 viral clearance and prolonged inflammatory response among hypertensive patients, which may contribute to greater disease severity.<sup>5</sup> Additional studies in separate cohorts are also needed to validate and assess the generalizability of our results. Given that hypertension is one of the most prevalent chronic medical conditions, affecting individuals across the age spectrum, concordant findings would suggest the need for further investigations focused on understanding the hypertension-specific risks from SARS-CoV-2 and on identifying individual- and population-level strategies for mitigating these risks as the pandemic transitions to an endemic.

## 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](mailto:biodatacore@cshs.org).

## ARTICLE INFORMATION

### Affiliation

Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA.

### Acknowledgments

The authors are grateful to all the front-line health care workers in our health care system who continue to be dedicated to delivering the highest quality care for all patients, as well as the invaluable contributions of the Coronavirus Risk Associations and Longitudinal Evaluation (CORALE) Study and the Emerging Beyond Acquired Risks in Communities (EMBARC) study investigators and staff.

### Author Contributions

J. Ebinger contributed to conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, and funding acquisition. M. Driver contributed to methodology, validation, formal analysis, writing—review and editing, and visualization. S. Joung and T. Tran contributed to methodology, validation, 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.

## Sources of Funding

This work was supported, in part, by the Cedars-Sinai Medical Center, the Erika J. Glazer Family Foundation, and the National Institutes of Health grants R01-HL131532 and K23-HL153888.

## Disclosures

None.

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