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Morbidity and Mortality of Hospital-Onset SARS-CoV-2 Infections Due to Omicron Versus Prior Variants

A Propensity-Matched Analysis

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Background: Many hospitals have scaled back measures to prevent nosocomial SARS-CoV-2 infection given large decreases in the morbidity and mortality of SARS-CoV-2 infections for most people. Little is known, however, about the morbidity and mortality of nosocomial SARS-CoV-2 infections for hospitalized patients in the Omicron era.

Objective: To estimate the effect of nosocomial SARS-CoV-2 infection on hospitalized patients' outcomes during the pre-Omicron and Omicron periods.

Design: Retrospective matched cohort study.

Setting: 5 acute care hospitals in Massachusetts, December 2020 to April 2023.

Patients: Adults testing positive for SARS-CoV-2 on or after hospital day 5, after negative SARS-CoV-2 test results on admission and on hospital day 3, were matched to control participants by hospital, service, time period, days since admission, and propensity scores that incorporated demographics, comorbid conditions, vaccination status, primary diagnosis category, vital signs, and laboratory test values.

Measurements: Primary outcomes were hospital mortality and time to discharge. Secondary outcomes were intensive care unit (ICU) admission, need for advanced oxygen support, discharge destination, hospital-free days, and 30-day readmissions.

Results: There were 274 cases of hospital-onset SARS-CoV-2 infection during the pre-Omicron period and 1037 cases during the Omicron period (0.17 vs. 0.49 cases per 100 admissions). Patients with hospital-onset SARS-CoV-2 infection were older and had more comorbid conditions than those without. During the pre-Omicron period, hospital-onset SARS-CoV-2 infection was associated with increased risk for ICU admission, increased need for high-flow oxygen, longer time to discharge (median difference, 4.7 days [95% CI, 2.9 to 6.6 days]), and higher mortality (risk ratio, 2.0 [CI, 1.1 to 3.8]) versus matched control participants. During the Omicron period, hospital-onset SARS-CoV-2 infection remained associated with increased risk for ICU admission and increased time to discharge (median difference, 4.2 days [CI, 3.6 to 5.0 days]). The association with increased hospital mortality was attenuated but still significant (risk ratio, 1.6 [CI, 1.2 to 2.3]).

Limitation: Residual confounding may be present.

Conclusion: Hospital-onset SARS-CoV-2 infection during the Omicron period remains associated with increased morbidity and mortality.

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Nosocomial infections and clusters due to SARS-CoV-2 have been widely reported. During community surges of COVID-19, 5% to 15% of SARS-CoV-2 infection cases in hospitals may be hospital-acquired (1–3). The morbidity and mortality associated with SARS-CoV-2 infection in the general population have decreased dramatically since the start of the pandemic because of high levels of immunity from vaccines and natural infections; the increasing availability of effective treatments; and new, less virulent variants (4–8). It is not clear, however, to what extent this amelioration applies to hospitalized patients, who tend to be vulnerable and more prone to adverse outcomes than the general population. During the initial period of the pandemic, crude mortality rates for patients with hospital-acquired SARS-CoV-2 infection were 25% to 35% (3, 9, 10). Crude mortality rates for those with hospital-acquired Omicron infections, by contrast, have ranged from 3% to 11% (11, 12).

Crude mortality rates are difficult to interpret, however, because they reflect patients' underlying illnesses and the possible added effect of SARS-CoV-2 infection. Older, sicker, and more frail patients are at greater risk for nosocomial SARS-CoV-2 infection than younger and healthier patients by virtue of their generally longer hospital stays (which increase time at risk for acquiring SARS-CoV-2 infection and facilitate case ascertainment) and their greater need for hands-on care (which leads to more close-range exposures to health care workers who may harbor unrecognized infections). These patients also have higher baseline rates

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of morbidity and mortality, making it challenging to know if poor outcomes among patients with nosocomial SARS-CoV-2 infection are because this infection preferentially occurs in more vulnerable patients, because of harm from infection, or both.

Elucidating the current effect of nosocomial SARS-CoV-2 infection on patient outcomes is critical to inform hospitals' deliberations on how best to calibrate the breadth and intensity of their infection control policies. During the first year of the pandemic, hospitals took very aggressive measures to prevent hospital-acquired SARS-CoV-2 infections, including in some cases restricting all visitors, requiring universal masking, instituting universal patient testing, modifying hospital ventilation systems, screening staff for symptoms, shifting from in-person to virtual care, and mandating vaccines for health care workers (13). Most hospitals have now reversed many if not all of these measures on the rationale that most SARS-CoV-2 infections are now mild and the measures taken to prevent transmission are disruptive to operations; expensive; and burdensome to staff, patients, and their families (14, 15). Others argue, however, that the frequency and morbidity of contemporary nosocomial SARS-CoV-2 infections are underappreciated and that they remain an important cause of harm for hospitalized patients that merits active mitigation (16, 17).

Given these questions, we undertook a comprehensive analysis of the frequency and morbidity of hospital-onset SARS-CoV-2 infections due to the Omicron variant versus prior variants. We analyzed consecutive cases identified in 5 Massachusetts hospitals with universal inpatient testing policies and used clinically detailed propensity scores to match infected patients with uninfected patients to elucidate the marginal effect of nosocomial SARS-CoV-2 infection on patient outcomes.

METHODS

Setting, Population, and Data Sources

We retrospectively identified all adult patients admitted to 5 Massachusetts hospitals affiliated with the Mass General Brigham system (Massachusetts General Hospital, Brigham and Women's Hospital, Faulkner Hospital, Newton-Wellesley Hospital, and Salem Hospital) between 1 December 2020 and 30 April 2023. Detailed clinical data on each patient were extracted from the hospital system's enterprise data warehouse. We used December 2020 as the starting point for the analysis because SARS-CoV-2 infection control policies and procedures in study hospitals had largely stabilized by this point. Infection control measures included universal masking for all patient encounters; SARS-CoV-2 testing using polymerase chain reaction (PCR) tests for all inpatients on admission and again 3 days later to identify community-acquired infections incubating on admission; and, starting in November 2021, mandatory vaccination for all health care workers. Study hospitals also began repeated testing of all inpatients every 5 days starting on hospital day 8 (that is, 5 days after their test with negative results on hospital day 3) starting in January 2022.

Definition of Hospital-Onset SARS-CoV-2 Infection Cases

Case patients were defined as those with a new positive result on PCR testing for SARS-CoV-2 on hospital day 5 or later and an active COVID-19 status in the electronic medical record for at least 4 days (or until death if this occurred <4 days after SARS-CoV-2 detection). We required all potential case patients to have an active COVID-19 status on their record for at least 4 days to limit the analysis to patients more likely to have true acute infections: The infection control teams in each hospital generally discontinued a newly positive patient's COVID-19 status within 4 days if the patient's clinical history, serial test results, and cycle threshold suggested that the newly positive PCR result was a false positive or residual RNA from a prior, resolved infection (18).

Matching Method

We matched each case patient to 2 uninfected control participants using a combination of exact matching criteria and propensity scores for likelihood of hospital-onset SARS-CoV-2 infection. Exact matching criteria included hospital, clinical service, and intensive care unit (ICU) status 2 days before the test with positive results, and period of hospitalization (control participants needed to be admitted within 90 days of the case patient's date of admission). In addition, each control participant was required to be hospitalized for at least as long as their matched case patient's time from admission to first positive test result. After applying exact match criteria, we implemented propensity score matching using the method of Zhang and colleagues (19). Each patient's time to case was modeled with a Cox proportional hazards model to generate survival probabilities $S(t)$, where t is the count of days since hospital admission. We then used a sequential matching strategy wherein for each case i identified at time t, we constructed a risk set $R(t_i)$, including all potential control participants still at risk for SARS-CoV-2 infection at time t_i. We then selected the 2 patients within this risk set that minimized the absolute differences between their propensity scores and the case patient's propensity score while also requiring their propensity scores to be within 0.2 SD of the case patient's propensity score (20).

The propensity score model included the following variables measured 2 days before the case patient's first test with positive results or on the corresponding day since admission for control participants: age, race and ethnicity, sex, ICU status, service, highest level of oxygen support (none, nasal cannula, advanced mask, or mechanical ventilation, including noninvasive and invasive positive pressure ventilation), maximum temperature,

median respiratory rate, median systolic blood pressure, median diastolic blood pressure, maximum leukocyte count, minimum hematocrit, minimum platelet count, maximum creatinine level, minimum albumin level, minimum sodium level, maximum glucose level, maximum alanine aminotransferase level, maximum total bilirubin level, selected comorbid conditions determined using the method of Elixhauser (anemia, autoimmune disease, cancer, cardiovascular disease, dementia, diabetes mellitus, heart failure, liver disease, chronic lung disease, neurologic disease, obesity, chronic kidney disease, drug and alcohol misuse, and weight loss), the Elixhauser Comorbidity Index, primary diagnosis category determined using Agency for Healthcare Research and Quality clinical classification software, and SARS-CoV-2 vaccination status (ever vaccinated, vaccinated within the preceding 4 months, and total number of vaccines received) (21, 22). If laboratory values were missing for the relevant day, then the most recent value was carried forward; if the value was never measured, a normal value was imputed.

Outcomes and Analysis

We divided the cohort into pre-Omicron (1 December 2020 through 14 December 2021) and Omicron (15 December 2021 to 30 April 2023) periods based on when the Omicron variant exceeded 50% of sequenced isolates in Massachusetts. We then compared baseline characteristics and outcomes in case patients versus control participants. The primary outcomes were in-hospital mortality and median days from match to discharge. Secondary outcomes included new admission to the ICU after match day, new need for advanced oxygen support (high-flow oxygen by nasal cannula, bilevel positive airway pressure noninvasive mechanical ventilation, or invasive mechanical ventilation), 30-day hospital-free days, discharge disposition (home, rehabilitation hospital, skilled-nursing facility, or hospice), and 30-day readmissions. We analyzed binary outcomes using risk ratios, continuous outcomes using median differences, and competing risk outcomes using Fine–Gray subdistribution hazard models for discharge-alive dispositions versus hospital death (23). Within the propensity-matched sample, we adjusted for any persistently unbalanced variables using robust Poisson regression for risk ratios, quantile regression for median differences, and weighted Cox regression for subdistribution hazards (24). We generated 95% CIs for all estimates.

Subgroup and Sensitivity Analyses

We did a subgroup analysis restricted to patients discharged to home to assess whether increased time to discharge in patients with hospital-onset SARS-CoV-2 infection was due to greater difficulty finding beds for infected patients in acute rehabilitation and skilled-nursing facilities rather than due to medical deterioration. We also did a sensitivity analysis using stricter matching criteria by imposing a caliper of 0.1 SD of the case patient's propensity score.

Calculations were performed using R, version 4.1.2 (R Foundation). The study was approved with a waiver of informed consent by the Mass General Brigham Institutional Review Board.

Role of the Funding Source

The study was funded by the Harvard Medical School Department of Population Medicine. Department leaders had no role in the design, conduct, interpretation, or publication of the study.

RESULTS

There were 160 334 hospitalizations during the pre-Omicron period, of which 69 552 were for 5 days or longer. During this period, 274 cases of hospital-onset SARS-CoV-2 infection were detected (0.17 case per 100 admissions overall; 0.40 case per 100 admissions lasting ≥5 days). There were 210 195 hospitalizations during the Omicron period, of which 88 371 were for 5 days or longer. During the Omicron period, 1037 cases of hospital-onset SARS-CoV-2 infection were detected (0.49 case per 100 admissions overall; 1.17 cases per 100 admissions lasting ≥5 days). Characteristics of patients with and without hospital-onset SARS-CoV-2 infection are presented in Table 1 (pre-Omicron period) and Table 2 (Omicron period). Rates of missingness for laboratory assays 2 days before match day were low: less than 2% for basic metabolic tests, less than 1% for complete blood cell counts, and less than 12% for liver function tests. During the pre-Omicron period, patients with hospital-onset SARS-CoV-2 infection were more likely to be male; to be admitted from a facility; to be receiving supplementary oxygen; and to have comorbid illnesses, including neurologic disease, dementia, chronic lung disease, or psychiatric disease. During the Omicron period, patients with hospital-onset SARS-CoV-2 infection were more likely to be male; to be older; to be receiving supplementary oxygen; and to have liver disease, neurologic disease, diabetes mellitus, renal failure, heart failure, dementia, or psychiatric disease.

Crude Outcomes

Hospital length of stay was greater for patients with hospital-onset SARS-CoV-2 than for uninfected patients hospitalized for 5 days or longer in both the pre-Omicron period (median, 18.5 days [IQR, 11.0 to 32.0 days] vs. 8.0 days [IQR, 6.0 to 12.0 days]) and the Omicron period (median, 18.0 days [IQR, 11.0 to 34.0 days] vs. 8.0 days [IQR, 6.0 to 12.0 days]). Likewise, crude mortality rates were higher for patients with hospital-onset SARS-CoV-2 infection than for uninfected patients hospitalized for 5 days or longer in both the pre-Omicron and Omicron periods, although the rate during the Omicron period was almost half that observed during the pre-Omicron period (32 of 274 [11.7%] for infected patients vs. 2079 of 67 854 [3.1%] for uninfected patients in the pre-Omicron

Table 1. Characteristics and Outcomes for Patients With Versus Without Hospital-Onset SARS-CoV-2 Infections Before and After Matching: Pre-Omicron Period

Characteristic or Outcome	Before Matching			After Matching		
	Hospital-Onset SARS-CoV-2 Infection ($n = 274$)	No SARS-CoV-2 Infection ($n = 67\,854$)	SMD	Hospital-Onset SARS-CoV-2 Infection ($n = 230$)	No SARS-CoV-2 Infection ($n = 460$)	SMD
Hospital cases, *n (%)*	–	–	0.33	–	–	<0.01
Community hospital 1	22 (8.0)	4054 (6.0)	–	18 (7.8)	36 (7.8)	–
Academic hospital 1	68 (24.8)	23 129 (34.1)	–	58 (25.2)	116 (25.2)	–
Academic hospital 2	107 (39.1)	26 554 (39.1)	–	90 (39.1)	180 (39.1)	–
Community hospital 2	60 (21.9)	7923 (11.7)	–	50 (21.7)	100 (21.7)	–
Community hospital 3	17 (6.2)	6194 (9.1)	–	14 (6.1)	28 (6.1)	–
Mean age at admission (SD), *y*	61.7 (18.3)	61.2 (18.8)	0.03	61.5 (18.6)	62.5 (18.1)	0.05
Race/ethnicity, *n (%)*						
Asian	5 (1.9)	2203 (3.3)	0.09	5 (2.2)	12 (2.6)	0.03
Black	26 (9.8)	5957 (8.9)	0.03	22 (9.6)	43 (9.3)	<0.01
Hispanic	19 (7.1)	3787 (5.7)	0.06	17 (7.4)	31 (6.7)	0.03
Other	2 (0.8)	974 (1.5)	0.07	2 (0.9)	8 (1.7)	0.08
≥2	16 (6.0)	2768 (4.1)	0.09	13 (5.7)	23 (5.0)	0.03
White	198 (74.4)	51 027 (76.5)	0.08	171 (74.3)	343 (74.6)	<0.01
Male, *n (%)*	157 (57.3)	32 138 (47.4)	0.20	132 (57.4)	256 (55.7)	0.04
Hospitalized in the prior 90 d, *n (%)*	15 (5.5)	5012 (7.4)	0.08	13 (5.7)	49 (9.3)	0.14
Admitted from a facility, *n (%)*	54 (19.7)	10 057 (14.8)	0.13	41 (17.8)	78 (17.0)	0.02
Clinical service, *n (%)**	–	–	0.41	–	–	<0.01
Cardiac surgery	4 (1.5)	2009 (3.0)	–	4 (1.7)	8 (1.7)	–
Cardiology	6 (2.2)	2583 (3.8)	–	6 (2.6)	12 (2.6)	–
Emergency	4 (1.5)	803 (1.2)	–	2 (0.9)	4 (0.9)	–
Medicine	130 (47.4)	28 222 (41.9)	–	108 (47.0)	216 (47.0)	–
Neurology	6 (2.2)	2479 (3.7)	–	6 (2.6)	12 (2.6)	–
Obstetrics	8 (2.9)	4272 (6.3)	–	8 (3.5)	16 (3.5)	–
Oncology	32 (11.7)	7846 (11.6)	–	30 (13.0)	60 (13.0)	–
Psychiatry	33 (12.0)	3286 (4.9)	–	30 (13.0)	60 (13.0)	–
Surgery	48 (17.5)	15 312 (22.7)	–	36 (15.7)	72 (15.7)	–
Comorbidities						
Cancer, *n (%)*	62 (22.6)	15 239 (22.5)	<0.01	52 (22.6)	117 (25.4)	0.07
Liver disease, *n (%)*	34 (12.4)	6696 (9.9)	0.08	30 (13.0)	66 (14.3)	0.04
Neurologic disease, *n (%)*	64 (23.4)	12 437 (18.3)	0.12	51 (22.2)	102 (22.2)	<0.01
Diabetes mellitus, *n (%)*	82 (29.9)	18 277 (26.9)	0.07	63 (27.4)	150 (32.6)	0.11
Renal failure, *n (%)*	67 (24.5)	14 134 (20.8)	0.09	54 (23.5)	129 (28.0)	0.11
Drug and alcohol use disorder, *n (%)*	31 (11.3)	7590 (11.2)	<0.01	28 (12.2)	66 (14.3)	0.06
Dementia, *n (%)*	26 (9.5)	3968 (5.8)	0.14	21 (9.1)	47 (10.2)	0.04
Heart failure, *n (%)*	70 (25.5)	15 065 (22.2)	0.08	54 (23.5)	125 (27.2)	0.09
Chronic lung disease, *n (%)*	81 (29.6)	15 960 (23.5)	0.14	65 (28.3)	135 (29.3)	0.02
Peripheral vascular disease, *n (%)*	26 (9.5)	5641 (8.3)	0.04	21 (9.1)	38 (8.3)	0.03
Psychoses, *n (%)*	48 (17.5)	6658 (9.8)	0.23	38 (16.5)	66 (14.3)	0.06
Mean Elixhauser Comorbidity Index (SD)	11.3 (18.0)	8.8 (16.2)	0.15	10.5 (17.7)	12.2 (18.3)	0.09
Primary diagnosis, *n (%)*						
Gastrointestinal	29 (10.6)	7506 (11.1)	0.02	25 (10.9)	46 (10.0)	0.03
Musculoskeletal	9 (3.3)	3625 (5.3)	0.10	6 (2.6)	11 (2.4)	0.01
Psychiatric	45 (16.4)	5766 (8.5)	0.24	38 (16.5)	72 (15.7)	0.02
Cardiovascular	40 (14.6)	12 797 (18.9)	0.11	36 (15.7)	60 (13.0)	0.07
Endocrine	8 (2.9)	2761 (4.1)	0.06	7 (3.0)	19 (4.1)	0.06
Infection	50 (18.2)	4409 (6.5)	0.36	39 (17.0)	60 (13.0)	0.11
Genitourinary	21 (7.7)	4714 (6.9)	0.03	18 (7.8)	43 (9.3)	0.05
Neurologic	10 (3.6)	2809 (4.1)	0.03	9 (3.9)	28 (6.1)	0.10
Trauma	26 (9.5)	8097 (11.9)	0.08	20 (8.7)	56 (12.2)	0.11
Neoplastic	26 (9.5)	7538 (11.1)	0.05	25 (10.9)	50 (10.9)	<0.01
Pulmonary	15 (5.5)	3394 (5.0)	0.02	14 (6.1)	15 (3.3)	0.13
Hematologic	2 (0.7)	1104 (1.6)	0.08	2 (0.9)	7 (1.5)	0.06
Dermatologic	4 (1.5)	1352 (2.0)	0.04	3 (1.3)	9 (2.0)	0.05
Obstetric	9 (3.3)	4456 (6.6)	0.15	8 (3.5)	17 (3.7)	0.01
Other	8 (2.9)	3536 (5.2)	0.12	5 (2.2)	13 (2.8)	0.04

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Table 1–Continued

Characteristic or Outcome	Before Matching			After Matching		
	Hospital-Onset SARS-CoV-2 Infection ($n = 274$)	No SARS-CoV-2 Infection ($n = 67\,854$)	SMD	Hospital-Onset SARS-CoV-2 Infection ($n = 230$)	No SARS-CoV-2 Infection ($n = 460$)	SMD
Vital signs (SD)*						
Maximum temperature, °C	37.2 (0.7)	37.0 (0.4)	0.35	37.2 (0.6)	37.1 (0.5)	0.14
Median respiratory rate, *breaths/min*	18.8 (3.1)	18.4 (2.2)	0.16	18.7 (2.8)	18.7 (2.5)	0.03
Median systolic BP, *mm Hg*	128.3 (19.6)	127.0 (18.4)	0.07	126.8 (18.6)	126.5 (19.0)	0.01
Median diastolic BP, *mm Hg*	69.0 (10.6)	69.1 (9.8)	0.02	68.8 (11.0)	68.9 (10.0)	0.02
Oxygen support, *n (%)*						
None	172 (62.8)	50 939 (75.1)	0.27	153 (66.5)	348 (75.7)	0.20
Nasal cannula	56 (20.4)	11 078 (16.3)	0.11	59 (25.7)	72 (15.7)	0.25
Advanced mask	12 (4.4)	1878 (2.8)	0.09	6 (2.6)	14 (3.0)	0.03
BIPAP or ventilator	34 (12.4)	3959 (5.8)	0.23	12 (5.2)	26 (5.7)	0.02
Laboratory values (SD)*						
Maximum leukocyte count, $\times 10^9$ *cells/L*	9.1 (6.1)	8.9 (7.6)	0.02	8.9 (5.9)	8.3 (5.4)	0.10
Minimum hematocrit	32.8 (7.1)	33.0 (6.4)	0.02	32.3 (6.8)	32.7 (6.8)	0.06
Minimum platelet count, $\times 10^9$ *cells/L*	214.1 (106.2)	222.9 (107.8)	0.08	225.7 (114.9)	240.3 (156.0)	0.11
Maximum creatinine level	–	–	0.05	–	–	0.05
μmol/L	110 (108)	101 (103)	–	110 (99)	116 (134)	–
mg/dL	1.2 (1.2)	1.1 (1.2)	–	1.2 (1.1)	1.3 (1.5)	–
Minimum sodium level, *mmol/L*	138.0 (4.3)	137.9 (3.8)	0.05	138.1 (4.4)	137.7 (3.9)	0.10
Maximum glucose level	–	–	<0.01	–	–	0.07
mmol/L	7.36 (3.22)	7.49 (3.56)	–	7.24 (3.08)	7.45 (3.18)	–
mg/dL	132.6 (58.0)	135.0 (64.2)	–	130.4 (55.4)	134.3 (57.3)	–
Maximum alanine aminotransferase level, *U/L*	34.6 (50.4)	36.3 (100.5)	0.02	34.6 (60.9)	27.6 (34.1)	0.14
Maximum bilirubin level	–	–	0.03	–	–	0.07
μmol/L	14.9 (29.8)	14.4 (28.1)	–	13.3 (26.2)	15.2 (28.4)	–
mg/dL	0.9 (1.7)	0.8 (1.6)	–	0.8 (1.5)	0.9 (1.7)	–
Minimum albumin level, *g/L*	32.7 (7.3)	35.6 (6.1)	0.43	33.1 (7.0)	33.4 (7.0)	0.05
ICU status, *n (%)**	37 (13.5)	3706 (5.5)	0.28	16 (7.0)	32 (7.0)	<0.01
SARS-CoV-2 vaccine*						
Ever, %	72 (26.3)	36 460 (53.7)	0.58	63 (27.4)	209 (45.4)	0.38
Within prior 4 mo, %	31 (11.3)	21 788 (32.1)	0.52	31 (13.5)	139 (30.2)	0.41
Mean total doses (SD), *n*	0.48 (0.87)	1.03 (1.04)	0.57	0.5 (0.9)	1.0 (1.2)	0.46
Mean days from admission to match (SD)	NA	NA	–	9.9 (16.3)	9.9 (16.2)	<0.01

BIPAP = bilevel positive airway pressure; BP = blood pressure; ICU = intensive care unit; NA = not applicable; SMD = standardized mean difference.
* Provided for hospital day 5 in the unmatched cohorts and 2 d before SARS-CoV-2 infection diagnosis date or match date in the matched population.

period and 73 of 1037 [7.0%] vs. 2724 of 88 371 [3.1%] in the Omicron period). Similarly, patients with hospital-onset SARS-CoV-2 infection were more frequently discharged to rehabilitation or skilled-nursing facilities and less often to home than uninfected patients.

Propensity-Matched Outcomes

Propensity matching of case patients to 2 control participants each was successful for 230 of 274 (84%) pre-Omicron period cases and 865 of 1037 (83%) Omicron period cases. Unmatched case patients with hospital-onset SARS-CoV-2 infection tended to have more comorbid conditions, were more likely to be in the ICU, and had higher crude mortality rates than patients with hospital-onset SARS-CoV-2 infection who were matched (**Supplement Table 1**, available at Annals.org). Characteristics of case patients and control participants were similar after matching (**Tables 1** and **2**). A few variables were persistently imbalanced despite matching; we adjusted for these when calculating risk ratios, median differences, and subdistribution hazards.

Crude and adjusted outcomes for patients with hospital-onset SARS-CoV-2 infection versus matched control participants are presented in **Table 3**. Hospital mortality was significantly higher for case patients than matched control participants during both the pre-Omicron period (23 of 230 [10.0%] vs. 18 of 460 [3.9%]; adjusted risk ratio, 2.0 [95% CI, 1.1 to 3.8]) and the Omicron period (56 of 865 [6.5%] vs. 70 of 1730 [4.0%]; risk ratio, 1.6 [CI, 1.2 to 2.3]), albeit less so than during the pre-Omicron period. Median time from match to discharge was also significantly longer for patients with hospital-onset SARS-CoV-2 infection than for matched control participants during both the pre-Omicron period (9.0 vs. 5.0 days; adjusted median difference, 4.7 days [CI, 2.9 to 6.6 days]) and the Omicron period (9.0 vs. 4.0 days; adjusted median difference, 4.2 days [CI, 3.6 to 5.0 days]).

Table 2. Characteristics and Outcomes for Patients With Versus Without Hospital-Onset SARS-CoV-2 Infections Before and After Matching: Omicron Period

Characteristic or Outcome	Before Matching			After Matching		
	Hospital-Onset SARS-CoV-2 Infection ($n = 1037$)	No SARS-CoV-2 Infection ($n = 88\,371$)	SMD	Hospital-Onset SARS-CoV-2 Infection ($n = 865$)	No SARS-CoV-2 Infection ($n = 1730$)	SMD
Hospital cases, *n (%)*	–	–	0.21	–	–	<0.01
Community hospital 1	85 (8.2)	5765 (6.5)	–	70 (8.1)	140 (8.1)	–
Academic hospital 1	302 (29.1)	29 663 (33.6)	–	251 (29.0)	502 (29.0)	–
Academic hospital 2	382 (36.8)	33 643 (38.1)	–	328 (37.9)	656 (37.9)	–
Community hospital 2	189 (18.2)	10 479 (11.9)	–	153 (17.7)	306 (17.7)	–
Community hospital 3	79 (7.6)	8821 (10.0)	–	63 (7.3)	126 (7.3)	–
Mean age at admission (SD), *y*	65.1 (17.3)	61.3 (19.0)	0.20	65.5 (17.4)	64.7 (17.5)	0.04
Race/ethnicity, *n (%)*						
Asian	26 (2.6)	3276 (3.8)	0.07	24 (2.8)	48 (2.8)	<0.01
Black	98 (9.7)	8104 (9.4)	0.01	85 (9.8)	171 (9.9)	<0.01
Hispanic	50 (4.9)	5089 (5.9)	0.04	45 (5.2)	92 (5.3)	<0.01
Other	16 (1.6)	1471 (1.7)	0.01	14 (1.6)	23 (1.3)	0.02
≥2	44 (4.3)	3769 (4.4)	<0.01	37 (4.3)	68 (3.9)	0.02
White	780 (76.9)	64 736 (74.9)	0.05	660 (76.3)	1328 (76.8)	0.01
Male, *n (%)*	549 (52.9)	41 479 (46.9)	0.14	454 (52.5)	886 (51.2)	0.03
Hospitalized in the prior 90 d, *n (%)*	228 (22.0)	18 484 (20.9)	0.03	195 (22.5)	410 (23.7)	0.03
Admitted from a facility, *n (%)*	176 (17.0)	12 193 (13.8)	0.09	135 (15.6)	274 (14.3)	0.04
Clinical service, *n (%)**	–	–	0.40	–	–	<0.01
Cardiac surgery	18 (1.7)	2746 (3.1)	–	20 (2.3)	40 (2.3)	–
Cardiology	28 (2.7)	3358 (3.8)	–	22 (2.5)	44 (2.5)	–
Emergency	29 (2.8)	1401 (1.6)	–	18 (2.1)	36 (2.1)	–
Medicine	574 (55.5)	37 465 (42.8)	–	469 (54.2)	938 (54.2)	–
Neurology	41 (4.0)	3120 (3.6)	–	32 (3.7)	64 (3.7)	–
Obstetrics	14 (1.4)	5886 (6.7)	–	13 (1.5)	26 (1.5)	–
Oncology	103 (10.0)	10 334 (11.8)	–	87 (10.1)	174 (10.1)	–
Psychiatry	50 (4.8)	3882 (4.4)	–	46 (5.3)	92 (5.3)	–
Surgery	173 (16.7)	18 638 (21.3)	–	157 (18.2)	314 (18.2)	–
Comorbidities						
Cancer, *n (%)*	240 (23.1)	20 064 (22.7)	0.01	200 (23.1)	395 (22.8)	0.01
Liver disease, *n (%)*	142 (13.7)	9090 (10.3)	0.11	112 (12.9)	231 (13.4)	0.01
Neurologic disease, *n (%)*	269 (25.9)	16 348 (18.5)	0.18	215 (24.9)	396 (22.9)	0.05
Diabetes mellitus, *n (%)*	354 (34.1)	23 917 (27.1)	0.15	288 (33.3)	550 (31.8)	0.03
Renal failure, *n (%)*	305 (29.4)	18 727 (21.2)	0.19	255 (29.5)	508 (29.4)	<0.01
Drug and alcohol use disorder, *n (%)*	123 (11.9)	8958 (10.1)	0.06	97 (11.2)	215 (12.4)	0.04
Dementia, *n (%)*	111 (10.7)	5095 (5.8)	0.18	89 (10.3)	155 (9.0)	0.05
Heart failure, *n (%)*	297 (28.6)	20 197 (22.9)	0.13	251 (29.0)	494 (28.6)	0.01
Chronic lung disease, *n (%)*	270 (26.0)	20 685 (23.4)	0.06	228 (26.4)	457 (26.4)	<0.01
Peripheral vascular disease, *n (%)*	115 (11.1)	7896 (8.9)	0.07	102 (11.8)	174 (10.1)	0.06
Psychoses, *n (%)*	143 (13.8)	8793 (10.0)	0.12	114 (13.2)	207 (12.0)	0.04
Mean Elixhauser Comorbidity Index (SD)	14.2 (18.6)	9.7 (16.8)	0.26	14.0 (18.2)	12.6 (17.7)	0.08
Primary diagnosis, *n (%)*						
Gastrointestinal	107 (10.3)	9383 (10.6)	0.01	92 (10.6)	205 (11.8)	0.04
Musculoskeletal	45 (4.3)	4636 (5.2)	0.04	37 (4.3)	75 (4.2)	0.01
Psychiatric	100 (9.6)	7023 (7.9)	0.06	78 (9.0)	147 (8.5)	0.02
Cardiovascular	178 (17.2)	16 553 (18.7)	0.04	157 (18.2)	313 (18.1)	<0.01
Endocrine	54 (5.2)	3411 (3.9)	0.07	44 (5.1)	85 (4.9)	0.01
Infection	140 (13.5)	6189 (7.0)	0.22	103 (11.9)	180 (11.4)	0.05
Genitourinary	91 (8.8)	5989 (6.8)	0.08	81 (9.4)	148 (8.6)	0.03
Neurologic	67 (6.5)	3524 (4.0)	0.11	53 (6.1)	95 (5.5)	0.03
Trauma	130 (12.5)	10 584 (12.0)	0.02	109 (12.6)	249 (14.4)	0.05
Neoplastic	101 (9.7)	9562 (10.8)	0.04	85 (9.8)	170 (9.8)	<0.01
Pulmonary	49 (4.7)	5173 (5.9)	0.05	46 (5.3)	99 (5.7)	0.02
Hematologic	13 (1.3)	1621 (1.8)	0.05	13 (1.5)	25 (1.4)	<0.01
Dermatologic	16 (1.5)	1664 (1.9)	0.03	13 (1.5)	38 (2.2)	0.05
Obstetric	16 (1.5)	6152 (7.0)	0.27	13 (1.5)	28 (1.6)	0.01
Other	48 (4.6)	4637 (5.2)	0.03	42 (4.9)	78 (4.5)	0.02

Continued on following page

Table 2–Continued

Characteristic or Outcome	Before Matching			After Matching		
	Hospital-Onset SARS-CoV-2 Infection (*n* = 1037)	No SARS-CoV-2 Infection (*n* = 88 371)	SMD	Hospital-Onset SARS-CoV-2 Infection (*n* = 865)	No SARS-CoV-2 Infection (*n* = 1730)	SMD
Vital signs (SD)*						
Maximum temperature, *°C*	37.1 (0.6)	36.9 (0.4)	0.25	37.0 (0.5)	37.0 (0.5)	0.06
Median respiratory rate, *breaths/min*	18.8 (2.7)	18.4 (2.2)	0.18	18.6 (2.2)	18.5 (2.3)	0.04
Median systolic BP, *mm Hg*	127.9 (19.4)	126.8 (18.2)	0.06	126.1 (19.1)	126.0 (18.7)	<0.01
Median diastolic BP, *mm Hg*	68.9 (10.5)	69.9 (9.8)	<0.01	68.0 (9.8)	68.1 (9.6)	0.01
Oxygen support, *n (%)*						
None	172 (62.8)	50 939 (75.1)	0.27	628 (72.6)	1249 (72.2)	0.01
Nasal cannula	56 (20.4)	11 078 (16.3)	0.11	152 (17.6)	331 (19.1)	0.04
Advanced mask	12 (4.4)	1878 (2.8)	0.09	41 (4.7)	49 (2.8)	0.10
BIPAP or ventilator	34 (12.4)	3959 (5.8)	0.23	44 (5.1)	101 (5.8)	0.03
Laboratory values (SD)*						
Maximum leukocyte count, $\times 10^9$ *cells/L*	9.0 (6.1)	8.8 (7.7)	0.03	8.8 (5.4)	9.0 (5.4)	0.03
Minimum hematocrit	31.7 (6.5)	32.0 (6.4)	0.05	32.4 (6.8)	32.5 (6.4)	0.01
Minimum platelet count, $\times 10^9$ *cells/L*	223.4 (116.1)	221.9 (115.1)	0.01	243.0 (129.0)	242.5 (133.2)	<0.01
Maximum creatinine level	–	–	0.15	–	–	0.01
µmol/L	118.5 (122.0)	100.8 (104.3)	–	114.9 (119.3)	114.0 (122.9)	–
mg/dL	1.3 (1.4)	1.1 (1.2)	–	1.3 (1.4)	1.3 (1.4)	–
Minimum sodium level, *mmol/L*	137.9 (4.5)	138.0 (3.8)	0.04	137.7 (4.2)	137.8 (4.1)	0.03
Maximum glucose level	–	–	0.12	–	–	0.04
mmol/L	7.90 (3.74)	7.46 (3.52)	–	7.59 (3.59)	7.47 (3.40)	–
mg/dL	137.4 (64.0)	129.0 (59.0)	–	136.8 (64.7)	134.6 (61.2)	–
Maximum alanine aminotransferase level, *U/L*	29.4 (42.7)	37.2 (122.0)	0.09	30.4 (46.5)	31.1 (44.8)	0.01
Maximum bilirubin level	–	–	0.01	–	–	0.06
µmol/L	18.81 (59.86)	17.10 (44.47)	–	14.20 (38.48)	12.31 (18.64)	–
mg/dL	0.8 (2.3)	0.8 (1.6)	–	0.8 (2.3)	0.7 (1.1)	–
Minimum albumin level, *g/L*	34.3 (6.8)	35.9 (6.2)	0.24	34.2 (6.6)	34.8 (6.4)	0.09
ICU status, *n (%)**	89 (8.6)	5137 (5.9)	0.11	41 (4.7)	82 (4.7)	<0.01
SARS-CoV-2 vaccine*						
Ever, %	807 (77.8)	70 620 (79.9)	0.05	689 (79.3)	1420 (82.1)	0.07
Within prior 4 mo, %	247 (23.8)	22 878 (25.9)	0.05	218 (25.2)	385 (22.3)	0.07
Mean total doses (SD), *n*	2.3 (1.5)	2.4 (1.5)	0.08	2.3 (1.5)	2.6 (1.6)	0.19
Mean days from admission to match (SD)	NA	NA	–	9.9 (12.5)	9.9 (12.5)	<0.01

BIPAP = bilevel positive airway pressure; BP = blood pressure; ICU = intensive care unit; NA = not applicable; SMD = standardized mean difference.

* Provided for hospital day 5 in the unmatched cohorts and 2 d before SARS-CoV-2 infection diagnosis date or match date in the matched population.

Competing risks analysis using Fine–Gray subdistribution hazard ratios (SHRs) suggested that hospital-onset SARS-CoV-2 infection was associated with longer stays (SHR for discharge alive, 0.7 [CI, 0.6 to 0.8]) and hospital death (SHR, 2.0 [CI, 1.1 to 3.8]) during the pre-Omicron period. Results were similar and still significant but attenuated during the Omicron period (SHR for discharge alive, 0.8 [CI, 0.7 to 0.8]; SHR for hospital death, 1.6 [CI, 1.2 to 2.3]).

During the pre-Omicron period, hospital-onset SARS-CoV-2 infection was associated with significantly greater risk for ICU admission (risk ratio, 1.9 [CI, 1.1 to 3.6]) and need for high-flow oxygen by nasal cannula (risk ratio, 5.2 [CI, 2.1 to 13.2]). During the Omicron period, increased risk for ICU admission persisted (risk ratio, 2.0 [CI, 1.4 to 2.7]), need for high-flow oxygen was attenuated (risk ratio, 1.4 [CI, 0.9 to 2.3]), and risk for mechanical ventilation was increased (risk ratio, 1.6 [CI, 1.1 to 2.2]). Thirty-day readmission rates were similar for patients with and without hospital-onset SARS-CoV-2 infection during both the pre-Omicron and Omicron periods.

The subgroup analysis restricted to patients discharged to home included 122 cases of hospital-onset SARS-CoV-2 infection during the pre-Omicron period and 479 cases during the Omicron period. After propensity matching, hospital-onset SARS-CoV-2 infection remained associated with increased days to discharge in the pre-Omicron period (median difference, 3.0 days [CI, 1.6 to 4.4 days]) and during the Omicron period (median difference, 3.0 days [CI, 2.0 to 3.8 days]).

The results of the sensitivity analysis using stricter matching criteria were very similar to those of the primary analysis (**Supplement Tables 2** and **3**, available at Annals.org).

Table 3. Comparative Outcomes for Patients With Hospital-Onset SARS-CoV-2 Infection Versus Matched Control Participants

Outcome	Before Matching		After Matching		Effect Estimate (95% CI)*
	Hospital-Onset SARS-CoV-2 Infection	No SARS-CoV-2 Infection	Hospital-Onset SARS-CoV-2 Infection	No SARS-CoV-2 Infection	
Pre-Omicron					
Total patients, *n*	274	67 854	230	460	
Progression to severe illness, *n (%)*†					
Admission to intensive care	27 (9.9)	1882 (2.8)	21 (9.1)	22 (4.8)	1.94 (1.06 to 3.57)
Need for high-flow oxygen	17 (6.2)	801 (1.2)	15 (6.5)	6 (1.3)	5.21 (2.06 to 13.2)
Need for BIPAP	9 (3.3)	852 (1.3)	7 (3.0)	9 (2.0)	1.54 (0.59 to 4.03)
Need for mechanical ventilation	23 (8.4)	2338 (3.4)	17 (7.4)	24 (5.2)	1.25 (0.66 to 2.37)
Effect on length of stay					
Median days from match to discharge (IQR), *d*†	13.5 (6.0 to 27.0)	3.0 (1.0 to 7.0)	9.0 (6.0 to 17.8)	5.0 (2.0 to 12.0)	4.65 (2.90 to 6.64)
Median hospital length of stay (IQR), *d*	18.5 (11.0 to 32.0)	8.0 (6.0 to 12.0)	17.0 (11.0 to 30.0)	12.5 (8.0 to 22.3)	5.99 (3.06 to 8.41)
Median 30-d hospital-free days (IQR), *d*	10.0 (0.0 to 21.8)	25.0 (16.0 to 28.0)	16.0 (4.0 to 23.0)	21.5 (10.0 to 26.0)	−6.55 (−8.68 to −2.75)
Discharge disposition, *n (%)*					
Home	138 (50.4)	49956 (73.6)	122 (53.0)	284 (61.7)	0.85 (0.74 to 0.98)
Rehabilitation	32 (11.7)	4494 (6.6)	24 (10.4)	35 (7.6)	1.47 (0.92 to 2.36)
Skilled-nursing facility	56 (20.4)	8689 (12.8)	46 (20.0)	94 (20.4)	1.08 (0.78 to 1.50)
Hospice	9 (3.3)	1746 (2.6)	8 (3.5)	14 (3.0)	0.97 (0.37 to 2.54)
Hospital death	32 (11.7)	2079 (3.1)	23 (10.0)	18 (3.9)	2.04 (1.09 to 3.84)
Readmission within 30 d, *n (%)*†	26 (9.5)	11026 (16.2)	26 (11.3)	77 (16.7)	0.62 (0.43 to 1.01)
Competing risks analysis, *n (%)*					
Discharge alive (excluding hospice)	226 (82.5)	63 139 (93.1)	192 (83.5)	413 (89.8)	0.68 (0.57 to 0.80)
Discharge to facility	97 (35.4)	14 929 (22.0)	78 (33.9)	143 (31.1)	1.14 (0.85 to 1.52)
Hospital death	32 (11.7)	2079 (3.1)	23 (10.0)	18 (3.9)	2.00 (1.05 to 3.81)
Omicron					
Total patients, *n*	1037	88 371	865	1730	
Progression to severe illness, *n (%)*†					
Admission to intensive care	99 (9.5)	2593 (2.9)	67 (7.7)	67 (3.9)	1.96 (1.41 to 2.72)
Need for high-flow oxygen	47 (4.5)	1198 (1.4)	26 (3.0)	36 (2.1)	1.41 (0.86 to 2.30)
Need for BIPAP	47 (4.5)	1195 (1.4)	20 (2.3)	31 (1.8)	1.29 (0.75 to 2.24)
Need for mechanical ventilation	99 (9.5)	3211 (3.6)	63 (7.3)	81 (4.7)	1.57 (1.14 to 2.15)
Effect on length of stay					
Median days from match to discharge (IQR), *d*†	13.0 (6.0 to 29.0)	3.0 (1.0 to 7.0)	9.0 (5.0 to 17.0)	4.0 (2.0 to 11.0)	+4.20 (3.60 to 5.00)
Median hospital length of stay (IQR), *d*	18.0 (11.0 to 34.0)	8.0 (6.0 to 12.0)	17.0 (11.0 to 29.0)	12.0 (8.0 to 23.0)	+5.33 (4.00 to 7.00)
Median 30-d hospital-free days (IQR), *d*	12.0 (0.0 to 22.0)	25.0 (16.0 to 28.0)	16.0 (5.0 to 23.0)	22.0 (10.0 to 27.0)	−6.40 (−7.60 to −4.67)
Discharge disposition, *n (%)*					
Home	568 (54.8)	65 413 (74.0)	479 (55.4)	1102 (63.7)	0.86 (0.81 to 0.93)
Rehabilitation	101 (9.7)	6030 (6.8)	89 (10.3)	151 (8.7)	1.17 (0.91 to 1.51)
Skilled-nursing facility	231 (22.3)	10737 (12.1)	189 (21.8)	316 (18.3)	1.23 (1.05 to 1.44)
Hospice	39 (3.8)	2209 (2.5)	35 (4.0)	63 (3.6)	1.11 (0.74 to 1.66)
Hospital death	73 (7.0)	2724 (3.1)	56 (6.5)	70 (4.0)	1.63 (1.16 to 2.28)
Readmission within 30 d, *n (%)*†	116 (11.2)	13 704 (15.5)	115 (13.3)	277 (16.0)	0.84 (0.69 to 1.03)
Competing risks analysis, *n (%)*					
Discharge alive (excluding hospice)	900 (86.8)	82 180 (93.0)	757 (87.5)	1569 (90.7)	0.76 (0.70 to 0.83)
Discharge to facility	371 (35.8)	18 976 (21.5)	313 (36.2)	530 (30.6)	1.20 (1.04 to 1.38)
Hospital death	73 (7.0)	2724 (3.1)	56 (6.5)	70 (4.0)	1.64 (1.16 to 2.33)

BIPAP = bilevel positive airway pressure.

* Effect estimates are risk ratios for categorical outcomes (progression to severe illness, discharge disposition, and readmission), median differences for length of stay, and subdistribution hazard ratios for competing risks analyses. All effect estimates are adjusted for any residual differences between case patients and their matched control participants.

† Measured from hospital day 5 in the unmatched cohort and from match day in the matched cohort.

DISCUSSION

Hospital-acquired SARS-CoV-2 infections have been reported since the start of the pandemic, but there is currently debate regarding the morbidity and mortality of these infections and hence what level of protective measures are commensurate to them (14–17). In this large cohort study across 5 hospitals, including more than 1300 cases of hospital-onset SARS-CoV-2 infection, we found that the morbidity and mortality of hospital-onset SARS-CoV-2 infections have decreased in the Omicron era compared with the pre-Omicron era but nosocomial SARS-CoV-2 infection continues to be associated with harm for some patients.

Hospital-onset SARS-CoV-2 infection in the year before Omicron was associated with increased need for ICU admission, increased need for high-flow oxygen, a 5-day increase in days to discharge, and a 2-fold increase in hospital mortality. Since the arrival of Omicron, hospital-onset SARS-CoV-2 infection continues to be associated with increased risk for ICU admission

and prolonged length of stay. Hospital mortality rates have dropped almost in half, however, compared with the pre-Omicron era but are still significantly elevated compared with matched patients without hospital-onset SARS-CoV-2 infection.

We found substantial differences between patients with hospital-onset SARS-CoV-2 infection and the general hospital population. Patients infected with SARS-CoV-2 tended to be older, were more likely to be receiving supplementary oxygen, and tended to have more chronic conditions. The increased likelihood of infection in patients with these characteristics likely reflects their greater length of stay and greater need for hands-on care, 2 factors that put patients at increased risk for infection from staff, roommates, and visitors. Impaired immunity due to immunocompromising conditions, treatments, or frailty may also contribute.

The decrease in morbidity associated with nosocomial SARS-CoV-2 infection during the Omicron period likely reflects a combination of less virulent variants, high levels of acquired immunity from vaccines and prior infections (about 80% of study patients from the Omicron period had been vaccinated), and receipt of effective treatments. Surveys suggest that 98% of Americans have acquired some degree of immunity to SARS-CoV-2 (7). Nonetheless, we did still find that hospital-onset SARS-CoV-2 infection was associated with increased hospital mortality and more time to discharge. Although some of the increased length of stay may be due to delays in facilities accepting patients because of their infections, we found that even patients discharged to home stayed a median of 3 days longer than matched control participants. Possible reasons for longer stays and the persistent increase in mortality include medical complications of viral infection, such as pneumonia, heart failure or chronic lung disease exacerbations, myocardial ischemia, arrythmias, thromboembolic disease, and bacterial or fungal superinfections (25). Length of stay may also be extended by postponed procedures, increased need for monitoring, inpatient treatment with remdesivir, patient reluctance for discharge due to fear for their own health or fear of infecting friends and family, and greater difficulty finding skilled-nursing and rehabilitation facilities willing or able to accept infected patients.

Our study has several strengths. We could analyze large numbers of hospital-onset cases; used highly detailed clinical data to generate propensity scores, an essential step to mitigate confounding; and had high capture of nosocomial cases due to study hospitals' aggressive serial testing policies. Likewise, study hospitals screened all patients via PCR on admission and again on hospital day 3, making it likely that new positive results on hospital day 5 or later were true nosocomial infections rather than delayed detection of infections present on admission.

Limitations of our analysis include the focus on a single, well-resourced hospital system with mature infection control policies in a jurisdiction with high vaccination rates. These factors may limit generalizability. Rates of hospital-onset SARS-CoV-2 infection may be higher in hospitals with more shared rooms, less admission testing, and less use of masks. Similarly, outcomes of hospital-onset SARS-CoV-2 infection may be worse in jurisdictions with lower rates of vaccination and less access to treatments. Our 5-day threshold for defining hospital-onset SARS-CoV-2 infection may have misclassified some community-acquired cases as hospital-acquired cases; however, patients tested negative twice before being classified as hospital-onset. Furthermore, whole-genome sequencing studies suggest that a 5-day threshold is conservative; many cases diagnosed before hospital day 5 are also nosocomial (26–28). Nonetheless, we are careful to use the nomenclature of "hospital-onset" rather than "hospital-acquired" to acknowledge the possibility of misclassification. Conversely, our estimates of the morbidity of hospital-onset Omicron infections may be lower than others' estimates because of the study hospitals' policy of testing patients every 5 days from day 8 onward regardless of symptoms. This may have increased detection of less severe cases, leading to lower (but more accurate) estimates of attributable morbidity and mortality. Residual confounding is possible despite the extensive array of clinical variables included in our propensity scores. Findings were consistent, however, in a sensitivity analysis using stricter matching criteria. Some patients had missing laboratory values that we imputed as normal, possibly leading to confounding, although missingness was low. Finally, we calculated the effect of hospital-onset infections on multiple outcomes but could not characterize additional possible harms, such as patient discomfort, anxiety, costs of care, delays in care, and secondary transmissions to family members and other caregivers.

The persistent association between hospital-onset SARS-CoV-2 infection and increased morbidity and mortality during the Omicron era begs the question of what measures hospitals ought to take to protect patients from hospital-acquired SARS-CoV-2 infection. Of note, this study was done during a period when many measures to prevent transmission were in place, including universal masking, universal admission testing and retesting 3 days later, employee attestations of health before every shift, visitor screening for symptoms, and mandatory SARS-CoV-2 vaccination for health care workers. Possible reasons for the persistence of hospital-onset infections despite these measures include staff working despite being ill, visitors seeing patients despite being ill, lapses in masking, inadequate ventilation in some locations, and the limited effectiveness of surgical masks for both source control and exposure control (29–33). Informal audits during this period suggest that staff were highly adherent to masking during patient interactions, patients were generally poor about masking, and visitors were intermediate. This fits with laboratory

and epidemiologic data suggesting that regular surgical masks decrease viral emissions and transmissions by about half but do not eliminate them (31–36).

A range of possible measures could be used to prevent more nosocomial transmissions. Possibilities include enacting stronger policies to discourage staff from working when ill (such as more flexible sick policies), actively screening visitors to stop symptomatic persons from visiting, mandating SARS-CoV-2 vaccines for health care workers, improving ventilation, decreasing or eliminating shared rooms, adding air cleaners, encouraging more consistent masking, and using respirators rather than surgical masks (37–42). These measures can be challenging, costly, or onerous to implement, however, so hospitals need to balance their ethical obligation to protect patients against the burden of added measures on health care workers and hospitals. One potential strategy is to calibrate infection control measures to community transmission rates with a view to activating selected measures (such as admission testing, employee attestations of health, and effective masking) only when community incidence rates of SARS-CoV-2 infection are elevated (43).

In summary, we document high rates of hospital-onset infections during the Omicron era and a substantial decline in the morbidity and mortality associated with hospital-onset infections in the Omicron era, but persistent associations of hospital-onset SARS-CoV-2 infections with increased mortality and time to discharge. The frequency and persistent morbidity associated with hospital-onset SARS-CoV-2 infections in the Omicron era suggest that hospitals should implement measures to prevent nosocomial SARS-CoV-2 infections, particularly when community SARS-CoV-2 rates are elevated.

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Author contributions are available at Annals.org.

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