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CLINICAL RESEARCH STUDY

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Association of COVID-19 Hospitalization Volume and Case Growth at US Hospitals with Patient Outcomes

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ABSTRACT

BACKGROUND: Whether the volume of coronavirus disease 2019 (COVID-19) hospitalizations is associated with outcomes has important implications for the organization of hospital care both during this pandemic and future novel and rapidly evolving high-volume conditions.

METHODS: We identified COVID-19 hospitalizations at US hospitals in the American Heart Association COVID-19 Cardiovascular Disease Registry with ≥10 cases between January and August 2020. We evaluated the association of COVID-19 hospitalization volume and weekly case growth indexed to hospital bed capacity, with hospital risk-standardized in-hospital case-fatality rate (rsCFR).

RESULTS: There were 85 hospitals with 15,329 COVID-19 hospitalizations, with a median hospital case volume was 118 (interquartile range, 57, 252) and median growth rate of 2 cases per 100 beds per week but varied widely (interquartile range: 0.9 to 4.5). There was no significant association between overall hospital COVID-19 case volume and rsCFR (rho, 0.18, P = .09). However, hospitals with more rapid COVID-19 case-growth had higher rsCFR (rho, 0.22, P = 0.047), increasing across case growth quartiles (P trend = .03). Although there were no differences in medical treatments or intensive care unit therapies (mechanical ventilation, vasopressors), the highest case growth quartile had 4-fold higher odds of above median rsCFR, compared with the lowest quartile (odds ratio, 4.00; 1.15 to 13.8, P = .03).

CONCLUSIONS: An accelerated case growth trajectory is a marker of hospitals at risk of poor COVID-19 outcomes, identifying sites that may be targets for influx of additional resources or triage strategies. Early identification of such hospital signatures is essential as our health system prepares for future health challenges.

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KEYWORDS: COVID-19; Health services research; Outcomes research; Quality of care; SARS-CoV2

BACKGROUND

The coronavirus disease-19 (COVID-19) pandemic challenged hospitals to adapt their care procedures for a novel disease process with an unknown trajectory. Simultaneously, hospitals were also overwhelmed by a disease that poses a substantial threat to health care resources, such as intensive care unit (ICU) and ventilator capacity,[1,2] and puts the health care workforce at personal health risk.[3]

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Therefore, although hospitals caring for COVID-19 patients gained institutional knowledge and experience that may help improve patient outcomes, a surge of patients that overwhelms available resources might negatively impact care. In this respect, care for COVID-19 differs from care for other conditions, in which hospitals with more experience consistently demonstrate better outcomes, especially for new areas of care.[4-7]

Thus far, the assessment of COVID-19 outcomes has focused on patient features that portend adverse outcomes.[8-12] However, how hospitals responded to COVID-19 represents an important avenue into evaluating whether our care processes are designed to be resilient to large and dynamic case volumes of acute illnesses and can achieve similar outcomes despite these pressures. The knowledge gained from understanding these associations of volumes and outcomes for COVID-19 can inform care processes such as regionalization of care and sharing of resources across health systems as our health system continues to adapt to the COVID-19 pandemic and considers preparation for future health crises and challenges.

In a nationwide registry of hospitalized COVID-19 patients, we evaluated 2 distinct aspects of the experience of hospitals with COVID-19 case volumes. We assessed the overall case volumes at each participating hospital, which is a commonly used metric for volume-outcome studies, and assessed for its association with survival to discharge after accounting for patient and hospital features. In addition, we constructed a novel case growth measure that accounted for rate of growth of COVID-19 as a function of hospital bed capacity to assess whether rapid acceleration of COVID-19 case volumes relative to hospital capacity was associated with outcomes.

CLINICAL SIGNIFICANCE

- In a study of coronavirus disease 2019 (COVID-19) hospitalizations at 85 US hospitals, despite similar care processes, a rapid increase in COVID-19 cases relative to bed capacity, as opposed to overall hospital case volume, was significantly associated with worse risk-standardized in-hospital case-fatality rate.
- An accelerated case growth trajectory is a marker of hospitals at risk of poor COVID-19 outcomes, identifying sites that may be targets for influx of additional resources or triage strategies.

METHODS

Data Source

We used patient and hospital data from the American Heart Association (AHA) COVID-19 Cardiovascular Disease (CVD) Registry. The registry was designed to collect high-quality information on patient characteristics and outcomes leveraging the Get With The Guidelines (GWTG) infrastructure in place for collecting data for AHA registries.[8,13] The registry includes data from patients with completed hospitalizations for COVID-19 at participating hospitals defined by a positive polymerase chain reaction or an antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and a clinical presentation consistent with COVID-19. The online data entry process ensured completeness of records and consistency in data fields across centers through internal logic checks. The current analysis is based on a data release that includes hospitalizations through August 2020 and captures hospitalizations in the early phase of the pandemic. Because the registry is designed as a quality improvement tool, with no intervention or participant contact, and collection of only a limited data set, informed consent was not obtained. The Duke University institutional review board provided approval.

Study Population and Exposures

Hospitals represented the unit of the analysis, and all hospitals with at least 10 COVID-19 cases were included. All COVID-19 cases reported from these hospitals were included. Two exposures were defined. First, overall COVID-19 case volume was defined as the absolute number of COVID-19 hospitalizations at individual hospitals across the same reporting period. The overall case volume represents the most commonly used unit of analyses in volume-outcome assessments.[7,14,15]

Second, to specifically isolate the potential effect of rapid case growth at hospitals, we constructed a novel measure of case growth rate as a function of a hospital's total bed capacity. This case growth rate was defined as the average weekly change in the proportion of hospitalized COVID-19 patients relative to hospital bed number, beginning with the week when the first case was recorded and ending the week with the peak case load at the hospital across the study period (Supplementary Figure 1, available online). The weekly hospital census of COVID-19 cases was based on hospital admission and discharge dates and included all patients who had a COVID-19 hospitalization spanning a given calendar week.

Study Covariates and Outcome

To ensure our analyses compared similar patients presenting to similar hospitals, we identified detailed patient and hospital characteristics. For patients, these included demographics and comorbid health conditions (eMethods, available online). Further, in-hospital care features of ICU care and mechanical ventilation or renal replacement therapy were included. We identified several hospital characteristics, including teaching status, census region, number of hospital beds, and average daily patient census in 2019 that were available from the AHA data merged with the AHA COVID-19 CVD registry.

Study Outcome

The outcome of the study was hospital risk-standardized in-hospital mortality. This was computed using hierarchical models that accounted for patient and hospital characteristics. The construction of the model is described in eMethods and Supplementary Table 1, available online.

Statistical Analysis

We classified hospitals into quartiles based on each of the 2 hospital volume exposures: overall hospital COVID-19 volume and hospital COVID-19 case growth. We compared characteristics of hospitals across these quartiles, including their location, teaching status, bed size, and average daily hospital census in the pre-COVID-19 era. Next, we evaluated differences in characteristics of patients across the hospital volume quartiles including demographics, comorbid conditions, and in-hospital care needs and treatments. To evaluate directional difference in characteristics across quartiles, we used the Cochran Armitage test for the categorical variables and Jonckheere-Terpstra trend test for continuous variables. We parametrized quartiles as an ordinal categorical variable from lowest- to highest-volume quartiles for these assessments.

To assess the association with mortality for each of the 2 exposures, we evaluated continuous associations between hospital case volumes and hospital risk-standardized mortality using Spearman correlation. Conceptually, these analyses quantified the differences in hospital rankings for risk-standardized mortality that could be ascribed to overall volumes or their case growth. We repeated an assessment of mean risk-standardized mortality across hospital quartiles of volume and case growth using linear regression with hospital quartiles parameterized as ordinal categories from lowest to highest. We also calculated the odds ratio of above median risk-standardized mortality rates across volume and case growth quartiles with the lowest volume and case growth quartiles as referents, respectively.

Secondary Analysis

To account for temporal evolution of care practices that may have potentially led to the observed improvements in patient outcomes over time[16] and may confound volume-outcome assessments, we created a temporally restricted cohort for sensitivity analyses. In these analyses, we limited our assessment of both volume-outcome and case-growth-outcome relationships to hospitals that reached their case peak in the first half of the year, specifically before June 30, 2020.

The level of significance was set at 0.05. All analyses were performed using R 3.9 (R foundation).

RESULTS

Hospital and Patient Characteristics

There were 104 hospitals with 15,397 patients in the AHA COVID-19 CVD registry, of which 85 reported at least 10 COVID-19 cases and were included in the study. There were 15,329 COVID-19 hospitalizations recorded at these hospitals during the study period. There was a large variation in volumes across hospitals, with median case volume of 118 (interquartile range [IQR], 57, 252) (Figure 1). Hospitals in the highest-case volume quartiles were larger, with larger bed size, and average daily hospital census in the preceding year (Table 1). There were no significant differences in teaching status or urban or rural location across hospital quartiles of case volumes.

Patients in hospitals in the highest COVID-19 volume quartile were modestly younger (mean, 61.1 years in highest-volume quartile vs 62.0 years in the lowest-volume quartile) but without significant differences in either sex or race or ethnicity distributions or for cardiovascular and non-cardiovascular comorbidities (Table 2, $P > .05$ for all comparisons). There were similarly no significant differences in proportions of patients receiving ICU care or those requiring mechanical ventilation, hemodialysis, or vasopressors. Lower-volume hospitals had higher use of glucocorticoids, but there was no difference in the proportion of patients receiving remdesivir, interleukin-6 (IL-6) antagonists, or hydroxychloroquine across volume quartiles.

Association Between COVID-19 Case Volumes and Risk Standardized In-Hospital Case-Fatality

There was a large variation in patient mortality, with a median in-hospital case-fatality rate (CFR) of 14.3% (IQR 8.5%, 18.7%) and risk-standardized case-fatality rate of 15.9% (12.5%, 20.0%) across hospitals. The median unadjusted in-hospital CFR was 14.2% in the lowest-volume quartile (Q1), 12.6% in Q2, 12.8% in Q3, and 16.8% in Q4. There was no significant association between overall COVID-19 case volume and risk-standardized CFR (Spearman correlation, 0.18, $P = .09$) (Figure 2). Mortality was numerically higher but not significantly different across quartiles based on COVID-19 volumes, with median risk-standardized CFR of 15.5% (IQR 12.7%, 18.5%) in the lowest-volume quartile and 18.2% (IQR, 14.9%, 21.5%, P for trend across quartiles, .34). Hospitals in the highest COVID-19 volume quartile had higher odds of having above median risk-standardized CFR compared with lowest-volume quartile hospitals; however, these findings did not reach statistical significance (odds ratio [OR], 3.56; 95% confidence interval [CI] 0.99-12.7, $P = 0.05$).

Hospital COVID-19 Case Growth and Risk Standardized Mortality

The median COVID-19 hospitalizations case growth was 2 cases per 100 beds per week but varied widely (IQR: 0.9 cases/100 beds/wk to 4.5 cases/100 beds/wk) (Figure 1). There was a modest positive correlation between hospital case growth rate and total hospital COVID-19 volume

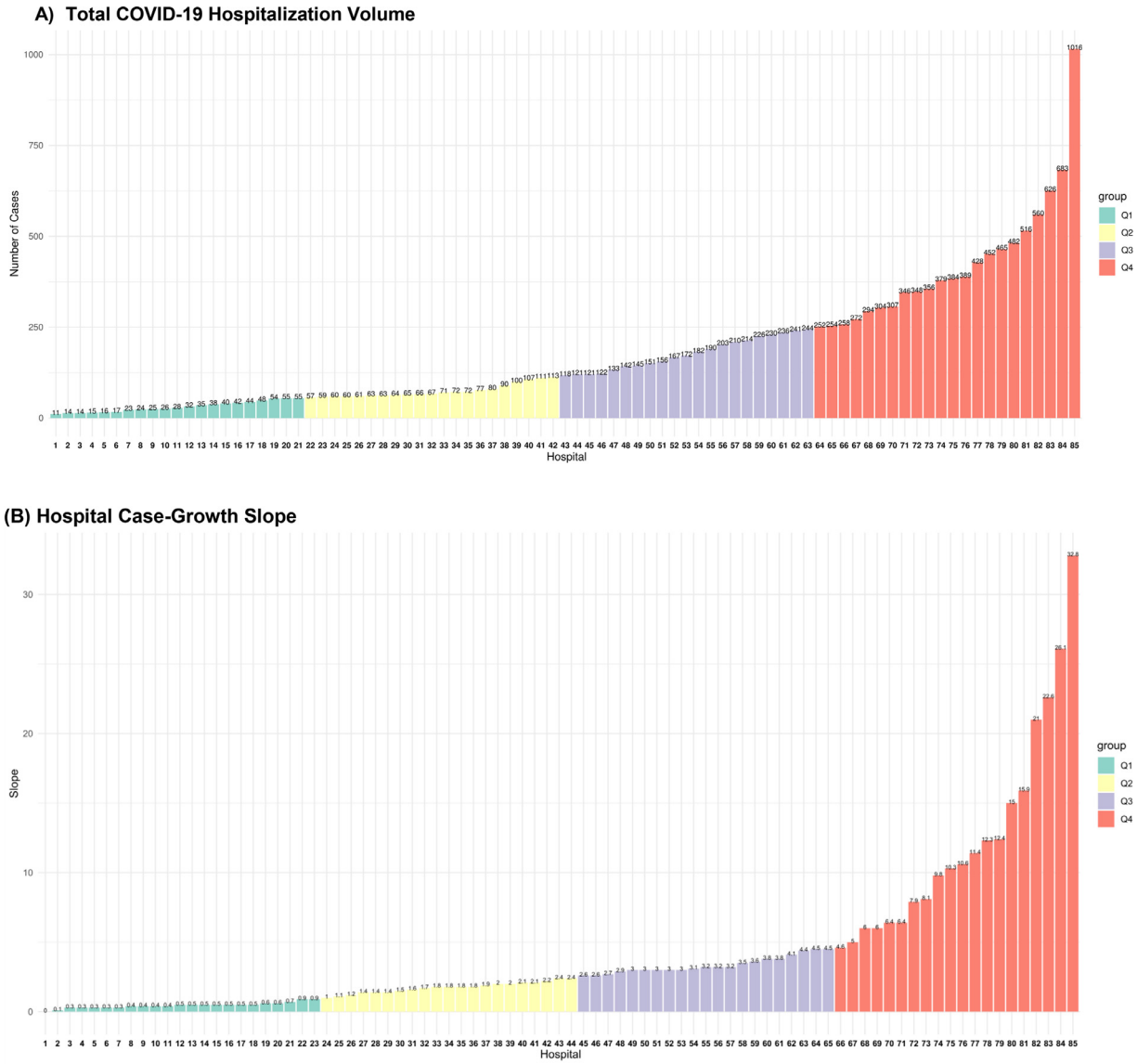

Figure 1 COVID-19 **(A)** hospitalization volumes, and **(B)** average weekly case growth slope across hospitals in the AHA COVID-19 CVD Registry. The units of the *y*-axis are number of cases in **(A)** and case increase per 100 beds per week in **(B)** and represents the average weekly case growth from the week of first case to that of the peak case volume. The *x*-axis represents individual hospitals ordered by their case volumes in **(A)** and their case-growth slope in **(B)**. COVID-19 = coronavirus disease 2019.

(Spearman correlation coefficient, 0.22, P = .046, Supplementary Figure 2, available online). There were notable differences in hospital characteristics with large bed size and teaching hospitals less likely to be in the highest-case growth rate quartile, even though they represented the largest group in the highest-volume quartile (Supplementary Table 2, available online). There were, however, no significant differences in patient characteristics across case-growth quartiles (Supplementary Table 3, available online).

There was a significant positive correlation between case growth and risk-standardized hospital CFR, with hospitals with the most rapid case-growth having a significantly higher risk-standardized CFR (Spearman correlation coefficient: 0.22, P = .047) (Figure 3). Median risk-standardized CFR was 13.9 (IQR 10.6%, 17.2%) in the lowest case-growth quartile and 17.8% (IQR, 14.1%, 21.5%, P for trend across quartiles, .03). Hospitals in the highest case-growth quartile had 4-fold higher odds of having above median risk-standardized CFR, compared with hospitals in the lowest case-growth quartile (OR, 4.00; 95% CI, 1.15 to 13.8, P = .03).

Secondary Analysis

In analyses that restricted the assessment of volumes and outcomes to early part of the pandemic, a total of 70

Table 1 Characteristics of Hospitals Across COVID-19 Overall Case Volume Quartiles.

	Q1	Q2	Q3	Q4	P Value
Hospitals, N	21	21	21	22	
Hospital Bed Size					.01
≥500	9 (42.9)	9 (42.9)	11 (52.4)	14 (63.6)	
250-499	7 (33.3)	11 (52.4)	10 (47.6)	4 (18.2)	
<250	5 (23.8)	0 (0.0)	0 (0.0)	0 (0.0)	
NA	0 (0.0)	1 (4.8)	0 (0.0)	4 (18.2)	
Hospital Location					.24
Urban	19 (90.5)	20 (95.2)	21 (100.0)	18 (81.8)	
Rural	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	
NA	0 (0.0)	1 (4.8)	0 (0.0)	4 (18.2)	
Teaching Status					.12
Major	9 (42.9)	9 (42.9)	10 (47.6)	10 (45.5)	
Minor	5 (23.8)	10 (47.6)	10 (47.6)	7 (31.8)	
Nonteaching	7 (33.3)	1 (4.8)	1 (4.8)	1 (4.5)	
NA	0 (0.0)	1 (4.8)	0 (0.0)	4 (18.2)	
Annual Hospitalizations, median (IQR)*	14,840 (5344, 29682)	18,633 (12174, 25443)	20,715 (16817, 27910)	34,368 (24510,41483)	<.001
Average daily census, median (IQR)*	207 (69, 463)	288 (195, 366)	327 (209, 455)	645 (367,707)	<.001
Total hospital beds, median (IQR)*	281 (152, 594)	373 (251, 534)	436 (279, 591)	820 (502, 942)	<.001

COVID-19 = coronavirus disease 2019; IQR = interquartile range.
*P value for Jonckheere-Terpstra trend test

hospitals that had a peak case volume in June or earlier were included. Among these hospitals, there was a significant correlation between hospital volumes and hospital risk-standardized CFR (Spearman correlation coefficient, 0.32, P = .008). Among hospitals with an early case peak, those in the highest-volume quartile had 11-fold higher odds of above median risk-standardized CFR (OR 11.43, 95% CI 1.97, 66.36, P = .007). Hospitals in the highest-quartile of case growth who reached their peak volumes in the first half of the year had more than 4-fold higher odds of above median risk-standardized CFR (OR 4.67; 95% CI, 0.96, 22.79, P = .057) similar to the primary analyses but did not reach our predefined threshold of significance.

DISCUSSION

In a large nationwide registry of 85 hospitals with 15,329 confirmed COVID-19 hospitalizations and detailed phenotypic characterization, there was a large variation in both the overall volume of COVID-19 cases as well as the trajectory of case growth. Hospitals had a large variation in patient mortality, even after accounting for differences in patient and hospital characteristics. The overall volume of COVID-19 cases at hospitals was not significantly associated with in-hospital CFR, but in analyses of hospitals with early peaks in COVID-19 volumes, higher COVID-19 volume was associated with higher risk standardized CFR. We also found that the rate at which hospitals experienced an increase in their cases relative to their capacity across the study period was significantly associated with CFR, with faster rise in cases associated with higher risk-standardized CFR.

The challenges faced by hospitals in the COVID-19 pandemic have consistently been interpreted in light of their bed capacity or the vulnerability of their health care providers. However, from a patient outcomes perspective, in addition to volume, the rapidity with which a hospital experiences an increase in their case volume likely has important implications for patients receiving care at those hospitals. Hospital case growth and overall case volumes may potentially create a challenge for staffing, bed capacity, and ICU care needs,[17] which are frequently in flux due to the hazard for infection among health care workers. Despite this uncertainty about the mechanism, case growth, which can be assessed prospectively, may play a role in identifying hot spots that may benefit from an urgent influx of additional personnel and resources to care for the surge.

These observations also identify a potential explanation for the observed variation in risk-adjusted outcomes across hospitals that has been suggested in prior studies,[12,16] especially because this variation in hospital outcomes cannot be explained by differences in measured patient characteristics. Of note, a recent study that addressed variation in outcomes across hospitals included individuals from a single payer and did not have the entire census of hospitalized COVID-19 patients, as was possible in our study using an all-comer registry.[16] Although larger hospitals had higher case volumes, there was no correlation of COVID-19 volumes with patient comorbidities or illness severity based on the need for ICU

Table 2 Characteristics of Patients Across Hospital COVID-19 Overall Case Volume Quartiles*

	Q1	Q2	Q3	Q4	*P* Value
Number of patients	656	1578	3724	9371	
Age (mean [SD])†	62.0 (17.2)	63.0 (17.5)	61.0 (18.0)	61.1 (17.6)	.01
Female sex	261 (39.8)	704 (44.6)	1683 (45.2)	4324 (46.1)	.24
Race					
Non-Hispanic white	349 (53.3)	925 (59.0)	1524 (40.9)	2851 (30.4)	<.001
Non-Hispanic black	133 (20.3)	351 (22.4)	1083 (29.1)	2437 (26.0)	
Hispanic	113 (17.3)	133 (8.5)	777 (20.9)	2690 (28.7)	
Others	60 (9.2)	158 (10.1)	340 (9.1)	1393 (14.9)	
Comorbidities					
Atrial fibrillation/flutter	79 (12.0)	211 (13.4)	350 (9.4)	767 (8.2)	.33
Cancer	86 (13.1)	188 (11.9)	346 (9.3)	1403 (15.0)	.38
Cerebrovascular disease (stroke/TIA)	56 (8.5)	155 (9.8)	360 (9.7)	1418 (15.1)	.43
Currently on dialysis	15 (2.3)	49 (3.1)	124 (3.3)	346 (3.7)	.46
Diabetes mellitus	211 (32.2)	567 (35.9)	1353 (36.3)	3269 (34.9)	.31
Dyslipidemia	199 (30.3)	659 (41.8)	1352 (36.3)	3005 (32.1)	.29
Heart failure	75 (11.4)	209 (13.2)	413 (11.1)	989 (10.6)	.36
Hypertension	400 (61.0)	972 (61.6)	2206 (59.2)	5285 (56.4)	.24
Peripheral artery disease	20 (3.0)	54 (3.4)	94 (2.5)	246 (2.6)	.42
Chronic kidney disease	84 (12.8)	247 (15.7)	455 (12.2)	1156 (12.3)	.35
History of DVT	20 (3.0)	56 (3.5)	123 (3.3)	276 (2.9)	.43
History of smoking	63 (9.6)	90 (5.7)	256 (6.9)	604 (6.4)	.37
Immune disorders					
HIV	5 (0.8)	13 (0.8)	34 (0.9)	115 (1.2)	.48
SLE	7 (1.1)	6 (0.4)	21 (0.6)	54 (0.6)	.45
Rheumatoid	7 (1.1)	17 (1.1)	45 (1.2)	105 (1.1)	.46
Other immune disorder	10 (1.5)	41 (2.6)	60 (1.6)	174 (1.9)	.45
History of pulmonary embolism	16 (2.4)	40 (2.5)	72 (1.9)	173 (1.8)	.43
Pulmonary disease					
COPD	60 (9.1)	176 (11.2)	277 (7.4)	702 (7.5)	.36
ILD	5 (0.8)	5 (0.3)	10 (0.3)	42 (0.4)	.46
Asthma	60 (9.1)	150 (9.5)	271 (7.3)	892 (9.5)	.38
Other pulmonary	26 (4.0)	72 (4.6)	78 (2.1)	163 (1.7)	.38
Organ transplant	11 (1.7)	24 (1.5)	42 (1.1)	152 (1.6)	.45
Congenital heart disease	2 (0.3)	3 (0.2)	9 (0.2)	19 (0.2)	.48
Prior CABG	14 (2.1)	59 (3.7)	116 (3.1)	231 (2.5)	.44
Prior MI	38 (5.8)	96 (6.1)	193 (5.2)	445 (4.7)	.39
Prior PCI	33 (5.0)	83 (5.3)	148 (4.0)	398 (4.2)	.40
No medical history	112 (17.1)	248 (15.7)	736 (19.8)	1608 (17.2)	.35
Treatments					
Glucocorticoid	238 (36.3)	471 (29.8)	1005 (27.0)	2574 (27.5)	<.001
Interleukin-6 agents	23 (3.5)	124 (7.9)	402 (10.8)	1124 (12.0)	.20
Remdesivir	54 (8.2)	216 (13.7)	365 (9.8)	976 (10.4)	.22
Hydroxychloroquine	297 (45.3)	458 (29.0)	1502 (40.3)	3740 (39.9)	.25
Critical illness					
ICU use	267 (40.7)	678 (43.0)	1115 (29.9)	2543 (27.1)	.29
Vasopressor	77 (11.7)	176 (11.2)	456 (12.)	1058 (11.3)	.45
Mechanical ventilation	147 (22.4)	340 (21.5)	715 (19.2)	1879 (20.1)	.11
Hemodialysis/CRRT, new	36 (5.5)	53 (3.4)	145 (3.9)	396 (4.2)	.10

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disorder; CRRT = continuous renal replacement therapy; DVT = deep vein thrombosis; HIV = human immunodeficiency virus; ICU = intensive care unit; ILD = interstitial lung disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; SLE = systemic lupus erythematosus; TIA = transient ischemic attack.

*Values represent numbers (percentage), unless otherwise specified.

†*P* value for Jonckheere-Terpstra trend test

care. Moreover, volume itself is an imperfect surrogate for burden, as has been observed in care for acute cardiovascular conditions and cardiovascular surgery.[7,14,15,18] Our hypothesis-driven metric that captures the rate of case growth as a function of a hospital's capacity may offer a more nuanced and accurate assessment of burden on hospitals. Further, our findings may explain the high CFR for certain patient groups in communities with high incidence of COVID-19

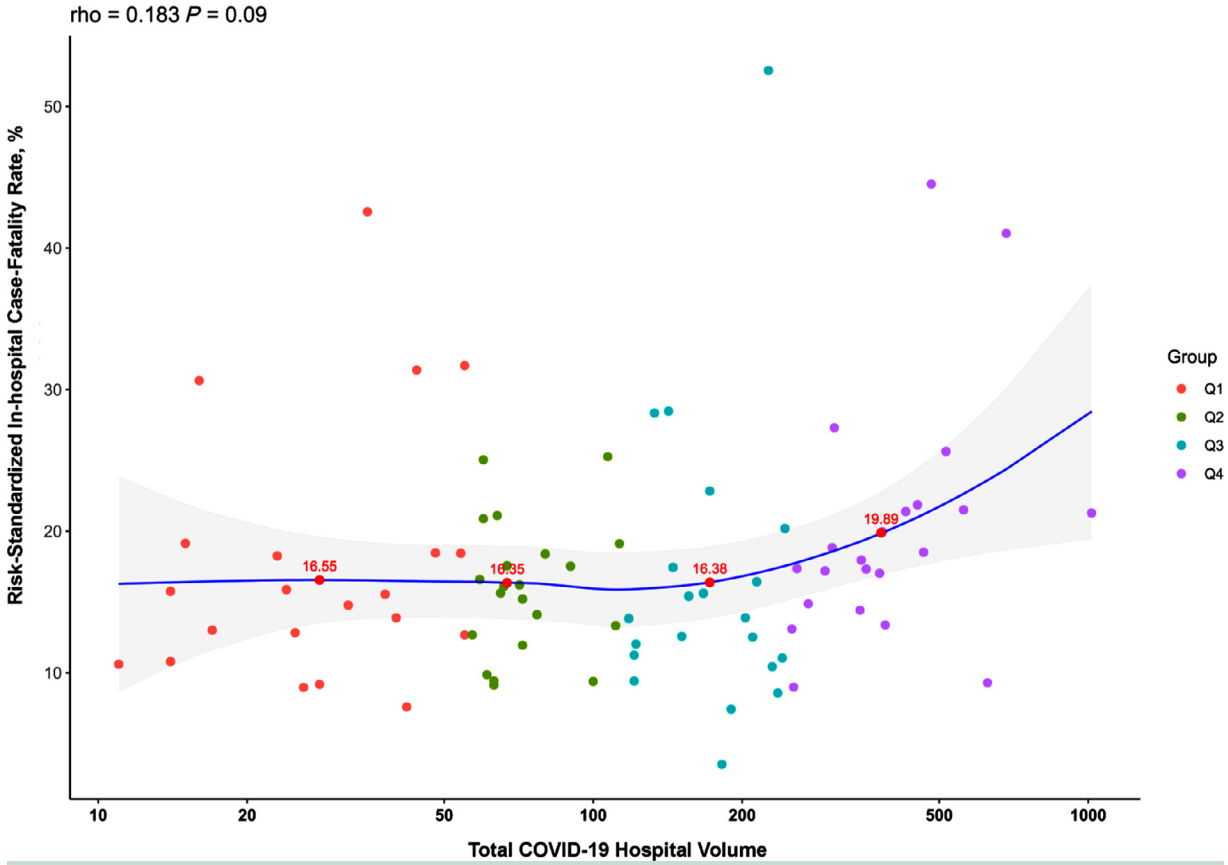

Figure 2 Correlation between COVID-19 hospitalization volume and risk-standardized in-hospital case-fatality rate. Spearman correlation for hospital volume and risk-standardized mortality is 0.18, P = .09. Labeled points represent risk-standardized in-hospital case-fatality rate for the median hospital based on volume in each quartile. COVID-19 = coronavirus disease 2019.

infections[9,12,19] because we found that racial or ethnic minorities more frequently presented to hospitals that were more rapidly approaching their capacity. These hospitals may be ideal sites for interventions aimed at reducing mortality from COVID-19 potentially through regionalization of care and sharing of staff and resources to allow continued high-quality supportive care. Further, interventions that decrease hospital length of stay,[20-22] in addition to other outcomes, may have a role in improving the hospital census and the overwhelming of capacity by rapid case growth.

Our study has certain limitations. First, our observations are limited to hospitals participating in the AHA COVID-19 CVD registry and may not be representative of all US community hospitals. However, the registry has specifically included geographically dispersed hospitals across bed capacity strata. Second, the participation of the hospitals was voluntary, and they have not yet been subject to an audit ensuring all cases were reported. However, the data entry platform was based on a familiar infrastructure that is used by other registries by the AHA in its broader Get With The Guidelines program. Third, we modeled hospital volumes using 2 standards, but there could be other unsupervised models that better capture the trajectory of the curves for each hospital's case volume. However, as we hoped to gain actionable insights from this study, we applied either existing or hypothesis-driven strategies to the choice of our exposures. Nevertheless, a better understanding of the entirety of the case volume trajectory may offer additional insights about the effect of case volumes on patient outcomes. Fourth, the registry included data through August, and the case-growth patterns in the most recent winter peak of COVID-19 cases and its association with outcomes may differ. Fifth, there could be unmeasured variation in patient features, including income and education, that are not accounted for in the models. However, our risk-adjustment models were robust and had a model discrimination of 0.73 at a patient level, suggesting successful capture of patient features that predicted outcomes. We also did not find a significant difference in patient characteristics across hospitals based on their case volumes or their use of drug therapies. Moreover, although there appear to be patterns in sensitivity analyses suggestive of a stronger volume-outcome relationship during the early part of the pandemic, we were limited by statistical power in subsetting the time period into smaller units. Sixth, we did not capture outcomes of patients after hospital discharge, limiting our ability to assess overall case fatality rates for hospitalized patients. Finally, the case volumes and case growth do not explain the majority of variation in outcomes

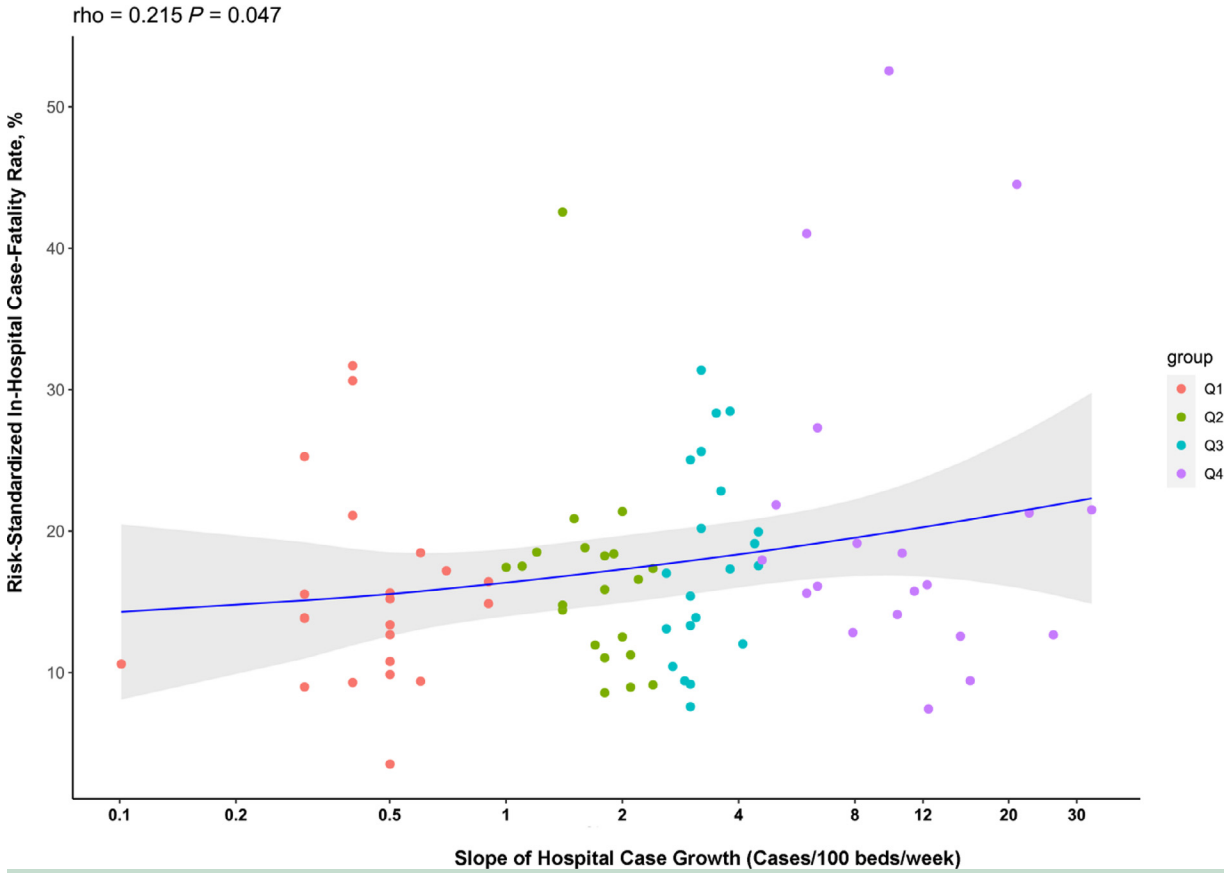

Figure 3 Correlation between COVID-19 case growth slope and risk-standardized in-hospital case-fatality rate. Spearman correlation coefficient 0.22, P = .047. The line represents the loess curve corresponding to the volume slope-outcome relationship. The units of the x-axis are cases increase per 100 beds per week and represents the average weekly case growth from the week of first case to that of the peak case volume. Labeled points represent risk-standardized in-hospital case-fatality rate for the median hospital based on case growth in each quartile. COVID-19 = coronavirus disease 2019.

across hospitals, which requires dedicated investigation into differences in other hospital care practices.

CONCLUSION

In conclusion, an accelerated case-growth trajectory is a marker of hospitals at risk of poor COVID-19 outcomes. These sites may be targets for influx of additional resources or triage strategies. Early identification of such hospital signatures that may portend poor outcomes is essential as our health system prepares for future health challenges.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2021.06.034.

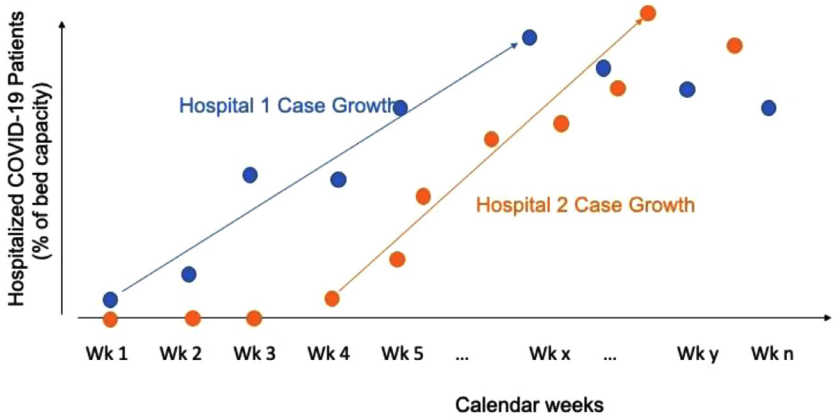
EMETHODS

Study Covariates: Patient Characteristics

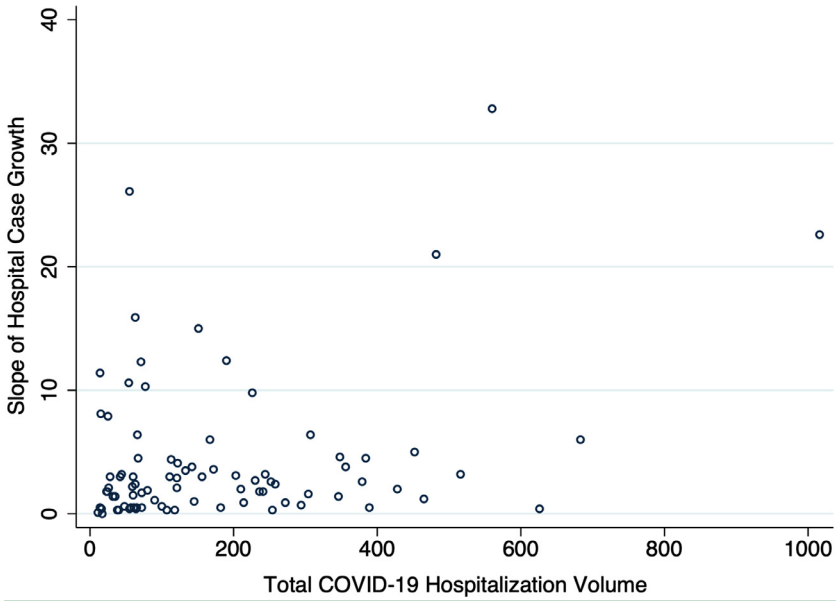
Patient characteristics included demographics (age, sex, race or ethnicity), comorbid health conditions, including cardiovascular disease (prior myocardial infraction, prior coronary artery bypass grafting, prior percutaneous coronary intervention, cerebrovascular disease, peripheral artery disease, heart failure, atrial fibrillation, atrial flutter), cardiometabolic risk factors (hypertension, diabetes mellitus, dyslipidemia), pulmonary and pulmonary vascular diseases (chronic pulmonary disease, including chronic obstructive pulmonary disease, interstitial lung disease, asthma, and pulmonary embolism), renal disease (chronic kidney disease, chronic hemodialysis), and other disorders (history of deep vein thrombosis, cancer, immune disorders including human immunodeficiency virus infection, systemic lupus erythematosus, rheumatoid arthritis, organ transplant).

Risk-Standardized In-Hospital Case-Fatality Rate

For this, we constructed logistic regression models that included in-hospital case-fatality as the dependent variable,



Supplementary Figure 1 Schematic representation of the case growth trajectory at 2 hospitals.



Supplementary Figure 2 Correlation between total hospital volume and hospital case growth slope. Horizontal axis is the total case volume, and the vertical axis is case increase per 100 beds per week and represents the average weekly case growth from the week of first case to that of the peak case volume. Spearman correlation coefficient, 0.22 (P = .046).

Supplementary Table 1 Patient-Level Covariates Included in the Risk-Adjustment Model (Model C-Statistic 0.73)

Covariates
Age
Sex
Cancer
Atrial fibrillation or atrial flutter
Cerebrovascular disease
Current hemodialysis
Diabetes mellitus
Dyslipidemia
Heart failure
Hypertension
Prior myocardial infarction
Systemic lupus erythematosus
Rheumatoid arthritis
History of pulmonary embolism
Chronic obstructive pulmonary disease
Interstitial lung disease
Asthma
Congenital heart disease
Smoking history

patient characteristics as fixed effects, and hospital site as a random effect. A hospital's risk-standardized case-fatality rate (CFR) represents a ratio of the predicted to expected rate of CFR multiplied by the overall CFR in the population. Predicted rate for the hospital based on its site-specific intercept or the mortality accounting for its own case mix and the expected rate is the overall hospital intercept representing the CFR at an average hospital with the case mix identical to the overall population. The patient-level covariates included detailed demographic characteristics and comorbid conditions selected based on a stepwise regression model applied to all comorbidities and had model c-statistic of 0.73 (Supplementary Table 1). Of note, race or ethnicity was not an independent predictor of CFR in our assessment that included comorbid conditions and was not explicitly included in the risk-adjustment model. This is consistent with observation from other studies that also found that race or ethnicity is not an independent predictor of in-hospital CFR.[9,12]

We included categorical hospital bed number (<250 beds, 250-499 beds, and ≥500 beds) as a hospital-level covariate in the model to allow standardization of outcome assessment for hospitals with different capacity and as a surrogate for their available health services and experience with high acuity conditions. To account for the expected random variation at low-volume centers, all hierarchical models employed an empiric Bayes approach that limits the impact of large random variation of estimates from centers with very few cases.[16]

Supplementary Table 2 Characteristics of Hospitals Across COVID-19 Case Growth Quartiles

	Overall	Q1	Q2	Q3	Q4	*P* Value
N	85	23	21	21	20	
Hospital Bed Size						<.001
≥500	43 (50.6)	14 (60.9)	16 (76.2)	11 (52.4)	2 (10.0)	
250-499	32 (37.6)	7 (30.4)	5 (23.8)	6 (28.6)	14 (70.0)	
<250	5 (5.9)	1 (4.3)	0 (0.0)	2 (9.5)	2 (10.0)	
NA	5 (5.9)	1 (4.3)	0 (0.0)	2 (9.5)	2 (10.0)	
Hospital Location						<.001
Rural	2 (2.4)	1 (4.3)	0 (0.0)	1 (4.8)	0 (0.0)	
Urban	78 (91.8)	21 (91.3)	21 (100.0)	18 (85.7)	18 (90.0)	
NA	5 (5.9)	1 (4.3)	0 (0.0)	2 (9.5)	2 (10.0)	
Teaching Status						.004
Major	38 (44.7)	14 (60.9)	12 (57.1)	9 (42.9)	3 (15.0)	
Minor	32 (37.6)	6 (26.1)	9 (42.9)	9 (42.9)	8 (40.0)	
Nonteaching	10 (11.8)	2 (8.7)	0 (0.0)	1 (4.8)	7 (35.0)	
NA	5 (5.9)	1 (4.3)	0 (0.0)	2 (9.5)	2 (10.0)	
Annual Hospitalizations, median (IQR)	21,358 (13,790, 30,445)	20,841 (13,930, 30,400)	27,207 (19,350, 38,147)	21,630 (14,736, 31,620)	12,962 (8796,17,324)	.002
Total hospital beds, median (IQR)	457 (262, 637)	594 (259,655)	566 (407, 841)	445 (295, 582)	274 (160,354)	.003
Average daily census, median (IQR)	331 (198, 524)	437 (212, 526)	455 (301, 646)	342 (208, 463)	178 (106, 240)	.004

COVID-19 = coronavirus disease 2019; IQR = interquartile range.

Supplementary Table 3 Characteristics of Patients Across Hospital COVID-19 Case Growth Quartiles

	Overall	Q1	Q2	Q3	Q4	*P* Values
Number of patients	15,329	3114	3318	3875	5022	
Age (mean [SD])	61.29 (17.71)	58.69 (18.12)	60.76 (18.17)	63.17 (17.38)	61.81 (17.17)	<.001
Race (%)						
Black	7643 (49.9)	1599 (51.3)	1876 (56.5)	1783 (46.0)	2385 (47.5)	.267
White	4101 (26.8)	958 (30.8)	995 (30.0)	1091 (28.2)	1057 (21.0)	
Others	3569 (23.3)	557 (17.9)	446 (13.4)	989 (25.5)	1577 (31.4)	
Missing	16 (0.1)	0 (0.0)	1 (0.0)	12 (0.3)	3 (0.1)	
Female sex	8357 (54.5)	1598 (51.3)	1776 (53.5)	2069 (53.4)	2914 (58.0)	.28
Atrial fibrillation/flutter	1407 (9.2)	299 (9.6)	349 (10.5)	403 (10.4)	356 (7.1)	.36
Cancer	2023 (13.2)	385 (12.4)	387 (11.7)	438 (11.3)	813 (16.2)	.393
Cerebrovascular disease (stroke or TIA)	1989 (13.0)	307 (9.9)	367 (11.1)	348 (9.0)	967 (19.3)	.437
Currently on dialysis	534 (3.5)	94 (3.0)	131 (3.9)	137 (3.5)	172 (3.4)	.431
Diabetes mellitus	5400 (35.2)	1191 (38.2)	1247 (37.6)	1420 (36.6)	1542 (30.7)	.264
Dyslipidemia	5215 (34.0)	1066 (34.2)	1257 (7.9)	1506 (38.9)	1386 (7.6)	.27
Heart failure	1686 (11.0)	396 (12.7)	445 (13.4)	456 (11.8)	389 (7.7)	.328
Hypertension	8863 (57.8)	1890 (60.7)	2028 (61.1)	2428 (62.7)	2517 (50.1)	.228
Peripheral artery disease	414 (2.7)	104 (3.3)	85 (2.6)	136 (3.5)	89 (1.8)	.412
Prior CABG	420 (2.7)	81 (2.6)	118 (3.6)	106 (2.7)	115 (2.3)	.424
Prior MI	772 (5.0)	209 (6.7)	206 (6.2)	210 (5.4)	147 (2.9)	.361
Prior PCI	662 (4.3)	140 (4.5)	177 (5.3)	178 (4.6)	167 (3.3)	.398
Chronic kidney disease	1942 (12.7)	448 (14.4)	429 (12.9)	538 (13.9)	527 (10.5)	.338
DVT	475 (3.1)	104 (3.3)	122 (3.7)	128 (3.3)	121 (2.4)	.413
History of smoking	1013 (6.6)	235 (7.5)	312 (9.4)	206 (5.3)	260 (5.2)	.359
Immune disorders	703 (4.6)	129 (4.1)	151 (4.6)	242 (6.2)	181 (3.6)	.416
HIV	167 (1.1)	22 (0.7)	34 (1.0)	50 (1.3)	61 (1.2)	.476
Lupus	88 (0.6)	21 (0.7)	20 (0.6)	24 (0.6)	23 (0.5)	.461
Rheumatoid	174 (1.1)	33 (1.1)	49 (1.5)	58 (1.5)	34 (0.7)	.447
Other immune disorder	285 (1.9)	60 (1.9)	53 (1.6)	120 (3.1)	52 (1.0)	.437
Pulmonary embolism	301 (2.0)	80 (2.6)	77 (2.3)	74 (1.9)	70 (1.4)	.417
Pulmonary disease	2703 (17.6)	574 (18.4)	630 (19.0)	767 (19.8)	732 (14.6)	.322
COPD	1215 (7.9)	232 (7.5)	333 (10.0)	331 (8.5)	319 (6.4)	.375
ILD	62 (0.4)	9 (0.3)	17 (0.5)	24 (0.6)	12 (0.2)	.474
Asthma	1373 (9.0)	290 (9.3)	286 (8.6)	409 (10.6)	388 (7.7)	.376
Other pulmonary	339 (2.2)	118 (3.8)	68 (2.0)	91 (2.3)	62 (1.2)	.393
Organ transplant	229 (1.5)	65 (2.1)	45 (1.4)	57 (1.5)	62 (1.2)	.432
Congenital heart disease	33 (0.2)	11 (0.4)	4 (0.1)	11 (0.3)	7 (0.1)	.471
Pulmonary arterial hypertension	57 (0.4)	27 (0.9)	8 (0.2)	19 (0.5)	3 (0.1)	.441
No medical history	2704 (17.6)	543 (17.4)	592 (17.8)	639 (16.5)	930 (18.5)	.349

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disorder; COVID-19 = coronavirus disease 2019; DVT = deep vein thrombosis; HIV = human immunodeficiency virus; ILD = interstitial lung disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; TIA = transient ischemic attack.