

## Observational Study

# Association of latitude and altitude with adverse outcomes in patients with COVID-19: The VIRUS registry

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## Abstract

### BACKGROUND

The coronavirus disease 2019 (COVID-19) course may be affected by environmental factors. Ecological studies previously suggested a link between climatological factors and COVID-19 fatality rates. However, individual-level impact of these factors has not been thoroughly evaluated yet.

### AIM

To study the association of climatological factors related to patient location with unfavorable outcomes in patients.

### METHODS

In this observational analysis of the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study: COVID-19 Registry cohort, the latitudes and altitudes of hospitals were examined as a covariate for mortality within 28 d of admission and the length of hospital stay. Adjusting for baseline parameters and admission date, multivariable regression modeling was utilized. Generalized estimating equations were used to fit the models.

### RESULTS

Twenty-two thousand one hundred eight patients from over 20 countries were evaluated. The median age was 62 (interquartile range: 49-74) years, and 54% of the included patients were males. The median age increased with increasing latitude as well as the frequency of comorbidities. Contrarily, the percentage of comorbidities was lower in elevated altitudes. Mortality within 28 d of hospital admission was found to be 25%. The median hospital-free days among all included patients was 20 d. Despite the significant linear relationship between mortality and hospital-free days (adjusted odds ratio (aOR) = 1.39 (1.04, 1.86),  $P = 0.025$  for mortality within 28 d of admission; aOR = -1.47 (-2.60, -0.33),  $P = 0.011$  for hospital-free days), suggesting that adverse patient outcomes were more common in locations further away from the Equator; the results were no longer significant when adjusted for baseline differences (aOR = 1.32 (1.00, 1.74),  $P = 0.051$  for 28-day mortality; aOR = -1.07 (-2.13, -0.01),  $P = 0.050$  for hospital-free days). When we looked at the altitude's effect, we discovered that it demonstrated a non-linear association with mortality within 28 d of hospital admission (aOR =

0.96 (0.62, 1.47), 1.04 (0.92, 1.19), 0.49 (0.22, 0.90), and 0.51 (0.27, 0.98), for the altitude points of 75 MASL, 125 MASL, 400 MASL, and 600 MASL, in comparison to the reference altitude of 148 m.a.s.l, respectively.  $P = 0.001$ ). We detected an association between latitude and 28-day mortality as well as hospital-free days in this worldwide study. When the baseline features were taken into account, however, this did not stay significant.

### CONCLUSION

Our findings suggest that differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship at the patient level.

**Key Words:** 28 d mortality; Altitude; COVID-19; Hospital-free days; Latitude; Outcomes

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**Core Tip:** We detected an association between latitude and mortality within 28 d of admission and hospital-free days in this worldwide study. When the baseline features were taken into account, however, this did not stay significant. Our findings suggest that differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship at the patient level.

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## INTRODUCTION

After being identified at the end of 2019, Coronavirus disease 2019 (COVID-19) rapidly disseminated worldwide and affected millions[1,2]. Although studies have shown the efficacy of some medications or the impact of certain conditions on the disease process[3-8], there are still unknown factors that affect the patient outcomes. The investigation of the relationship of disease severity with different environmental settings might provide better insight into the pathogenesis of COVID-19.

A link between climatological factors and Coronavirus Disease 2019 (COVID-19) fatality rates was previously suggested by ecological studies[9-13]. Geographic factors were also demonstrated to impact other respiratory infection processes[14,15]. However, these studies may be subject to the ecological fallacy, in which grouped population-level associations are not observed at the individual level[16]. Large-scale, patient-level cohort studies have thus far not evaluated associations between factors such as altitude and latitude with COVID-19 severity.

The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 registry[17-19] is a global collaboration of partners from 27 countries that provides a novel resource for the investigation of associations between altitude and latitude, with outcomes of individuals with COVID-19, allowing adjustment for baseline factors to evaluate the relationship between COVID-19 disease severity and geographical factors. Using this large cohort, we targeted to assess the relationship of altitude and latitude with unfavorable patient outcomes.

## MATERIALS AND METHODS

This study was conducted on the data collected within the scope of the VIRUS: COVID-19 registry. The project was approved as exempt by the institutional review board at Mayo Clinic (IRB:20-002610). Clinical Trials Database registration number for the registry is NCT04323787.

### Study population and data collection

All subjects hospitalized with a COVID-19 associated indication (laboratory-confirmed or clinically diagnosed infection) at participating institutions were eligible for inclusion in the VIRUS: COVID-19

registry[20]. The exclusion criteria for the VIRUS Registry study are non-COVID-19 related admissions, Minnesota patients who have not provided research authorization, and readmissions of already included patients. De-identified data were collected through Research Electronic Data Capture software (REDCap, version 8.11.11, Vanderbilt University, Nashville, Tennessee) and stored in a central database hosted by Mayo Clinic[21].

Regarding the analysis for this particular study, all adult subjects admitted between March 15, 2020, and January 15, 2021, were screened for inclusion. Although enrolled in the VIRUS: COVID-19 registry, we excluded pediatric patients (< 18 years old) from this project. Another exclusion criterion was patients enrolled from institutions reporting fewer than 65% of subjects with hospital discharge status. Since those participating centers were unlikely to represent a realistic distribution of outcomes, they were omitted as non-participating. After the application of exclusion criteria, patients of 143 participating hospitals in 21 countries were found to be eligible for inclusion. Detailed inclusion and exclusion criteria for the VIRUS Registry and this project is provided in [Supplementary Figure 1](#).

The patients' residential addresses at the time of diagnosis were not accessible due to the de-identified database. As a surrogate, the location of the participating institutions, which was available for all enrolled patients, was used to determine geographical variables. Latitude and altitude information was retrieved from the Google Earth software[22]. Based on their locations, subjects were grouped according to the elevation above the sea level and the distance from the Equator, regardless of the hemisphere of location[23,24]. Baseline information and disease-related specifics were gathered from the VIRUS Registry.

### Outcome of interest

The primary outcome was mortality within 28 d of admission, and the secondary outcome was length of hospital stay. The variable "hospital-free days" (HFD) was used to analyze the impact on hospital length of stay[25], calculated by subtracting the number of admission days from 28; which was 0 for patients who died in the hospital or stayed in the hospital for longer than 28 d. Both outcomes were evaluated independently.

### Statistical analyses

The statistical methodology was reviewed by our co-authors from the Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester.

The median and interquartile range (IQR) were used to summarize continuous data. Categorical variables were reported as numbers and percentages. Unadjusted and multivariable-adjusted logistic regression assessed the association with outcomes. To account for the clustering of patients within sites, models were fitted using generalized estimating equations using an exchangeable working correlation for individual hospitals. When the results indicated a non-linear functional structure, they were graphically summarized using the restricted cubic spline fit; otherwise, the linear relationship was defined. Age, gender, race, body mass index, number of days with symptoms prior to admission, symptom groups, the timing of admission with regards to the start of the pandemic, and comorbidities were factored into the models. Unadjusted and multivariable linear regression models assessed the association with HFD using a similar approach. Odds ratios (OR) and 95% confidence intervals for the mortality endpoint were determined per 10-degrees of latitude and 250-meters of altitude in relation to the median reference points, *i.e.*, 39° and 148 meters above sea-level (MASL), respectively. For HFD, the estimate is the expected difference in mean days, similarly displayed per 10 degrees of latitude and 250 meters of altitude.

For missing data among included institutions and patients, multiple imputations assuming data were missing at random using fully conditional specification with 100 imputations was used to impute missing covariates or outcomes. Analyses were performed on each dataset, and results combined to reflect uncertainty due to missingness. Without correcting for multiplicity related to testing the outcomes or testing both altitude and latitude in regression models, statistical significance was specified as  $P < 0.05$ .

## RESULTS

After exclusion of "non-participating sites," 23210 patients with complete data enrolled in the VIRUS registry were evaluated. Among those, 22108 met eligibility criteria after excluding pediatric patients ([Supplementary Figure 2](#), [Supplementary Table 1](#)). The median age was 62 (IQR 49-74) years, with 54% males. Among the subjects, 51% of the included were White, 26% were Black, and 65% of the patients were non-Hispanic; 86% had at least one comorbid condition, hypertension (46%) being the most prevalent. When baseline data were analyzed within latitude and altitude groups, patients were more often older on high-latitude locations (locations farther from the Equator). The frequency of patients with comorbidities and the proportion of females also increased with latitude. At higher altitudes, however, females and patients with comorbidities were less prevalent ([Table 1](#)).

**Table 1** Baseline characteristics and their distribution to latitude and altitudes

Variables	Total (n = 22108)	Latitude				Altitude		
		0-15° (n = 589)	16-30° (n = 1961)	31-45° (n = 19163)	46-60° (n = 395)	< 500 MASL (n = 21122)	500 - 1000 MASL (n = 765)	> 1000 MASL (n = 221)
Age, median, IQR	62 (49-74)	50 (36-62)	59 (47-70)	62 (49-74)	72 (59-83)	62 (59-74)	58 (46-69)	60 (49-71)
Gender								
Female	9804 (44%)	198 (34%)	797 (41%)	8626 (46%)	183 (46%)	9476 (45%)	255 (33%)	73 (33%)
Male	12025 (54%)	391 (66%)	1163 (59%)	10259 (54%)	212 (54%)	11367 (55%)	510 (67%)	148 (67%)
Race								
White	11210 (51%)	2 (0%)	471 (24%)	10449 (55%)	288 (73%)	10928 (52%)	227 (30%)	55 (25%)
African American	5757 (26%)	74 (13%)	505 (26%)	5145 (27%)	33 (8%)	5738 (27%)	17 (2%)	2 (1%)
Mixed race	785 (4%)	164 (28%)	119 (6%)	501 (3%)	1 (0%)	524 (2%)	129 (17%)	132 (60%)
Asian American	416 (2%)	-	9 (0%)	398 (2%)	9 (2%)	412 (2%)	4 (1%)	0 (0%)
Others	3940 (18%)	349 (59%)	857 (44%)	2670 (14%)	61 (15%)	3122 (15%)	371 (48%)	32 (1%)
Ethnicity								
Hispanic	4592 (21%)	88 (15%)	313 (16%)	4185 (22%)	6 (2%)	4322 (20%)	197 (26%)	73 (33%)
Non-Hispanic	14411 (65%)	354 (60%)	1250 (64%)	12571 (66%)	236 (60%)	14073 (67%)	281 (37%)	57 (26%)
BMI	29.0 (25, 35)	26.7 (24, 28)	28.0 (25, 34)	29.3 (25, 35)	26.7 (23, 32)	29.0 (25, 35)	28.6 (26, 33)	28 (26, 32)
Comorbidities (any)	18991 (86%)	295 (50%)	1580 (81%)	16753 (87%)	363 (92%)	18262 (86%)	578 (76%)	151 (68%)
Hypertension	10267 (46%)	191 (32%)	1050 (54%)	8785 (46%)	241 (61%)	9865 (47%)	322 (42%)	80 (36%)
Diabetes	6473 (29%)	134 (23%)	738 (38%)	5474 (29%)	127 (32%)	6163 (29%)	256 (33%)	54 (24%)
Coronary artery disease	4124 (19%)	29 (5%)	338 (17%)	3678 (19%)	79 (20%)	4017 (19%)	87 (11%)	20 (9%)
Obesity	3794 (17%)	34 (6%)	394 (20%)	3304 (17%)	62 (16%)	3640 (17%)	125 (16%)	29 (13%)
Dyslipidemia	3521 (16%)	7 (1%)	315 (16%)	3168 (17%)	31 (8%)	3422 (16%)	87 (11%)	12 (5%)
Chronic kidney disease	2609 (12%)	5 (1%)	233 (12%)	2295 (12%)	76 (19%)	2543 (12%)	56 (7%)	10 (5%)

BMI: Body mass index; IQR: Interquartile range; MASL: Meters above sea level.

A total of 3451 patients (25% of 13,959 patients with mortality data available) died within 28 d following admission. The median HFD for the general study population was 20 (IQR 3.0-24.0) days. The 28-day mortality rate was higher in higher-latitude locations. Mortality rates were also higher for patients hospitalized in higher altitudes. Additionally, the median HFD was lower for higher latitude and altitude levels (**Figure 1**).

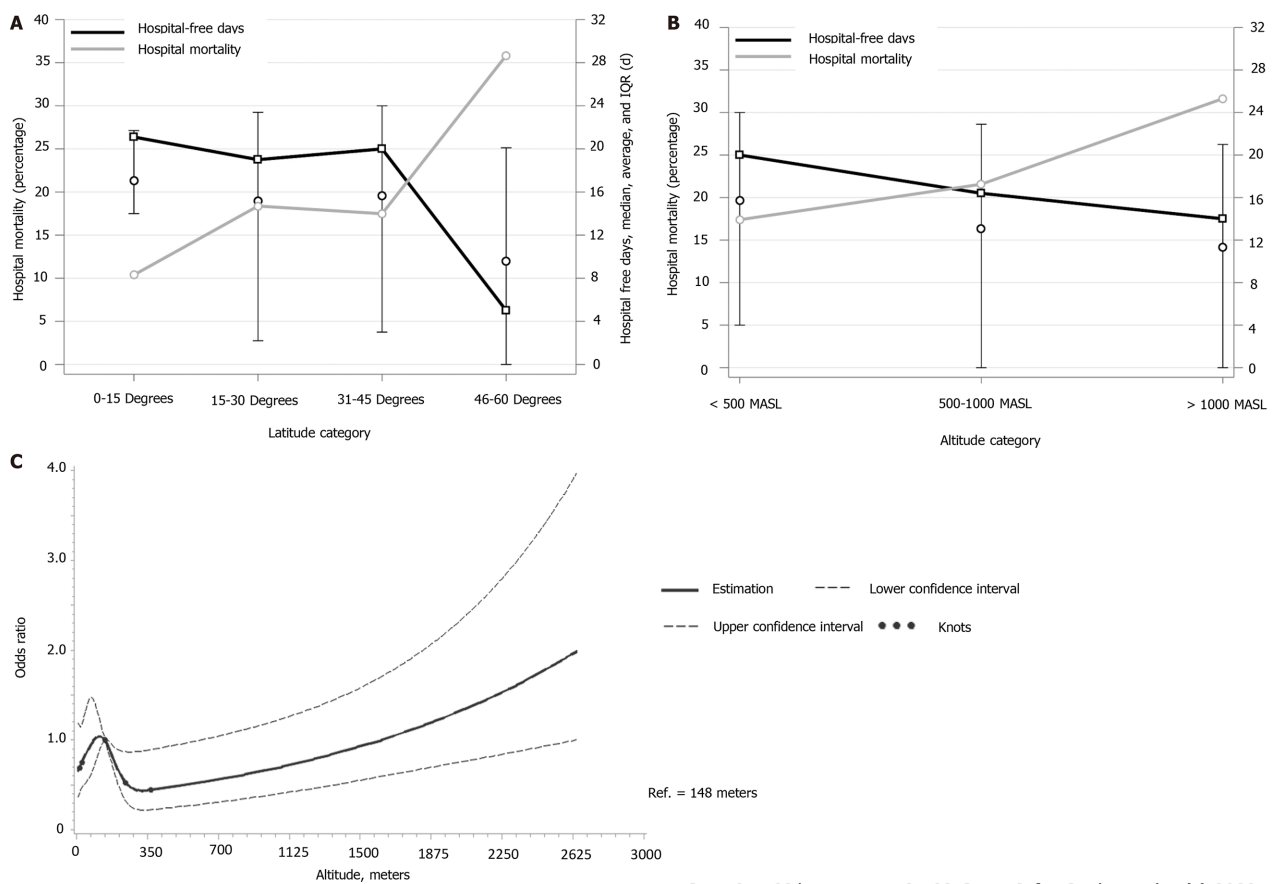
The unadjusted analysis showed a significant linear association of higher latitude locations associated with increased mortality (OR = 1.39, 95%CI = 1.04, 1.86,  $P = 0.025$ ) and lower number of HFD (Estimate = -1.47, 95%CI = -2.60, -0.33,  $P = 0.011$ ) per 10 (degree) latitude. However, after adjustment to the baseline characteristics, there was insufficient evidence to indicate a significant association with both outcomes (adjusted OR (aOR) = 1.32, 95%CI = 1.00, 1.74,  $P = 0.051$  for mortality, and adjusted Estimate = -1.07, 95%CI = -2.13, -0.01,  $P = 0.050$  for HFD) (**Table 2**).

When evaluating the impact of higher altitudes on adverse outcomes, there was a non-linear association with mortality, which remained significant after adjustment (aOR and 95%CI for the altitude points of 400 MASL and 600 MASL, compared to the reference altitude of 148 MASL were 0.49 (0.22, 0.90), and 0.51 (0.27, 0.98), respectively,  $P = 0.017$ ) (**Table 2**). The odds of fatal disease course slightly increased at altitude levels between 125 and 145 MASL; decreased to the lowest around the altitude of 350 MASL, and gradually increased after that point with the increasing altitude (**Figure 1C**). No association was present with HFD and altitude levels either before or after adjustment.

Table 2 Comparison of outcomes according to latitude and altitudes

Study outcomes	Latitude						Altitude					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
	Estimate	95%CI	P value	Estimate	95%CI	P value	Estimate	95%CI	P value	Estimate	95%CI	P value
28 d mortality	1.39	(1.04, 1.86)	0.025	1.32	(1.00, 1.74)	0.051	RCS, <i>P</i> value non-linearity $\leq 0.001$ , <i>P</i> value overall association = 0.001			RCS, <i>P</i> value non-linearity = 0.049, <i>P</i> value overall association = 0.017		
Hospital-free days	-1.47	(-2.60, -0.33)	0.011	-1.07	(-2.13, -0.01)	0.050	0.14	(-0.37, 0.64)	0.587	0.10	(0.37, 0.56)	0.683

For the altitude points of 75 MASL, 125 MASL, 400 MASL, and 600 MASL, compared to the reference altitude of 148 MASL; the adjusted odds ratios and 95% CIs regarding 28 d mortality were 0.96 (0.62, 1.47), 1.04 (0.92, 1.19), 0.49 (0.22, 0.90), and 0.51 (0.27, 0.98), respectively. CI: Confidence interval; ICU: Intensive care unit; MASL: Meters above sea level; RCS: Restricted cubic spline.



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**Figure 1** Distribution of outcomes and adjusted associations to different altitude and latitude levels. A: Outcomes and latitude; B: Outcomes and altitude; C: Adjusted associations between 28 d mortality with altitude, shown using restricted cubic spline with 5 knots. IQR: Interquartile range; MASL: Meters above sea level.

## DISCUSSION

We reported the distribution of patient outcomes to different altitudes and latitudes within an international COVID-19 registry. In our study, even though 28-day mortality increased and the number of HFD decreased in high-latitude locations on unadjusted estimates, the associations were not significant after adjustment for patients' characteristics. In the adjusted model, the odds of mortality were associated with altitude, gradually increasing after 350 MASL.



Older age and certain comorbidities were shown to be associated with unfavorable disease outcomes for COVID-19 patients[26,27]. Populations living in higher latitudes were shown to have a higher median age and more frequent comorbid conditions[28]. Furthermore, individuals living at higher elevations from the sea level were shown to have less comorbidity burdens[12]. Our study sample also noted a similar distribution of median age and comorbidities to different latitude and altitude levels.

Prior studies suggested that the variation of mortality rates in different latitude settings was partly attributable to baseline characteristics of populations[32,33]. However, others detected a relationship between humidity or sunlight exposure and case rates, which was thought to be related to viral dynamics[11,34]. In this study, the association of mortality within 28 d of admission and HFD with latitude, although statistically significant in the unadjusted analysis, was not statistically significant after case-mix adjustment. Our findings indicate that differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship with environmental factors at the individual level[16].

Studies evaluating the impact of altitude on case and fatality rates of COVID-19 illustrated that higher altitude had a protective effect, possibly due to physiological and habitual characteristics of the individuals and environmental factors impacting virus survival[12,35]. Conversely, in our study, mortality gradually increased with increasing altitude after 350 MASL, suggesting the impact of environmental hypoxia resulting in the fragility of pulmonary functions or coagulation disorders. Although our results might suggest an impact of different elevation levels on disease outcomes, not having enough variation in altitude to test the impact of atmospheric oxygen pressure impedes our ability to conclude the actual effect of higher altitudes. Thus, our analysis results should be interpreted with caution.

Studies that evaluated the effects of latitude and altitude in patients with COVID-19 were epidemiological investigations that were conducted on populations rather than on individual patients. Thus, they are subject to the bias of aggregated variables rather than providing insight for a causal relationship[16]. This is the first study to evade ecological fallacy by considering individual baseline characteristics to the best of our knowledge. Thus, it might provide a better insight into the causal effect of environmental factors on adverse outcomes.

The most important limitation was the small sample variety in lower latitude and higher altitude environments. Especially not having patients from a wide range of altitude levels precluded drawing definitive conclusions about the impact of higher altitudes. Another limitation is being conducted exclusively on hospitalized patients, which might subject our results to collider bias[36]. Although our outcomes of interest might have ameliorated this limitation's impact, it still hampers the generalizability of our results. Additionally, variations in patient management among different regions might have an impact on our results. Another weakness of our analysis is the lack of information about patients' home location (exempt IRB only allowed de-identified data use) and institutions' geographical locations as a surrogate. However, travel restrictions imposed during the study period might have kept patients confined to their primary residence and resultant nearby hospital admissions. Furthermore, although it was suggested as a contributor to disease severity, especially in higher latitudes, vitamin D levels were not incorporated in the analysis due to the unavailability. However, the timing of the study encompassing enough sunlight hours for the Northern Hemisphere might mitigate this limitation's impact. Also, the number of patients included from the countries outside of the United States was limited. Moreover, to increase the accuracy of the frequency measurement, several institutions were not included in the study due to incomplete data variables.

## CONCLUSION

Although 28 d mortality and HFD seemed to be associated with latitude, the association did not remain significant after adjustment. Our results might indicate that reported variations in COVID-19 in different environmental conditions might be based on individual patient characteristics rather than geographic factors.

## ARTICLE HIGHLIGHTS

### Research background

The coronavirus disease 2019 (COVID-19) has taken the world by storm. Several factors were attributed to the spread of the virus including altitude and latitude. We studied the relationship of location with unfavorable patient outcomes in COVID-19.

### Research motivation

There were variations in the case and fatality rates in different regions of the world. Using a large cohort, we aimed to assess if latitude or altitude had an impact on the disease course of the COVID-19

on the individual patient level.

### Research objectives

To study the association of certain aspects of location with unfavorable outcomes in COVID-19.

### Research methods

An observational study using the Virus COVID-19 Registry was used to analyze for mortality within 28 d of admission and hospital length of stay. Adjusting for baseline parameters and admission date, multivariable regression modeling was utilized.

### Research results

Twenty-two thousand one hundred eight patients from 21 countries were included. Mortality within 28 d of hospital admission was found to be 25%. The median number of hospital-free days among all included patients was 20 days. Despite the linear association between mortality within 28 d of hospital admission and hospital-free days and increasing latitude being significant, indicating that adverse disease outcomes were more frequent in locations further away from the Equator, the association was not significant after adjusting for baseline characteristics. A non-linear association between altitude and 28-day mortality was seen.

### Research conclusions

There seemed to be an association of latitude with mortality within 28 d of admission and hospital-free days, which was nonsignificant when adjusted for baseline characteristics.

### Research perspectives

The differences observed in previous epidemiological studies may be due to ecological fallacy rather than implying a causal relationship with environmental factors at the individual level.

## FOOTNOTES

**Author contributions:** Tekin A and Kashyap R prepared the first draft of this manuscript; Qamar S, Singh R, Bansal V, Sharma M, Bogojevic M, and Deo N contributed to the design of the study and the data collection; LeMahieu AM, Hanson AC, and Schulte PJ conducted the analysis of the data; Zec S, Valencia Morales DJ, Belden KA, Heavner SF, Kaufman M, Cheruku S, Danesh VC, Banner Goodspeed VM, St. Hill CA, Christie AB, and Khan SA contributed to data collection; Retford L and Boman K helped with the data retrieval; Kumar VK, O'Horo JC, Domecq JP, Walkey AJ, Gajic O, and Surani S reviewed, edited, and provided critical feedback on the manuscript.

**Institutional review board statement:** The study approval was obtained by the Mayo Clinic IRB.

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**Data sharing statement:** Data would be available from Dr. Aysun Tekin and Dr. Rahul Kashyap.

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