OBSERVATIONAL STUDY

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Causes of Death Among Medical ICU Patients With Pneumonia Due to COVID-19 in a Safety-Net Hospital

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OBJECTIVES: We sought to identify the primary causes of death of adult patients admitted to the medical ICU with symptomatic COVID-19 who ultimately suffered in-hospital mortality over the span of three major waves of COVID-19: Wild-type, alpha/epsilon, and delta.

DESIGN: Retrospective single-center cohort study from March 2020 to December 2021.

SETTING: One medical ICU in a 600-bed Tertiary Care Hospital in Los Angeles, CA.

PATIENTS: Adult ($n = 306$) ICU patients admitted with symptomatic COVID-19 who suffered in-hospital mortality.

INTERVENTIONS: None.

MAIN RESULTS: Of the 306 patients with COVID-19 who died in the hospital, 86.3% were Hispanic/Latino. The leading cause of death was respiratory failure, occurring in 57.8% of patients. There was no significant change in the rate of pulmonary deaths across the three waves of COVID-19 in our study period. The mean time from symptom onset to admission was 6.5 days, with an average hospital length of stay of 18 days. This did not differ between pulmonary and other causes of death. Sepsis was the second most common cause of death at 23.9% with a significant decrease from the wild-type wave to the delta wave. Among patients with sepsis as the cause of death, 22% ($n = 16$) were associated with fungemia. There was no significant association between steroid administration and cause of death. Lastly, the alpha/epsilon wave from December 2020 to May 2021 had the highest mortality rate when compared with wild-type or delta waves.

CONCLUSIONS: We found the primary cause of death in ICU patients with COVID-19 was acute respiratory failure, without significant changes over the span of three waves of COVID-19. This finding contrasts with reported causes of death for patients with non-COVID-19 acute respiratory distress syndrome, in which respiratory failure is an uncommon cause of death. In addition, we identified a subset of patients (5%) who died primarily due to fungemia, providing an area for further investigation.

KEY WORDS: COVID-19; death; fungemia; respiratory distress syndrome; respiratory failure

The novel severe acute respiratory syndrome coronavirus 2, the cause of the COVID-19 pandemic, was first identified in Wuhan, China in the winter of 2019 and was declared a global pandemic by March 2020. By December 2021, there were over 300 million confirmed cases of COVID-19 and over 5.5 million related deaths (1). Each wave of a new COVID-19 variant was associated with new mutations that conferred differing levels of infectivity or virulence (2).

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KEY POINTS

Question: As ICUs experienced successive waves of patients with different severe acute respiratory syndrome coronavirus 2 variants, we sought to learn if the primary cause of death among patients with COVID-19 differed across the wild-type, alpha/epsilon, and delta waves.

Findings: In this retrospective, single-center cohort study, we found the primary cause of death was respiratory failure in 57.8% of patients without significant variation across different waves of COVID.

Meanings: In contrast to non-COVID-19 acute respiratory distress syndrome, many patients with COVID-19 ultimately died from insupportable respiratory failure, prompting further study into the unique pathophysiology of COVID-19.

The clinical presentation of COVID-19 varies widely from asymptomatic carriers to respiratory distress, acute respiratory distress syndrome (ARDS), multiple organ failure, and death. Of patients admitted to the hospital with COVID-19, the mortality rate has ranged from 15% to 40% (3, 4). Despite the high burden of this disease, there have been few studies identifying the cause of death among these patients.

The aim of this study was to identify the primary causes of death among patients that were admitted to the medical ICU (MICU) with COVID-19. We also sought to evaluate how the rates and causes of mortality varied among the COVID-19 waves.

MATERIALS AND METHODS

Study Design and Setting

We performed a single-center, retrospective cohort study of all adult (> 18 yr of age) patients admitted to the MICU at Los Angeles County (LAC) + University of Southern California (USC) Medical Center, a 600-bed tertiary care safety-net hospital in LAC, between March 2020 and December 2021 with a laboratory-confirmed, symptomatic case of COVID-19, who subsequently experienced in-hospital death. There were no specific exclusion criteria. The USC institutional review board deemed this study exempt from review, according to §46.104 (d) as category (4), (submission number HS-21-00445). The management of patients with COVID-19 during the study period was at the discretion of the primary team and was based on the current global trends in management and recommendations by the Centers for Disease Control and Prevention.

Definitions and Data Collection

Clinical data including demographics, symptom onset, microbiological data, treatments, outcomes, and causes of death were extracted via manual chart review of the electronic medical record by three physician-reviewers. Using data from the World Health Organization and the California Department of Public Health (CDPH), we defined three waves of COVID-19 during the study period as follows: 1) from March 2020 to November 2020 (wild-type), 2) from December 2020 to May 2021 (alpha/epsilon), and 3) from June 2021 to December 2021 (delta) (1, 2, 5). To calculate mortality rates by COVID-19 wave, the total number of patients admitted to the ICU with COVID-19 during each wave was also collected, but no data were collected from individual patients who survived their hospitalization. Study data were recorded in Research Electronic Data Capture (6, 7).

Outcomes

The primary cause of death of each patient was the primary outcome. This was evaluated in the three COVID-19 waves which occurred during the study period. The primary cause of death was defined as the organ system that most directly led to the patient's death or the decision to withdraw life support. This definition of organ system failure was adapted from Ketcham et al (8) and is outlined in **Table 1**. This approach has been found to have excellent interrater reliability in prior studies (9). Pulmonary causes of death were further broken down into hypoxia, hypercapnia, or both. Hypoxic causes of death were defined as Spo_2 less than 88% or Pao_2 less than 55 mm Hg despite maximum support based on hospital guidelines including noninvasive ventilation, invasive mechanical ventilation, and proning/sedation where appropriate. Hypercapneic causes of death were defined as respiratory acidosis with a pH below 7.15 despite maximal ventilatory support. Similarly, sepsis was subdivided into pneumonia, bacteremia,

TABLE 1.
Definitions of Sepsis and Severe Organ System Dysfunction Adapted From Ketcham et al (8)

Pulmonary	Inability to liberate from mechanical ventilation, noninvasive ventilation, or heated high-flow nasal cannula due to inadequate oxygenation or ventilation without aforementioned support
Neurologic	Glasgow coma scale < 8, or < 6 if intubated
Renal	Either creatinine > 5.0 mg/dL or requiring hemodialysis
Cardiac	Either cardiac output < 2.0 L/min/m^2 or documented cardiogenic shock (or) reversible ventricular fibrillation or asystole
Hematologic	Either fibrinogen < 100 mg/dL, prothrombin time and partial thromboplastin time >1.5 times the upper limit of normal, or platelets < 60,000 µL
Hemorrhagic	Mean arterial pressure < 65 mm Hg for > 2 hr (or requiring vasopressors) necessitating blood transfusions and excluding other causes of hypotension
Gastrointestinal	Resectable ruptured or necrotic bowel, or pancreatitis causing mean arterial pressure < 65 mm Hg for > 2 hr (or requiring vasopressors)
Hepatic	Bilirubin > 5.0 mg/dL and albumin < 3.0 g/dL and prothrombin time or partial thromboplastin time > 1.5 times upper limit of normal
Septic	Mean arterial pressure < 65 mm Hg for >2 hr (or requiring vasopressors) attributed to either COVID-19 or other documented infection
Multiple organ failure	Presence of at least two dysfunctional organ systems

fungemia, urinary tract infection, or other/unknown based on available sputum, blood, or urine cultures. To ensure inter-reviewer reliability, the first 20 charts were reviewed by all three reviewers with complete agreement on the causes of death.

Sample Size and Power

During the study period, 3,654 adults were admitted to the hospital with a diagnosis of COVID-19, 1,876 of whom were admitted to the MICU during their hospital course. From this population, we identified a fixed sample size of 306 patients with in-hospital mortality (**eTable 1**, http://links.lww.com/CCX/B222). We, therefore, calculated the detectable effect size for estimating the relationship between pulmonary/respiratory causes of death and the three COVID-19 waves using logistic regression, with the wild-type wave as the comparator. On the basis of the data and assuming 80% power, the proportion of patients with respiratory failure of 58%, the proportion of patients in the second wave of 46.1%, an R^2 of 0.1 between covariates, and a two-sided type I error rate of 5%, we would have sufficient power to detect a two-fold increase in pulmonary deaths (odds ratio [OR] = 2.06) between the first and second waves with the available study population. Assuming the proportion of patients in the third wave is 9.2%, we can detect an effect size of OR equals to 3.97 between the first and third waves. Power was calculated using power analysis & sample size software (NCCS, LLC, Kayesville, UT).

Statistical Analyses

Demographics and clinical characteristics of the primary study population, stratified by pulmonary deaths and all other causes of death, are presented using mean and SD for continuous variables, whereas categorical variables are presented as count and frequency. Differences between groups were tested using *t* tests for continuous variables and chi-square or Fisher exact test for categorical variables, based on expected counts. A post hoc analysis comparing the subset of patients who died from fungemia to all other causes of death was performed using the same methods described above. The in-hospital mortality rates of patients admitted to the ICU in each of the three COVID-19 waves during the study period were compared using the chi-square test, with the wild-type wave as the comparator.

We compared the frequency of pulmonary/respiratory causes of death between the three COVID-19 waves using logistic regression, with the wild-type wave as the comparator. Covariates considered included age,

sex, race/ethnicity, multiple organ failure, steroid use, time from admission to death, and remdesivir use. Only those variables that were statistically significant, confounders, or improved model fit were included in the final model. A confounder was defined as any variable which, when included in the model, altered the effect size by greater than 15%. Model fit was evaluated via the Hosmer-Lemeshow goodness-of-fit test as well as inspection of residuals, deviance, and leverage and found to be acceptable. The same methods were used to create a model assessing factors associated with sepsis as a primary cause of death. A two-sided *p* value of less than 0.05 was considered statistically significant. All analyses were conducted using Stata 17 (StataCorp, College Station, TX).

RESULTS

Demographics and Clinical Characteristics

We identified 306 patients with in-hospital mortality after being admitted to the MICU with COVID-19, this population was predominantly Hispanic/Latino (86%). Demographics and clinical characteristics are presented in **Table 2**. The most common cause of death was pulmonary/respiratory in 177 (57.8%) of the cases, followed by sepsis in 73 cases (23.9%) (**Fig. 1**). Patients whose primary cause of death was respiratory were less likely to have multiple organ dysfunction present (69.5% vs 93.8%, $p < 0.001$) and were more likely to have received steroids or remdesivir when compared with all other causes of death (91.5% vs 83.7%, $p = 0.04$; 24.9% vs 8.5%, $p < 0.001$, respectively). There were no statistically significant differences by race/ethnicity, with the majority in both groups being Hispanic/Latino (84.8% vs 88.4%, $p = 0.67$). Time from symptom onset to hospital admission in both groups was approximately 6.5 days ($p = 0.77$), and time from admission to death was approximately 17 days in both groups ($p = 0.27$).

Hospital Mortality

Figure 2 depicts the total number of deaths that occurred each month during the study period as differentiated by the date of admission. Across the three waves of COVID-19, there was a statistically significant difference in the mortality rate among patients admitted to the ICU with COVID-19, ($p < 0.001$). During the wild-type wave, there was a 17% mortality among ICU admissions, compared with 25% and 6% during the alpha/epsilon and delta waves, respectively.

Causes of Death

Figure 3 displays the causes of death stratified by COVID-19 wave. **Table 3** displays the results of the multivariable model for the odds of a pulmonary cause of death according to COVID-19 wave. We observed a nonsignificant and independent increase in respiratory deaths in both the second (OR = 1.29; 95% CI, 0.78–2.14; $p = 0.33$) and third waves (OR = 1.56; 95% CI, 0.66–3.73; $p = 0.31$) compared with the first wave; a test for trend was nonsignificant ($p = 0.22$). **eTable 2** (http://links.lww.com/CCX/B222) depicts the breakdown of hypoxic versus hypercapneic versus mixed respiratory causes of death. The odds of death due to sepsis were statistically significantly lower during the third, but not the second, COVID-19 wave, after adjusting for remdesivir use and respiratory deaths. Specifically, the second wave demonstrated a nonsignificant 37% decrease in the risk of sepsis death (OR = 0.63; 95% CI, 0.36–1.13; $p = 0.12$, **eTable 3**, http://links.lww.com/CCX/B222), whereas the odds of death due to sepsis were reduced by 83% in the third wave (OR = 0.17; 95% CI, 0.04–0.78; $p = 0.02$) as compared with the first wave. Remdesivir use was associated with increased odds of pulmonary death and reduced odds of sepsis death (OR = 3.91; 95% CI, 1.88–8.15; $p < 0.001$; OR = 0.41, 95% CI, 0.18–0.95; $p = 0.04$).

We identified a clinically significant cohort of patients ($n = 16$, 5% of the total cohort) whose primary cause of death was fungemia. A post hoc analysis was performed comparing clinical characteristics of this group to the remainder of the study population (**eTable 4**, http://links.lww.com/CCX/B222). Multiple organ failure at the time of death was more prevalent among this patient group (100%) compared with those who died of all other causes (78.6%, $p = 0.05$). In addition, time from admission to death was borderline significantly longer in those who died due to fungemia compared with those who died from all other causes (23.1 ± 11.8 d vs 17.1 ± 12.4 d, respectively, $p = 0.06$). During their clinical course, all 16 patients were on at least one vasopressor, had a central venous catheter present, and received invasive mechanical

TABLE 2.
Demographics and Clinical Characteristics of the Study Population Stratified by Death Due to Pulmonary Causes

Variable[a]	All Other Deaths (*n* = 129)	Pulmonary Deaths (*n* = 177)	*p*[b]
Age	70.0 ± 13.6	65.7 ± 15.5	0.324
Sex			0.185
Female	45 (34.9)	75 (42.4)	
Male	84 (65.1)	102 (57.6)	
Race/ethnicity			0.666
White	2 (1.6)	7 (4.0)	
Hispanic	114 (88.4)	150 (84.8)	
Black	6 (4.7)	6 (3.4)	
Asian	5 (3.9)	10 (5.6)	
Not documented	2 (1.6)	4 (2.3)	
Time from symptom onset to hospitalization (d)[c]	6.5 ± 4.7	6.6 ± 5.1	0.770
Time from admission to death (d)	16.5 ± 12.5	18.1 ± 12.3	0.271
Multiple organ failure at death			< 0.001
No	8 (6.2)	54 (30.5)	
Yes	121 (93.8)	123 (69.5)	
Steroids			0.036
No	21 (16.3)	15 (8.5)	
Yes	108 (83.7)	162 (91.5)	
Convalescent plasma			0.923
No	112 (86.8)	153 (86.4)	
Yes	17 (13.2)	24 (13.6)	
Remdesivir			< 0.001
No	118 (91.5)	133 (75.1)	
Yes	11 (8.5)	44 (24.9)	
Tocilizumab			0.149
No	127 (98.5)	169 (95.5)	
Yes	2 (1.6)	8 (4.5)	
Therapeutic anticoagulation			0.978
No	53 (41.1)	73 (41.2)	
Yes	76 (58.9)	104 (58.8)	
Hydroxychloroquine			0.312
No	128 (99.2)	173 (97.7)	
Yes	1 (0.8)	4 (2.3)	

[a]Numeric variables are presented as mean ± SD while categorical variables are presented as count (frequency).
[b]*p* values were obtained using *t* test, Pearson's chi-square, or Fisher exact test.
[c]Missing 20 patients among other causes and 11 patients among pulmonary deaths.

ventilation. The average number of days between ICU admission and positive fungal blood culture result was 19.1 + 11.3 days. All patients had positive fungal blood cultures within 72 hours of death. All patients with fungemia grew *Candida* species in their blood, with multiple species identified, including: *Candida*

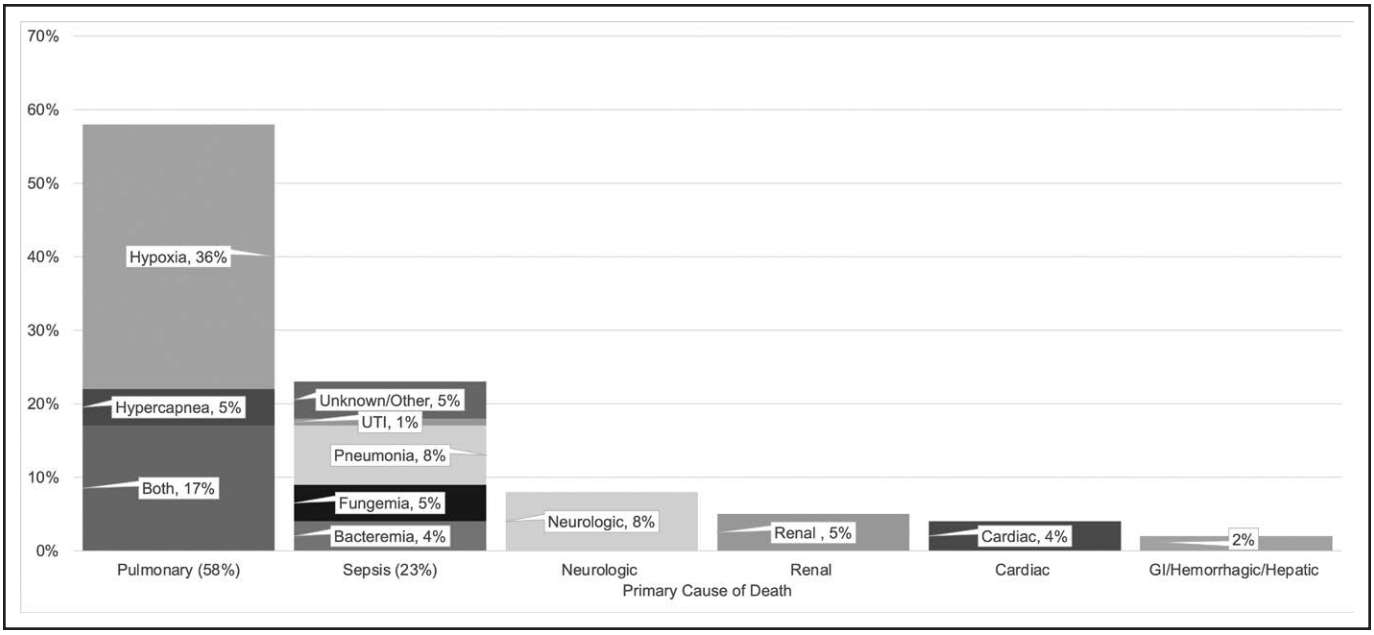

Figure 1. Causes of death among patients with COVID-19 admitted to the MICU from March 2020 to December 2021. MICU = medical ICU, UTI = Urinary tract infection identified by positive urine culture.

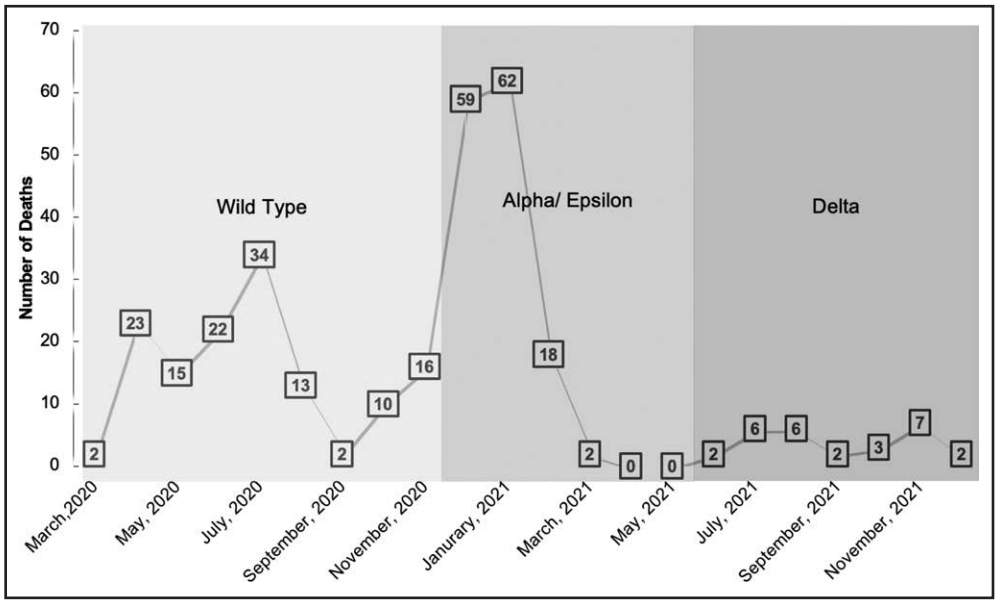

Figure 2. Total ICU deaths due to COVID-19 per month in a single safety-net hospital.

albicans, *Candida glabrata*, *Candida krusei*, *Candida orthopsilosis*, and *Candida tropicalis* (**eFig. 1**, http://links.lww.com/CCX/B222).

DISCUSSION

In this retrospective cohort study of adults admitted to the MICU with COVID-19, we found the majority of deaths were due to respiratory failure (57.8%). These findings support those of Ketcham et al (8), who had similar results, (56%), in a cohort that was predominantly black. Our study confirms these findings in a different, primarily Hispanic/Latino patient cohort, and demonstrates their persistence beyond the initial wild-type wave through the delta wave. These findings are notable, as previous studies examining causes of death in patients with non-COVID-19 ARDS identified the most common cause of death as sepsis, with respiratory failure contributing to only 13–22% of deaths (9, 10). The exact mechanism that may differentiate COVID lung injury from traditional ARDS is unclear; however, previous studies have histologically identified increased viral and inflammatory-mediated alveolar destruction and significantly increased rates of capillary microthrombi and intussusceptive angiogenesis within the lungs of COVID patients compared with other viral infections (11, 12).

In LA County, 68.8% of the adult population received 1 or more COVID vaccine doses through the alpha/epsilon wave, this rate increased to 85.2% during

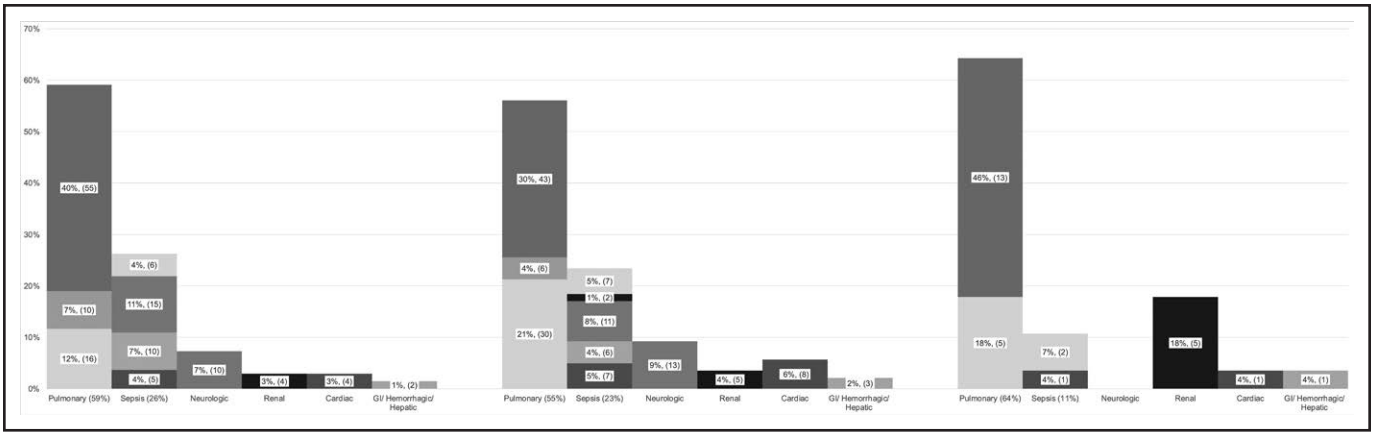

Figure 3. Causes of death among COVID-19 patients by wave of COVID-19. The pulmonary causes are subdivided from top to bottom as: hypoxic, hypercapneic, and both. There were no purely hypercapneic cases during the delta wave. Sepsis was subdivided from the top down as: other/unknown, urinary tract infection, pneumonia, fungemia, and bacteremia. There were no urinary tract infections during the wild wave. The delta wave sepsis was caused by only "other/unknown" and bacteremia.

the delta wave (13). Despite the increased prevalence of COVID vaccination, the rate of pulmonary causes of death did not vary significantly between waves. However, the overall mortality rate from COVID-19 was significantly lower by the third wave, so it may be that vaccinations and COVID-19 treatments decreased COVID-19-related organ failures and mortality equally across all organ systems. Pulmonary causes of death were also associated with the use of steroids. This association likely reflects our hospital's early adoption of steroids as a treatment modality for COVID-19, with 89% of our patients receiving steroids. Our statistical models demonstrated a significant association between increased pulmonary deaths and the use of remdesivir. These results are likely confounded by the fact that our hospital frequently used remdesivir as a salvage therapy.

Although the majority of our COVID-19-associated deaths were due to respiratory failure, 23% of our patients died of sepsis, similar to the findings by Ketcham et al (8) in 2021 of 27% mortality from sepsis. Previously reported rates of sepsis mortality in patients with ARDS range from 29% to 50% (9, 10, 14). We appreciated a significant decrease in the rate of sepsis mortality between the wild-type wave and the delta wave. It is unclear what mechanism explains the decreased rate of death due to sepsis by the delta wave, but it may be due to heightened surveillance for coinfections as we learned more about the disease process.

We found a relatively high rate of mortality from fungemia in our study cohort, approximately 5% of deaths. Previous studies have appreciated an approximately 8% incidence of secondary fungal bloodstream infections among critically ill patients with COVID-19. These studies; however, only identified coinfections and did not comment on causes of death (15, 16). Patients who died of fungemia-related sepsis had high illness severity; all were on invasive mechanical ventilation, required vasopressors, and had multiple organ failure present at the time of positive fungal blood culture and at the time of death. Fungal blood cultures first resulted positive approximately 20 days into ICU admission, and the average duration of fungemic patients' ICU stay was longer than those who died of other

TABLE 3.
Multivariable Model for Odds of Pulmonary Cause of Death ($n = 306$)

Variable	OR	95% CI	p^a
Wave			
Wild type	Referent	–	–
Epsilon/alpha	1.29	0.78–2.14	0.327
Delta	1.56	0.66–3.73	0.313
p for trend	–	–	0.221
Remdesivir			
No	Referent	–	–
Yes	3.91	1.88–8.15	< 0.001

OR = odds ratio.
[a]*p* were obtained using multivariable logistic regression. Variables shown are mutually adjusted.
Dashes indicate no value.

causes. Interestingly, although we did not prospectively limit ourselves to *Candida* species, no other fungal species were isolated in blood cultures in our study cohort. Due to a limited sample size and high utilization of systemic corticosteroids at this institution even in the early days of the pandemic, we were unable to fully evaluate whether steroid administration was associated with these deaths. It is unclear if fungal prophylaxis may have a role in this population—further studies would be needed to evaluate this possibility.

This study spanned from March 2020 to December 2021, covering three major waves of COVID-19 (wild-type, alpha/epsilon, and delta) and one regional COVID-19 wave, the epsilon wave. We found a significantly higher mortality rate during the alpha/epsilon wave from December 2020 to May 2021. During this wave, mortality was 25% for COVID-19 patients who required ICU admission, as compared with 17% during the initial wave and 6% during the delta wave. Numerous potential explanations for the difference in the mortality rates exist, including more effective COVID-19 treatments, vaccinations, and intrinsic differences in strain virulence. Interestingly, Hohl et al (17) noted that, after the wild-type wave, there was a higher threshold to admit COVID-19 patients to the ICU, resulting in a significantly sicker ICU cohort after the initial wave. The higher mortality during the alpha/epsilon wave may also be related to increased ICU strain. The Severe Acute Respiratory Infection Preparedness group identified high rates of ICU stress from December 2020 to March 2021, with significantly less ICU stress in LA County during the delta wave (18).

Although we do not have the exact variant breakdown of our cohort, per the CDPH, a unique wave of COVID-19 known as the epsilon variant coexisted with the alpha wave in California from December 2020 to March 2021. At its peak in January and February 2021, the epsilon wave was responsible for up to 74% of cases of COVID-19 in California (2). When performing secondary analyses of our data, we merged the California-specific epsilon wave (from December 2020 to March 2021) with the globally predominant alpha wave (from December 2020 to May 2020). Interestingly, during April and May 2021 (alpha wave), our hospital experienced zero COVID-19-associated in-hospital deaths among ICU patients (Fig. 2). These findings, although certainly not definitive, suggest the possibility that California's high COVID-19 mortality during the winter of 2020–2021 may have been driven primarily by the epsilon variant.

Our study has several limitations. First, the single-center nature and relatively small sample size limit generalizability. However, this study is substantially larger than the only other study of causes of death in COVID-19 and comes to similar conclusions despite evaluating a different patient population, strengthening our confidence in the results (8). Second, when identifying each wave of COVID-19, we relied on global and statewide data as opposed to hospital-specific or patient-specific data, which were not available. Furthermore, there may be some subjectivity in the identification of the primary cause of death. We attempted to minimize subjectivity by using a standardized protocol that has been validated by several previous studies and by checking for interrater reliability (8). In addition, given the retrospective nature of this study, we were unable to make definitive conclusions on how the use of specific treatment modalities such as remdesivir or steroids influenced the primary causes of death. Similarly, due to the retrospective nature, we have incomplete data regarding potentially relevant comorbidities (**eTable 5,** http://links.lww.com/CCX/B222). Lastly, when evaluating fungal causes of death, we limited ourselves to fungemia and did not evaluate fungal pneumonias separately given the well-documented difficulties in determining the pathogenicity of fungal elements isolated in respiratory cultures, particularly *Aspergillus* (19). Thus, the fungal burden of disease may be higher than reported.

Conclusions

In conclusion, we identified the most common cause of death among critically ill adults with COVID-19 as pulmonary through three distinct waves of COVID-19. The significant number of pulmonary-related deaths, which persisted even after the development of effective COVID-19 vaccines and treatments, highlights the burden of pulmonary disease from COVID-19 and the importance of identifying and implementing appropriate treatment regimens for COVID-19-related pneumonia and ARDS. Given the number of

sepsis-related deaths, infection control for critically ill patients admitted to ICUs should be a priority. Finally, the relatively high rate of fatal fungemia should be further studied, as the recognition, prompt treatment, and potential use of prophylaxis may improve outcomes in this patient population, but additional studies are needed to test this hypothesis.

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