Original Article

Incidence and inhospital outcomes of coronavirus disease 2019-associated pulmonary aspergillosis in the United States

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Abstract:

OBJECTIVE: The aim of this study was to estimate the predictors, associations, and outcomes of COVID-19-associated pulmonary disease (CAPA) in the United States.

STUDY DESIGN AND METHODS: This retrospective cohort study was performed by using the National Inpatient Sample Database 2020 to identify coronavirus disease 2019 (COVID-19) and CAPA hospitalizations. Baseline variables and outcomes were compared between COVID-19 hospitalizations without aspergillosis and those with aspergillosis. These variables were then used to perform an adjusted analysis for obtaining predictors and factors associated with CAPA and its inhospital mortality.

RESULTS: Of the 1,020,880 hospitalizations identified with the principal diagnosis of COVID-19, CAPA was identified in 1510 (0.1%) hospitalizations. The CAPA cohort consisted of a higher proportion of males (58%) as well as racial and ethnic minorities (Hispanics, Blacks, and others [including Asian or Pacific islanders, native Americans]). Inhospital mortality was significantly higher (47.35% vs. 10.87%, $P < 0.001$), the average length of stay was longer (27.61 vs. 7.29 days, $P < 0.001$), and the mean cost per hospitalization was higher ($121,560 vs. $18,423, $P < 0.001$) in the CAPA group compared to COVID-19 without aspergillosis. History of solid organ transplant, chronic obstructive pulmonary disease, and venous thromboembolism were associated with higher odds of CAPA among other factors. The use of invasive mechanical ventilation (adjusted odds ratio [aOR] 6.24, $P < 0.001$), acute kidney injury (aOR 2.02, $P = 0.028$), and septic shock (aOR 2.07, $P = 0.018$) were associated with higher inhospital mortality in the CAPA cohort.

CONCLUSION: While CAPA is an infrequent complication during hospitalizations for COVID-19, it significantly increases all-cause mortality, prolongs hospital stays, and leads to higher hospital expenses compared to COVID-19 cases without aspergillosis.

Keywords:

Aspergillosis, coronavirus disease 2019, outcome

In 2020, 20,063,033 people were diagnosed with coronavirus disease 2019 (COVID-19) in the United States.[1] Among patients hospitalized with COVID-19, the commonly observed complications included acute respiratory distress syndrome, arrhythmias, acute cardiac injury, heart failure, and acute kidney injury.[2] However, a smaller subgroup of patients developed a serious complication of COVID-19 known as COVID-19-associated pulmonary disease (CAPA), which is associated with a poor prognosis.[3,4]

While invasive pulmonary aspergillosis is typically seen in immunocompromised individuals, CAPA has been identified in immunocompetent hosts with

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COVID-19.[3,5] Although several case reports, case series, and retrospective cohort studies have documented cases of invasive aspergillosis in COVID-19 patients, comprehensive large-scale data on its epidemiology remain limited, with existing evidence primarily derived from small case series, reports, and observational studies mostly from Europe.[6-10]

With this study, we aim to present an overview of the epidemiology, clinical, and socioeconomic outcomes of CAPA by utilizing an administrative database, the National Inpatient Sample (NIS), for 2020. The NIS collects discharge data from a representative 20% sample of hospitals in the United States. This data source is particularly valuable for studying conditions with low incidence and prevalence, enabling the calculation of nationally representative estimates.

Methods

Data source

This retrospective cohort study aimed to investigate the factors associated with the diagnosis of CAPA and inhospital mortality. In addition, the study examined the relationship between CAPA and other socioeconomic and hospital-level factors, such as the length of stay and hospitalization cost. The study utilized the NIS database for 2020, which was developed for the Health-care Cost and Utilization Project sponsored by the Agency for Health-care Research and Quality. The NIS is a publicly available All-Payer Database of inpatient hospitalizations in the United States, providing nationally representative estimates of hospital inpatient stays. It contains a stratified sample of approximately 20% of all discharges from community hospitals in the country, estimating more than 35 million hospitalizations annually. Each observation in the database represents a hospitalization with one primary diagnosis, up to 39 secondary diagnoses, and 25 procedure diagnoses, coded using the International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) codes. The NIS data are depersonalized, and individual identities are protected. As the study used the NIS database, it was exempt from review by the Institutional Review Board.

Study population

The study identified COVID-19 hospitalizations in 2020 from April to December, using the ICD-10-CM code U07.1, and the subgroup with aspergillosis was identified using appropriate ICD-10-CM codes listed anywhere except the primary diagnosis column. Since U07.1 came into effect in April 2020, we excluded admissions before April.

Baseline variables and comparison groups

Baseline variables included demographic characteristics such as age, sex, median household income, and race, with categories of whites, Blacks, Hispanics, and others (including Asian or Pacific Islanders, and Native Americans). Comorbidities (asthma, chronic obstructive pulmonary disease, history of hematopoietic stem cell transplantation, solid organ transplantation, and obesity) and complications (acute kidney injury, acute respiratory failure, acute myocardial infarction, venous thromboembolism, disseminated intravascular coagulation, and septic shock) were identified using the ICD-10-CM codes and the Charlson Comorbidity Index. The study also investigated the utilization of various procedures, such as noninvasive ventilation, invasive mechanical ventilation, extracorporeal membrane oxygenation, and hospital characteristics, including teaching status and primary payer. These baseline variables were compared between COVID-19 hospitalizations with and without aspergillosis. The ICD-10-CM codes used in the study are listed in e-Appendix 1 in the supplemental materials section. The baseline characteristics and outcomes were compared between two groups (i.e., COVID-19 with and without aspergillosis). The results were reported as percentages and mean ± standard deviation for categorical and continuous variables, respectively.

Statistical analysis

The provided weights were used to generate national estimates using the methodology provided by the Health-care Cost and Utilization Project.[11] These variables were then utilized to perform adjusted analyses for predictors and factors associated with aspergillosis in COVID-19 admissions and their inhospital mortality. First, univariable logistic regression was performed on various demographic characteristics, comorbid conditions, and complications during hospitalization. Significant variables with a cutoff $P = 0.2$ were then utilized to build a multivariable logistic regression model to estimate predictors and associations of COVID-19-associated aspergillosis and inhospital mortality. The results are reported as adjusted odds ratio (aOR), 95% confidence interval, and P value. The analyses were performed using Stata software version 15.1 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

In 2020, there were 1,020,880 admissions for COVID-19 nationwide, of which 1510 (0.1%) were associated with CAPA. There was no difference between the mean age for cohorts of COVID-19 with and without aspergillosis (64.90 years vs. 64.77 years, $P = 0.861$). Although most of the admissions in both cohorts belonged to the 61–80 years age group, the proportion of admissions in this age group was higher, and the extreme

age groups lower in COVID-19 with aspergillosis than those without aspergillosis (61–80 years: 51.66% vs. 44.36%, 18–40 years: 3.64% vs. 8.36%, and >80 years: 12.91% vs. 18.51%, respectively, $P < 0.001$). Males comprised a higher percentage in CAPA than in COVID-19 without aspergillosis (58.28% vs. 52.69%, $P = 0.045$). While whites comprised a majority of admissions in both cohorts, the proportion of racial minorities was higher in the cohort with CAPA compared to COVID-19 without aspergillosis (Hispanics, Blacks, and others [including Asian or Pacific islanders and native Americans], 26.96% vs. 20.54%, 19.80% vs. 18.09%, and 12.63% vs. 8.24% respectively, $P < 0.001$).

The proportion of admissions between July and September was higher in CAPA than in COVID-19 without aspergillosis (33.89% vs. 24.53%, respectively, $P < 0.001$). Furthermore, admissions to teaching hospitals were higher for COVID-19 with aspergillosis than those without aspergillosis (76.82% vs. 68.48%, $P = 0.0023$). Noninvasive ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation were utilized more frequently in COVID-19 with aspergillosis than those without aspergillosis (16.23% vs. 5.65%, 66.89% vs. 9.22%, and 4.97% vs. 0.18%, respectively, $P < 0.001$ for each).

The cohort with aspergillosis compared to those without aspergillosis had a higher comorbidity burden (29.14% vs. 19.18% had a Charlson Comorbidity Index >3, $P < 0.001$) along with comorbid conditions, including chronic obstructive pulmonary disease and history of solid organ transplant (21.19% vs. 15.19%, $P = 0.003$ and 4.97% vs. 1.04%, $P < 0.001$). Complications such as acute respiratory failure, acute kidney injury, venous thromboembolism, disseminated intravascular coagulation, and septic shock were also more common in the CAPA group than in the COVID-19 without aspergillosis group [Table 1].

Outcomes

The all-cause inpatient mortality was higher for the CAPA group at 47.35% compared to 10.87% for the COVID-19 without aspergillosis group ($P < 0.001$). Most admissions with CAPA required transfer to a nursing or a rehabilitation facility (51.57%) at discharge compared to COVID-19 without aspergillosis (18.78%), and a higher proportion of COVID-19 without aspergillosis admissions had routine discharges (61.62%) than aspergillosis cohort (20.75%), $P < 0.001$.

The mean length of stay was 27.61 days for CAPA admissions, compared to 7.29 days for COVID-19 admissions without aspergillosis ($P < 0.001$). The mean total hospital charges were higher for the CAPA group than for the COVID-19 without aspergillosis group ($471,981 vs. $76,016, $P < 0.001$). The total hospital costs were similarly higher for the CAPA group than for the COVID-19 without aspergillosis group ($121,560 vs. $18,423, $P < 0.001$) [Table 1].

Predictors and associations

On a multivariable analysis, a longer length of stay (≥21 vs. ≤10 days; aOR = 12.53 vs. 11–20 vs. ≤10 days; aOR = 4.04, $P < 0.001$), invasive mechanical ventilation (aOR = 3.58, $P < 0.001$), solid organ transplant (aOR = 2.83, $P = 0.001$), disseminated intravascular coagulation (aOR = 2.06, $P = 0.043$), septic shock (aOR = 1.80, $P < 0.001$), acute kidney injury (aOR = 1.55, $P = 0.006$), venous thromboembolism (aOR = 1.53, $P = 0.015$), admission month (July to September vs. April to June, aOR = 1.49, $P = 0.012$), and chronic obstructive pulmonary disease (aOR = 1.43, $P = 0.033$) were associated with a higher risk of CAPA [Table 2].

Regarding inhospital mortality of CAPA on a multivariable logistic regression, invasive mechanical ventilation (aOR = 6.24, $P < 0.001$), septic shock (aOR = 2.07, $P = 0.018$), and acute kidney injury (aOR = 2.02, $P = 0.028$) were associated with higher odds of dying [Table 3].

Discussion

According to a meta-analysis that examined the epidemiology and outcomes of CAPA, which included 28 observational studies with a total of 3148 patients, the incidence of CAPA among all COVID-19 admissions in the intensive care unit was 10.2%, with a high mortality rate of 54.9%.[3] According to a task force that defined guidelines for diagnosis and treatment, there was a wide range in the prevalence of CAPA, ranging from 0% to 33%.[12] The lack of a specific and standardized definition for CAPA has resulted in significant variation in the reported prevalence.[12-14] Despite the identification of invasive aspergillosis as a potential complication of COVID-19, there is a scarcity of large-scale data indicating the burden of CAPA.

We identified 1510 cases of CAPA out of 1,020,880 COVID-19 hospitalizations in 2020, resulting in an incidence rate of 0.1%. This estimate is significantly lower compared to a previous large review that comprised 41 studies, which reported an incidence of CAPA to be 10.9% among 6193 COVID-19 patients and 11.1% among 5904 patients in intensive care unit-only trials.[15] To the best of our knowledge, this analysis represents the largest study conducted to date, utilizing a nationally representative database. Males were disproportionately affected by CAPA (58.28% vs. 52.69% in the cohort without aspergillosis); however, sex was not a factor associated with aspergillosis in COVID-19, which is consistent with other studies on

Table 1: Baseline characteristics of coronavirus disease 2019 admissions with aspergillosis and without aspergillosis

Variable	COVID-19 without aspergillosis (*n*=1,019,370) (%)	COVID-19 with aspergillosis (*n*=1510) (%)	*P*
Age at admission in years, mean±SD	64.77±15.95	64.90±13.18	0.861
Age group (years)			
18–40	8.36	3.64	<0.001
41–60	28.76	31.79	
61–80	44.36	51.66	
>80	18.51	12.91	
Race			
White	53.13	40.61	<0.001
Black	18.09	19.8	
Hispanic	20.54	26.96	
Others*	8.24	12.63	
Female	47.31	41.72	0.045
Quarter			
Quarter 2 (April–June)	23.9	29.24	<0.001
Quarter 3 (July–September)	24.53	33.89	
Quarter 4 (October–December)	51.57	36.88	
Median household income			
Quartile 1 (poorest)	34.41	36.12	0.369
Quartile 2	27.81	25.75	
Quartile 3	21.91	19.4	
Quartile 4 (wealthiest)	15.88	18.73	
Primary expected payer			
Medicare	52.49	50.5	0.118
Medicaid	11.54	15.95	
Private insurance	27.58	25.91	
Self-pay and other†	8.4	7.64	
Admitted to teaching hospital	68.48	76.82	0.002
Charlson Comorbidity Index			
0–1	55.58	39.74	<0.001
2–3	25.24	31.13	
>3	19.18	29.14	
Comorbidities			
Asthma	8.54	8.94	0.797
Chronic obstructive pulmonary disease	15.19	21.19	0.003
History of hematopoietic stem cell transplant	0.11	0.33	0.223
History of solid organ transplant‡	1.04	4.97	<0.001
Obesity	27.46	24.17	0.190
Complications			
Acute respiratory failure	60.65	87.75	<0.001
Acute kidney injury	24.89	63.58	<0.001
Acute myocardial infarction	7.4	8.61	0.415
Venous thromboembolism§	5.83	15.89	<0.001
Disseminated intravascular coagulation	0.22	3.31	<0.001
Septic shock	3.1	38.08	<0.001
Procedures			
Extracorporeal membrane oxygenation	0.18	3.31	<0.001
Noninvasive ventilation	5.65	16.23	<0.001
Invasive mechanical ventilation	9.22	66.89	<0.001
Disposition of patient			
Routine	61.62	20.75	<0.001
Transfer to a short-term hospital	3.31	10.06	
Transfer to a facility‖	18.78	51.57	
Home health care	15.11	16.98	
Left against medical advice	1.16	0.63	

Contd...

Table 1: Contd...

Variable	COVID-19 without aspergillosis (*n*=1,019,370) (%)	COVID-19 with aspergillosis (*n*=1510) (%)	*P*
Outcomes			
All-cause inpatient mortality	10.87	47.35	<0.001
Length of stay in days, mean±SD	7.29±7.74	27.61±21.6	<0.001
Total hospital charges in US dollars, mean±SD	76,016±141,593	471,981±562,177	<0.001
Total hospital costs in US dollars, mean±SD	18,423±31,363	121,560±136,156	<0.001

*Asian or Pacific Islanders, Native Americans, and others, †No charge, worker's compensation, CHAMPUS, CHAMPVA, Title V, and other government programs, ‡Solid organs include the heart, lung, kidney, liver, intestine, and intestine, §Both pulmonary embolism and deep-vein thrombosis, ‖Another type of facility. SNF=Skilled nursing facility, ICF=Intermediate care facility, SD=Standard deviation, COVID-19=Coronavirus disease 2019

Table 2: Factors associated with aspergillosis among coronavirus disease 2019 hospitalizations on multivariable logistic regression

Variable	aOR	95% CI (lower–upper)	*P*
Female	0.98	0.76–1.25	0.863
Race			
White		Reference	
Black	1.15	0.82–1.59	0.417
Hispanic	1.2	0.89–1.63	0.227
Charlson comorbidity index			
≤1		Reference	
2–3	1.06	0.77–1.46	0.725
≥3	1.02	0.72–1.44	0.906
Chronic obstructive pulmonary disease	1.43	1.03–1.98	0.033
Invasive mechanical ventilation	3.58	2.43–5.26	<0.001
History of solid organ transplant	2.83	1.53–5.24	0.001
Acute kidney injury	1.55	1.14–2.12	0.006
Septic shock	1.8	1.33–2.43	<0.001
Venous thromboembolism*	1.53	1.09–2.15	0.015
Disseminated intravascular coagulation	2.06	1.02–4.14	0.043
Admission month			
April–June		Reference	
July–September	1.49	1.09–2.03	0.012
October–December	1.14	0.84–1.55	0.410
Length of stay (days)			
≤10		Reference	
11–20	4.04	2.69–6.07	<0.001
≥21	12.53	8.19–19.18	<0.001

*Both pulmonary embolism and deep venous thrombosis. aOR=Adjusted odds ratio, CI: Confidence interval

CAPA.[16,17] It is widely recognized that COVID-19 has had a disproportionate impact on minority racial groups.[18] Furthermore, within the context of COVID-19, we have observed a higher incidence of CAPA among African American, Hispanic, Asian, and Pacific Islander, and other minority populations. Notably, among these minority populations, Hispanics exhibited the highest proportion of CAPA cases (26.96%), indicating that the burden of aspergillosis is even more pronounced within minority communities affected by COVID-19. However, providing an in-depth explanation for this observation falls outside the scope of the current paper. A higher proportion of CAPA admissions was observed between July and September, which could be attributed to increased awareness of aspergillosis as a complication of COVID-19 following the first wave of the pandemic; a similar trend was observed in a previous study from Europe.[19] We found a higher proportion of CAPA admissions to teaching hospitals than COVID-19 without aspergillosis (76.82% vs. 68.48%), similar to another article studying influenza-associated aspergillosis, with the likely reason being sicker patients with a greater likelihood of developing CAPA being transferred to academic centers, as well as increased awareness of CAPA in teaching hospitals.[20]

Extracorporeal membrane oxygenation has been used for severe respiratory failure in COVID-19.[21,22] Our findings demonstrate that the utilization of extracorporeal membrane oxygenation was more prevalent in CAPA admissions (3.31%), whereas it was only utilized in 0.18% of COVID-19 admissions without aspergillosis. We did not come across any specific studies that mentioned the use of extracorporeal membrane oxygenation in CAPA admissions. However, a previous British study reported that COVID-19 patients who were on extracorporeal membrane oxygenation had a 10% incidence of developing CAPA.[23] Similarly, invasive mechanical ventilation was more commonly used in CAPA (66.89%) compared to COVID-19 without aspergillosis (9.22%), which is consistent with findings from another study conducted on patients with CAPA.[5]

The burden of comorbidities was higher in the CAPA cohort than in the group without aspergillosis (29.14% vs. 19.18% had a Charlson Comorbidity Index >3, $P < 0.001$). Having more comorbid conditions predisposes to severe COVID-19,[24,25] which in turn may require more aggressive therapy such as corticosteroids and tocilizumab, which increase the risk of CAPA.[15,26] Acute kidney injury, septic shock, and disseminated intravascular coagulation are known to be serious complications that can occur in severe cases of COVID-19,[27] including CAPA, and these complications were more commonly seen in the CAPA cohort in our study. Similarly, venous thromboembolism was also more common in CAPA compared to COVID-19 without aspergillosis (63.58% vs. 24.89%; $P < 0.001$).

Table 3: Factors associated with mortality in coronavirus disease 2019-associated aspergillosis hospitalizations on multivariable logistic regression

Variable	aOR	95% CI (lower–upper)	*P*
Age (years)	1.02	1.00–1.05	0.051
Teaching versus nonteaching hospital	1.49	0.78–2.84	0.232
Noninvasive ventilation	1.83	0.82–4.06	0.140
Invasive mechanical ventilation	6.24	2.91–13.37	<0.001
Extracorporeal membrane oxygenation	3.43	0.61–19.20	0.160
Acute kidney injury	2.02	1.08–3.78	0.028
Septic shock	2.07	1.13–3.78	0.018
Length of stay (days)			
≤10		Reference	
11–20	1.82	0.77–4.28	0.172
≥21	0.58	0.24–1.41	0.231

CI=Confidence interval, aOR=Adjusted odds ratio

This could be a sign of more severe COVID-19 infection or longer hospitalization.[28] Traditionally, individuals who have received allogeneic hematopoietic stem cell and solid organ transplants, patients with hematologic malignancies or primary immunodeficiencies, those taking chronic corticosteroids, or undergoing treatment for malignancies have been acknowledged as being prone to developing invasive fungal infections.[29-31] However, there is insufficient data in the literature to determine specific risk factors for CAPA. The development of invasive aspergillosis in solid organ transplant recipients has been shown to have worse outcomes.[32-34] We found a history of solid organ transplantation in 4.97% of admissions with CAPA, compared to 1.04% of admissions without CAPA ($P < 0.001$). Furthermore, a history of solid organ transplant was observed to be associated with having higher odds of CAPA (aOR = 2.83, $P = 0.001$). Other factors associated with the development of CAPA were the use of invasive mechanical ventilation, septic shock, acute kidney injury, and disseminated intravascular coagulation, which are likely markers of severe infection and multi-organ failure in COVID-19. Chronic obstructive pulmonary disease was also associated with CAPA in our study (aOR = 1.43, $P = 0.033$). This is consistent with previous studies that show that patients with chronic obstructive pulmonary disease are at a higher risk for *Aspergillus*-related lung diseases.[35]

According to a meta-analysis published in 2021, which included a systematic review of 35 studies from January 2020 to October 2020, with data from 182 patients with CAPA and 49 patients with *aspergillus* colonization, the overall mortality rate was 52.2%.[10] Another meta-analysis published in 2022 reported a mortality rate of 42.6%.[16] In our study, the all-cause inpatient mortality was similar at 47.35%, which is significantly higher than the 10.87% mortality rate in the cohort of COVID-19 patients without aspergillosis ($P < 0.001$).

The use of invasive mechanical ventilation and the presence of complications such as acute kidney injury and septic shock were associated with higher odds of death in the CAPA cohort (aORs 6.24, $P < 0.001$; 2.02, $P = 0.028$; and 2.07, $P = 0.018$, respectively). Severe infection with both invasive aspergillosis and COVID-19 can result in organ failure, leading to acute kidney injury and disseminated intravascular coagulation.[36,37] Therefore, the development of severe infection with invasive aspergillosis in COVID-19, accompanied by multi-organ failure indicated by acute kidney injury and the need for invasive mechanical ventilation, is associated with increased odds of death. Another study has reported a higher mortality rate among patients with CAPA who required invasive ventilation during their hospital stays.[8] In a separate small study involving eight patients with CAPA, every patient required invasive mechanical ventilation, resulting in a 100% mortality rate.[38]

With an average length of stay of approximately 4 weeks, patients with CAPA likely experienced debility and deconditioning,[39] leading to a majority (51.57%) requiring transfer to a nursing or rehabilitation facility on discharge. Each hospitalization involving aspergillosis adds an additional $400,000 in costs compared to COVID-19 hospitalizations without aspergillosis. Overall, these findings emphasize the importance of recognizing and effectively managing aspergillosis in COVID-19 patients, considering its significant impact on patient outcomes, health-care resources, and financial burden.

While our study utilized a large, nationally representative database sample from the United States, it is essential to exercise caution when interpreting the results due to several limitations. First, the identification of aspergillosis relied on administrative codes, specifically the ICD-10-CM code descriptions, which introduces the possibility of misclassification bias.[40] Bronchoscopy with bronchoalveolar lavage and biomarkers (such as galactomannan and β-D-glucan) are crucial for diagnosing CAPA as they allow for the identification of invasive *Aspergillus* tracheobronchitis and provide reliable specimens for *Aspergillus* diagnostics.[12] Unfortunately, information regarding these diagnostic tools is not available in the NIS database. Therefore, we could not confirm the diagnosis of CAPA or differentiate between colonizers and noncolonizers using this database. Second, the NIS database lacks information about medication administration, which prevents us from studying the impact of corticosteroids, immunomodulatory agents, and antibiotic use on the development of COVID-19-associated aspergillosis. Furthermore, we were unable to obtain important clinical predictors of outcomes, such as whether antifungal

therapy was initiated or not, and the timing of treatment. Finally, due to the nature of this administrative database, there is a potential for inaccurate differentiation of comorbidities present on admission from complications that arise during hospitalization. Nevertheless, this study includes the largest number of patients diagnosed with CAPA, offering valuable insights into its incidence and associated outcomes.

Conclusion

This study emphasizes the significance of CAPA as a rare yet potentially severe complication of COVID-19. Although the inhospital mortality rate reported in this study is slightly lower compared to previous reports, it remains significant. Therefore, increasing awareness of CAPA is imperative to facilitate earlier diagnosis and potentially better outcomes.

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Conflicts of interest
There are no conflicts of interest.

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e-Appendix

e-Appendix 1: The e-appendix can be found in the supplemental materials section of the online article.

A. Diagnosis codes (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM])
   1. Acute kidney injury: N170 N171 N172 N178 N179
   2. Acute respiratory failure: J80 J95821 J95822 J9600 J9601 J9602 J9620 J9621 J9622 R092
   3. Aspergillosis: B440 B441 B442 B447 B448 B4481 B4489 B449 B488 B49
   4. Asthma: J4520 J4521 J4522 J4530 J4531 J4532 J4540 J4541 J4542 J4550 J4551 J4552 J45901 J45902 J45909 J45990 J45991 J8283 J45998
   5. Chronic obstructive pulmonary disease: J410 J411 J418 J42 J430 J431 J432 J438 J439 J440 J441 J449 J470 J471 J479
   6. COVID-19: U071
   7. Disseminated intravascular coagulation: D65 O45021 O45022 O45023 O45029
   8. History of hematological stem cell transplantation: Z9481 Z9484
   9. Obesity: E66*
   10. Septic shock: R6521 T8112XA
   11. Solid organ transplant: I25811 I25750 I25751 I25758 I25759 I25760 I25761 I25768 I25769 I25750 I25812 T8610 T8611 T8612 T8613 T8619 T8620 T8621 T8622 T8623 T86290 T86298 T8633 T8640 T8641 T86810 T86811 T86812 T86818 T86819 T8642 T8643 T8649 T86850 T86851 T86852 T86858 T86859 Z4821 Z4822 Z4823 Z4824 Z48280 Z48288 Z48298 Y830 Z940 Z941 Z942 Z943 Z944 Z9481 Z9482 Z9483
   12. Venous thromboembolism: I81 I820 I82210 I82211 I82220 I82221 I82290 I82291 I823 I82401 I82402 I82403 I82409 I82411 I82412 I82413 I82419 I82421 I82422 I82423 I82429 I82431 I82432 I82433 I82439 I82441 I82442 I82443 I82449 I82491 I82492 I82493 I82499 I824Y1 I824Y2 I824Y3 I824Y9 I824Z1 I824Z2 I824Z3 I824Z9 I82501 I82502 I82503 I82509 I82511 I82512 I82513 I82519 I82521 I82522 I82523 I82529 I82531 I82532 I82533 I82539 I82541 I82542 I82543 I82549 I82591 I82592 I82593 I82599 I825Y1 I825Y2 I825Y3 I825Y9 I825Z1 I825Z2 I825Z3 I825Z9 I82621 I82622 I82623 I82629 I82721 I82722 I82723 I82729 I82A11 I82A12 I82A13 I82A19 I82A21 I82A22 I82A23 I82A29 I82B11 I82B12 I82B13 I82B19 I82B21 I82B22 I82B23 I82B29 I82C11 I82C12 I82C13 I82C19 I82C21 I82C22 I82C23 I82C29 I2602 I2609 I2692 I2699 I2782 Z86711.

B. Procedure codes (International Classification of Diseases, Tenth Revision, Procedure Coding System [ICD-10-PCS])
   1. Extracorporeal membrane oxygenation: 5A15223 5A1522F 5A1522G 5A1522H 5A15A2F 5A15A2G 5A15A2H
   2. Invasive mechanical ventilation: 5A1935Z 5A1945Z 5A1955Z 0BH17EZ 0BH18EZ
   3. Noninvasive ventilation: 5A09357 5A09457 5A09557 5A09358 5A09458 5A09558.

C. Median household income values

The quartile classification of the estimated median household income of residents in the patient's ZIP code varies every year. Listed below are the dollar ranges for the study year 2020:

Year	Quartile 1	Quartile 2	Quartile 3	Quartile 4
2020	1–49,999	50,000–64,999	65,000–85,999	86,000+