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Abstract

Objective To examine age, gender, and temporal differences in baseline characteristics and clinical outcomes of adult patients hospitalized with COVID-19.

Design Retrospective cohort study using de-identified EMR from a global research network.

Setting/Participants 67,456 adult patients hospitalized with COVID-19 from the US;7,306 from Europe, Latin America, and Asia-Pacific between February 2020 and January 2021.

Results In the US cohort, compared to patients 18 to 34 years old, patients ≥ 65 had a greater risk of ICU admission ([adjusted Hazard Ratio (aHR) 1·73, 95% CI 1·58-1·90), acute respiratory distress syndrome(ARDS)/Respiratory failure (aHR 1·86, 95% CI 1·76-1·96), invasive mechanical ventilation (IMV, aHR 1·93, 95% CI, 1·73-2·15), and all-cause mortality (aHR 5·6, 95% CI 4·36-7·18). Men appeared to be at a greater risk for ICU admission (aHR 1·34, 95% CI 1·29-1·39), ARDS/respiratory failure (aHR 1·24, 95% CI1·21-1·27), IMV (aHR 1·38, 95% CI 1·32-1·45), and all-cause mortality (aHR 1·16, 95% CI 1·08-1·24) compared to women. Moreover, we observed a greater risk of adverse outcomes during the early pandemic (i.e., February - April 2020) compared to later periods. In the ex-US cohort, the age and gender trends were similar; as for the temporal trend, the highest proportion of patients with all-cause mortality were also in February - April 2020; however, the highest percentages of patients with IMV and ARDS/Respiratory failure were in August - October 2020 followed by February - April 2020.

Conclusions This study provided valuable information on the temporal trend of characteristics and outcomes of hospitalized adult COVID-19 patients in both US and ex-US. It also described the population at a potentially greater risk for worse clinical outcomes by identifying the age and

gender differences. Together, the information could inform the prevention and treatment strategies of COVID-19. Furthermore, it can be used to raise public awareness of COVID-19's impact on vulnerable populations.

Strengths and limitations of this study

- The study included COVID-19 patients from the US and outside of the US using electronic medical record data
- Summarized the 1-year temporal trend of clinical characteristics and adverse clinical outcomes of hospitalized adult COVID-19 patients between February, 2020 and January, 2021
- Identified the sub-population at potentially greater risk of worse clinical outcomes by identifying the age and gender differences
- Modelled the prognosis of hospitalized adult COVID-19 US patients using covariate-adjusted competing risks survival analyses
- Statistical capacity was limited for the ex-US analysis

Introduction

The novel coronavirus disease 2019 (COVID-19) is a newly discovered infectious viral disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The virus not only affects the respiratory system but also causes damage to other systems, and may act as a precipitating factor to worsen existing conditions, potentially leading to death.[1,2] The first human case was reported in December 2019 in Wuhan City, China.[3] World Health Organization declared the COVID-19 outbreak a public health emergency of international concern on January 30, 2020 and a pandemic on March 11, 2020.[4] As of March 22, 2021, the pandemic has resulted in over 123·6 million cases and 2·7 million deaths globally across 218 countries worldwide.[5] The first case of COVID-19 in the United States (US) was reported on January 20, 2020 in Washington State.[6,7] As of March 22, 2021, the US had the highest number of reported infections, with more than 29·9 million confirmed cases and more than 0·54 million deaths.[5] A study conducted in China found higher cases of COVID-19 among men compared to women with higher case fatality in men compared to women (2·8% vs. 1·7%).[8] Similar gender disparity in mortality has been seen in reports from Italy[9], England, and Wales.[10] The Centers for Disease Control and Prevention also reported higher fatality among older adults with 80% of all COVID-19 deaths reported in the US occurring in adults aged 65 years and older.[11]

As new COVID-19 cases have risen exponentially in the US and around the world since the start of the pandemic, there is a necessity to document the temporal changes in patient characteristics, and the impact of real-world clinical practice on outcomes including ICU admissions (US cohort only), ARDS/respiratory failure, invasive mechanical ventilation (IMV), and all-cause mortality over time among COVID-19 patients. The objectives of this study were to provide real-world

evidence on gender and age differences in COVID-19 outcomes and to understand temporal trends in outcomes among patients with COVID-19 in the US and outside of the US.

Methods

Data Source

This study used TriNetX® (www.trinetx.com), a global federated research network. The details of TriNetX database have been described in other published papers.[12-16] TriNetX network provides a dataset of electronic medical records (EMR, diagnoses, procedures, medications, laboratory values, genomic information) from different healthcare organizations (HCOs). The HCOs contributing EMR data to the TriNetX network are large academic medical institutions, specialty physician services, and community hospitals providing on average, seven years of historical patient data from both inpatient and outpatient facilities. The US analysis was conducted utilizing EMR data download from 44 different health care organizations (HCOs) covering over 61 million patients that reside predominantly in the US; the data is de-identified based on the standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which Data Sets are de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. The ex-US analysis used the federated cloud-based TriNetX network, representing 6.6 million patients from 12 HCOs in Spain, the United Kingdom (UK), Brazil, Australia, India, Malaysia, and Taiwan, as of January 31, 2021. The ex-US TriNetX platform provides aggregated counts and statistical summaries of de-identified information. Protected Health Information (PHI) or Personal Data is not available to the users of the platform. As TriNetX allows real-time access to the data, the platform was queried to generate results for this study. The network contains data that are provided by participating Health Care Organizations (HCOs), each of which represents and

warrants that it has all necessary rights, consents, approvals and authority to provide the data to TriNetX so long as their name remains anonymous as a data source and their data are utilized for research purposes. The data shared through the TriNetX platform are attenuated to ensure that they do not include sufficient information to facilitate re-identification nor allow for the determination of which HCO contributed which specific information about a patient. Within HIPAA, TriNetX has a business associate agreement (BAA) with each of the HCOs. Overall, the TriNetX EMR database includes COVID-19 patients from mixed payer types, geographies, and demographic backgrounds, representing a geographically and socioeconomically diverse population both in and outside of the US.

Study Design, Setting, and Participants

This was a retrospective observational cohort study that identified patients at their earliest episode of COVID-19 and subsequently followed up to describe their disease progression, treatment received, and outcomes using EMR. This study included patients hospitalized with COVID-19 who were at least 18 years old. COVID-19 diagnosis was defined as the first occurrence from February 1, 2020 to January 31, 2021 of any of the following: 1) positive SARS-CoV-2 ribonucleic acid (RNA) or antigen test; 2) ICD-10-CM diagnosis code U07·1, J12·81, J12·89, or J80 on or after February 2020; 3) ICD-10-CM code B97·29 or B34·2 occurring between February 1, 2020 and April 30, 2020.

Patients were excluded, if 1) first COVID-19 diagnosis occurring within the last 28 days of the available data; 2) missing data on age or gender; 3) continuous hospitalization starting > 10 days before COVID-19 diagnosis date; 4) with diagnosis or procedure codes for labor and delivery during the index hospitalization; or 5) with diagnosis codes for trauma, injury, fracture, or poisoning during the first two days of the earliest hospitalization. See Figure 1a and 1b for the

patient flow diagram for the US and ex-US analyses respectively. If a patient had multiple hospitalizations that met the study criteria, only the earliest hospitalization was included in this study.

The index date was defined as the first COVID-19 diagnosis date or hospital admission date, whichever comes earlier; the follow-up window was from the index date to the earliest of the following: the end of data availability, discharge date, or death date. Health outcomes were assessed within the duration from the first COVID-19 related hospital admission date to the earliest of the following events: hospital discharge, death, end of data, or 28 days after hospital admission.

For temporal trend analysis, patients were stratified into four time periods based on their month of index date (February 2020 - April 2020, May 2020 - July 2020, August 2020 - October 2020, and November 2020 - January 2021) for all analyses.

Variables

The primary outcomes of interest were ICU admission, ARDS/respiratory failure, IMV, and all-cause mortality (please see medical codes in eAppendix Table 1). For ex-US, ICU admission was not reported given the consideration of potential misclassification of ICU admission. To comply with the data privacy agreement, only the patient's death month is available in the US data. Thus, the patient death date was inferred from a patient's last physically present/recorded date using the following: procedure (date), diagnosis (date), encounter (end date), vital signs (date), and medication (prescribing date).[17] In the ex-US analysis, the death date was used as reported in the platform.

Patient characteristics such as demographics (age, sex, race, geographic region, and ethnicity), and calendar month of index COVID-19 hospitalization were reported. The baseline comorbid conditions were evaluated using 12-month data prior to the index date (excluding index date).

Statistical methods

The demographic and clinical characteristics of the primary cohort and sub-cohorts at the index date are summarized using descriptive statistics. Mean, standard deviation (SD), standard error (SE), and 95% confidence interval (CI) were reported for continuous variables, and counts and percentages were reported for categorical variables.

For the US cohort, the proportional sub-distribution hazard model by Fine and Gray was used for estimating the hazard ratios (HRs) and cumulative incidence function (CIF) for all four outcomes; the hospital discharge date was treated as a competing risks in estimating HRs and CIF for mortality, whereas hospital discharge and death were treated as competing risks in estimating HRs and CIF for the other outcomes.[18,19] Three separate Fine and Gray models were developed stratified by age group, gender, and index calendar month; each model used the other two main categories of risk exposure (for example, gender and calendar month in the age group model) as covariates. The other covariates in each model were race, ethnicity, US region, hypertension, diabetes (Type I and II), active cancer, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea. The cumulative incidence of selected outcomes was plotted against time from the day of admission through 28 days assuming censoring at the study end date (i.e., January 31, 2021) and stratified by gender, by age, and by calendar month. All of the US analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA.) with a two-tailed *P*-value of <0.05 considered statistically significant. As for the ex-US cohort, the

analysis was performed using a cloud-based TriNetX analytical platform. The platform provided aggregated counts and statistical summaries, but did not allow the estimation of adjusted hazard ratios and model-adjusted cumulative incidences.

As some diagnosis codes used to identify US COVID-19 patients in the study were not specific to COVID-19, we performed sensitivity analyses that include only patients with "confirmed" (at least one positive SARS-CoV-2 RNA or antigen test within 21 days of their index date) and "probable" COVID-19 diagnosis (no documented positive lab test for COVID-19 within 21 days following the index date). In the sensitivity analyses, we also examined the patient's baseline characteristics, treatment during hospitalization, and selected outcomes consistent with the 'confirmed' and 'probable' cohorts in the US, respectively. The sensitivity analysis was not available for the ex-US study due to the limitation of the TriNetX ex-US analytical platform.

Patient and Public Involvement

No patient involved.

Results

A total of 67,456 patients hospitalized with COVID-19 were identified from February, 2020 to January 2021 in the US (Figure 1a), with a mean (SD) age of 58·3(17·3) years old; 51·2% (n=34,518) were men (Table 1). The highest proportion of patients in the US cohort had their index hospitalization in November 2020 and Dec'20 (15·9% and 17·7%, respectively). The most common comorbid condition was cardiovascular disease (n=25,970, 38·5%) including patients with hypertension (n=23,272, 34·5%), followed by gastrointestinal disorders (n=15,987, 23·7%), and type II diabetes (n=14,031, 20·8%) (Table 1). The proportion of patients with chronic lung diseases was higher in women compared to men, driven by a higher proportion of asthma in women (eAppendix Table 2). The burden of comorbidities increased with age (eAppendix Table

3 in the Supplement). In the US, the proportion of White patients with index COVID-19 hospitalization increased over subsequent months with the highest proportion seen during November 2020 - January 2021; on the contrary, the proportion of African American and Hispanic patients with index COVID-19 hospitalizations decreased over subsequent months with the lowest proportion seen during November 2020 - January 2021. In the US, the index COVID-19 hospitalizations in the Northeast region was highest at the beginning of the pandemic (27·7%), followed by a subsequent drop in infection rates between May 2020 - October 2020 followed by a sharp rise in November 2020 - January 2021 (14·7%). The Midwest region of the US saw a gradual uptick in the rates of infections over the course of the pandemic with the highest rates (21·9%) seen from November 2020 - January 2021. The US patients hospitalized with COVID-19 during November 2020 - January 2021 seemed to have more cardiovascular diseases compared to the patients in the earlier months (eAppendix Table 3 in the Supplement).

The ex-US cohort included a total of 7,306 patients hospitalized with COVID-19 (Figure 1b), with 91.4% of them from Europe (eAppendix Table 4). The mean (SD) age, 61·0 (16·9), was greater than that in the US cohort, 55·1% of the cohort were men, and the 48·5% patients had their index hospitalization in February 2020 - April 2020. A detailed description of the ex-US cohort was presented in Table 1.

In the US cohort, the most commonly used medications post index were acetaminophen 45,269 (67·1%) followed by enoxaparin 33,370 (49·5%), insulin (32·7%), heparin (14·8%), aspirin (26·7%), azithromycin (23·7%), and methylprednisolone (19·8%). The most commonly-used antiviral among the US cohort was remdesivir 13,667 (20·3%). Among the ex-US cohort, the most frequently used medication post index was also acetaminophen 4,719 (64·6%), followed by azithromycin 2,842 (38·9%), hydroxychloroquine 2,119 (29·0%), methylprednisolone 1,563

(21·4%), insulin 1,476 (20·2%), dexamethasone 1,454 (19·9%), and amoxicillin 1,381 (18·9%). For additional details refer to eAppendix Tables 5 and 6 in the Supplement.

Among US patients, this study showed worse outcomes in patients ≥65 years compared to patients aged 18 to 34 years old for ICU admission (17·6% vs 7·2%; aHR 1·73, 95% CI 1·58-1·90, p<0.0001), ARDS/respiratory failure (43·1% vs 18·3%; aHR 1·86, 95% CI 1·76 - 1·96, p<0.0001), IMV (13·8% vs 5·1%; aHR 1·93, 95% CI, 1·73-2·15, p<0.0001), and all-cause mortality (9·6% vs. 0·8%; aHR 5·6, 95% CI 4·36-7·18, p<0.0001). In contrast to women, men were more often admitted to the ICU (16·9% vs 12·3%; aHR 1·34, 95% CI 1·29-1·39, p<0.0001), and were at higher risk for ARDS/respiratory failure (41·0% vs 32·8%; aHR 1·24, 95% CI 1·21-1·27, p<0.0001), IMV (13·7% vs 9·4%; aHR 1·35, 95% CI 1·32-1·45, p<0.0001), and all-cause mortality (6·1% vs 4·6%; aHR 1·16, 95% CI 1·08-1·24, p<0.0001). Moreover, we observed the highest risk of worse outcomes during the early pandemic (i.e., February 2020 - April 2020) compared to the later three time periods (May 2020 - July 2020, August 2020 - October 2020, and November 2020 - January 2021) with significantly higher aHRs for ICU admission, ARDS/respiratory failure, IMV, and all-cause mortality. The risk of ICU admission and IMV period decreased across the four time periods. The risk of ARDS/respiratory failure during the summer period of May 2020 - July 2020 were lowest among all 4 periods, while the all-cause mortality of August 2020 - October 2020 and November 2020 - January 2021 were lower, compared to the periods of February 2020 - April 2020, or May 2020 - July 2020. (Figure 2 and eAppendix Table 7 in the Supplement)

In the US analysis, the model-adjusted cumulative incidence for ICU admissions, ARDS/respiratory failure, IMV, and all-cause mortality at 7, 14, and 28 days were consistently higher among men compared to women, and among patients over 50 years of age compared to

18 - 49 years old. With respect to calendar month, the adjusted cumulative incidence for ICU admission, ARDS/respiratory failure, and IMV was markedly greater among patients with index date in February 2020 - April 2020 as compared to patients having their index COVID-19 hospital admission during the other three time periods. (Figure 3)

The ex-US analysis demonstrated similar age, and gender trends, although the data format and availability did not allow for similarly detailed analyses. Patients aged 65 years or older, compared to patients aged 18 to 49 years, had a higher incidence of ARDS/respiratory failure (31·5% vs 17·4%) and all-cause mortality (23·4% vs. 1·0%). A higher percentage of patients aged between 50-64 years old had IMV compared to the other two age groups. The differences in adverse clinical events were also evident across gender; with higher proportions of men experienced ARDS/respiratory failure (29·0% vs 23·4%), IMV (5·0% vs 2·3%), and all-cause mortality (13·8% vs 10·4%) compared to women. The proportion of patients with ARDS/respiratory failure and IMV were highest in August 2020 - October 2020 and lowest in May 2020 - July 2020. As for the temporal trend, though the highest all-cause mortality was also observed in the period of February 2020 - April 2020, the highest and lowest percentages of patients with IMV and ARS/respiratory failure were found in August 2020 - October 2020 and May 2020 - July 2020, respectively (Figure 4).

In the US analysis, the sensitivity analyses among subgroups of patients with confirmed COVID-19 diagnosis showed similar distributions of baseline characteristics, as well as comparable trends in adjusted cumulative incidence and adjusted hazard ratios for the primary outcomes of interest across age, gender, and calendar months. Similar trends were also observed in the probable cohort. Details of sensitivity analysis results are presented in eAppendix Tables 8 - 13 and Figures 1 - 6 in the supplement.

Discussion

The COVID-19 pandemic has been rapidly evolving in the US and other countries. It is critical to understand the demographic distribution and temporal trends in adverse clinical events associated with the disease such as ICU admissions, ARDS/respiratory failure, IMV, and all-cause mortality across the globe. The evidence generated from this study showed that patients ≥ 65 years seemed to have an approximately 2-fold increased risk of ICU admission, ARDS/respiratory failure, and IMV; and about a 5.6-fold increase in all-cause mortality. The 7, 14, and 28 day (post hospital admission date) adjusted cumulative incidence of these adverse clinical events was consistently higher in patients ≥ 65 years compared to those aged 18 - 49 years, suggesting elevated risk throughout the course of disease among older patients. Similar trends were observed in ex-US patients for ARDS/respiratory failure and all-cause mortality, while the risk of IMV was similar among patients aged 18 - 49 and aged 65 or over. These results were in accordance with prior reports from studies across the globe.[6,20-23]

Men had an approximate 20% - 41% increased risk of all-cause mortality, ARDS/respiratory failure, IMV, and ICU admissions compared to women. The increased risk of these clinical outcomes remained consistently higher in men over 7 - 28 days post index suggesting worse disease prognosis in men. These results were also in line with prior reports.[6,21,24-29] For example, Fried et al. showed increased mortality and morbidity associated with older age and male sex using medical claims data.[6] Palaiodimos *et al.*, reported increasing age and male sex were independently associated with worse in-hospital outcomes.[21] However, Fried's study only covered the period from February 2020 - April 2020 while the study by Palaiodimos *et al.* only included 200 patients from one medical center in New York. Our study included longitudinal data from thousands of patient lives in the US and outside of the US, thereby providing further

support for the observation that gender seemed to be a differential factor in adverse clinical outcomes. Studies from national statistical agencies across England and Wales, France, Germany, Italy, Netherlands, Portugal, Korea, and Spain also observed that men had twice the risk of death from COVID-19 using data collated by the National Institute for Demographic Studies.[20] The study conducted by Iwasaki *et al.* showed that immune responses to SARS-CoV-2 differed between men and women. Compared to women, men had higher plasma levels of innate immune cytokines and poorer T cell activation. Other studies also supported that declined T-cell response is associated with increased age. These studies could provide a possible explanation for the sex and age difference observed in this study.

Results of this study found a significantly higher cumulative rate and adjusted HR for ARDS/respiratory failure, and IMV among patients ≥ 65 years and men, in line with prior reports of hospitalized COVID-19 patients showing greater risk among these demographic subgroups.[30,31] Analysis of the trends of ICU admissions in the US and all-cause mortality over calendar months in both US and ex-US revealed that patients with index date in February 2020 - April 2020 were at increased risk of death compared to patients diagnosed in the later months. This could potentially be due to healthcare facilities being overwhelmed with the volume of COVID-19 admissions at the onset of the pandemic in some areas. In addition, limited information about COVID-19, and lack of experience in the clinical management of the disease leading to a trial and error approach using different pharmaceutical and non-pharmaceutical interventions to manage disease progression and spread, and inexperience in resource management of the healthcare staff in the early stage of COVID-19 pandemic[32-34] could have resulted in poorer outcomes among patients diagnosed at the beginning of the pandemic. Besides, the lack of SARS-CoV-2 diagnosis kits in the early pandemic could play an important

role. Thus, the diagnosis kits were likely to have been reserved for the sickest patients, with the consequence that rates of ICU admission, ARDS/respiratory failure, IMV, and death will appear higher at earlier time points. It was also possible that these trends were confounded by other unobserved patient-related or environmental risk factors.

This study was not meant to compare the US and ex-US cohorts; however, there are some differences between ARDS/Respiratory failure and IMV in temporal trend. For example, ex-US patients seemed to have a much lower ARDS/Respiratory failure and IMV in May 2020 - July 2020, compared to the US cohort. Additionally, ARDS/Respiratory failure and IMV proportion in November 2020 - January 2021 were much lower compared to August 2020 - October 2020 in the ex-US cohort; while the proportions of these two outcomes during these two periods were closer in the US cohort. This is very likely due to different non-pharmaceutical intervention for the COVID-19 pandemic (e.g., lockdown policies) implemented by each country within the ex-US cohorts as well as different response strategies each country's HCO took. Besides, there were some variations in the patient baseline characteristics of two cohorts, which may be due to the disparities in the underlying demographic distribution, and different healthcare systems across countries.

Our study has certain limitations. First, there is often a trade-off between sensitivity and specificity in defining a representative real-world cohort of COVID-19 patients. We performed a sensitivity analysis using only patients with COVID-19 specific clinical diagnosis, and patients with lab confirmation of disease. The results from our sensitivity analyses were similar to those from our primary analyses, suggesting that the potential effect of misclassification was minimal and did not impact the study conclusion. Second, compared to claims data, the EMR database may provide more timely, detailed, and accurate patient health information, but it only reflects

the patient experience in the participating healthcare systems within the research network[35,36], and the information from medical encounters before the COVID-19 hospitalization or with other doctors/providers outside the research network is not captured[36]. Third, among deceased patients, as the death information was available at a monthly level, the patients' last physically present date in the database was used to infer the death date, but this measurement error should be non-differential and bias the results towards null. Fourth, for the ex-US analysis, the statistical analysis has been built into the platform and does not allow customization, which has limited the ability to calculate statistics such as standard error, confidence interval, and model the risk. Moreover, due to data privacy, the number of COVID-19 patients contributed by each country could not be specified. Finally, though COVID-19 patients included in this study were from multiple participating HCOs in the US and outside of the US, it may not fully represent the wider population across the globe.

Conclusions

Temporal trends in adverse clinical outcomes among patients with COVID-19 from this multinational EMR database comprising of patients from diverse demographic backgrounds suggest that older age, male gender, and diagnosis in earlier months of the pandemic conferred greater risk for ICU admissions, ARDS/respiratory failure, IMV, and all-cause mortality over 7 - 28 days post index hospital admission. This evidence may be helpful in identifying patients at greater risk of these adverse clinical events, and in so doing, inform clinical interventions, and increase public awareness.

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Competing Interests:

Ying Bao, Xiu Chen, Jenny Jiang, Qian Xia, Manasi Suryavanshi, Zhongyuan Wei, and Julia Zhu are employees of Bristol Myers Squibb and hold stock or stock options at Bristol Myers Squibb.

Brian D. Bradbury, Corinne Brooks, Carolyn A. Brown, Alvan Cheng, Cathy W. Critchlow, Ajit A. Londhe, Junjie Ma, Jie Zhang are employees and stockholders of Amgen, Inc.

Olulade Ayodele, Giovanna Devercelli, Vivek Gandhi, Kathleen Gondek, Hillary A. Keenan, Sudhakar Manne, Kaili Ren, Lynn Sanders, Peter Yu, Linyun Zhou are employees and stockholders in Takeda, Pharmaceutical Company Limited.

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Patient consent for publication: Not required.

Ethical approval:

This study was approved by Observational Protocol Review Committee at Bristol-Myers Squibb Co.. This work used existing de-identified data which does not constitute research with human subjects because there is no interaction with any individual and no identifiable private information were used. No ethical approval was considered necessary.

Data sharing:

Data for this study are not publicly available; access to which is restricted on commercial terms. Please contact authors for information on data availability.

Supplemental materials: This content has been supplied by the author(s).

Figure Caption

Figure 1. Flow Diagram of US and ex-US Study Cohorts

Figure 2. The Forest Plots of Model-adjusted Hazard Ratios among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month

Figure 3. Model-adjusted Cumulative Incidence Plots of Selected Outcomes among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month

Figure 4. The Selected Outcomes among ex-US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month

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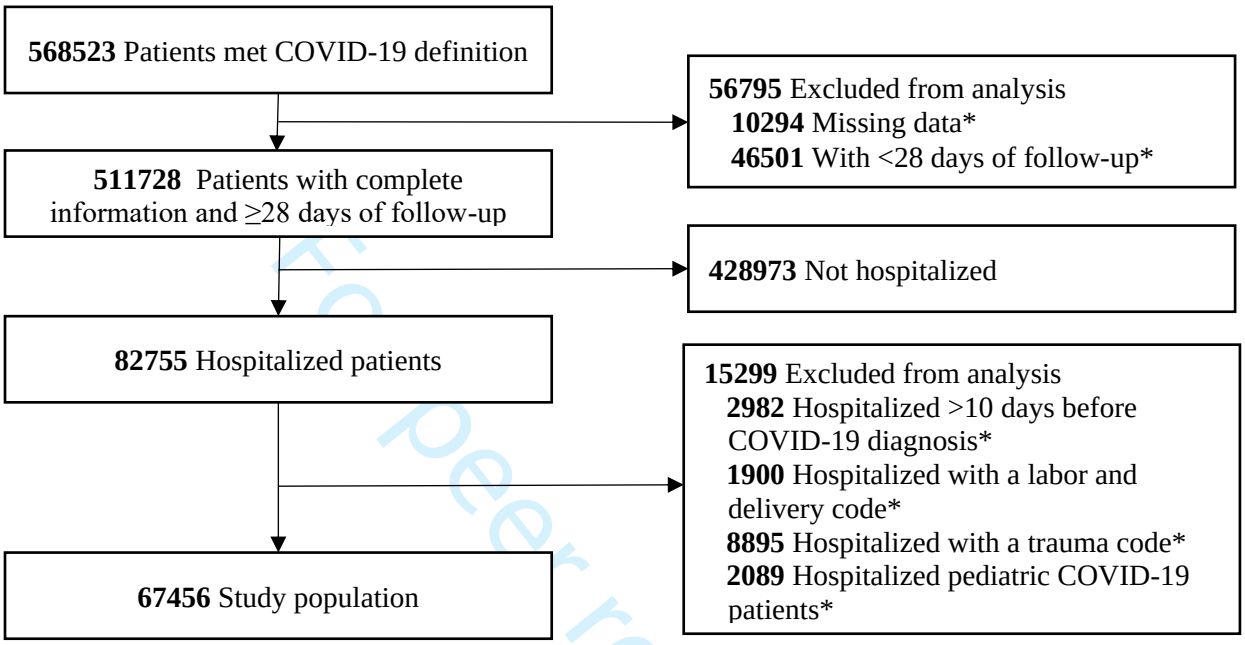
Table 1. Baseline Characteristics of US and ex-US Hospitalized Adult Patients with COVID-19

Characteristic	Patient, %	
	US Cohort (n=67456)	**Ex-US Cohort** (n=7306)
Age, Mean[SD], y	58.3(17.3)	61.0 (16.9)
Male	51.2	55.1
Race		
White	56.1	19.4
Black or African American	23.7	0.8
Asian	3.2	0.8
American Indian or Other Pacific Islander	0.9	NA
Unknown	16.1	79.0
Ethnicity		
Hispanic	24.8	NA
Month of index		
February, 2020	1.2	0.3
March, 2020	6.7	30.1
April, 2020	11.1	18.4
May, 2020	7.3	6.0
June, 2020	7.8	3.2
July, 2020	11.1	2.4
August, 2020	6.5	8.5
September, 2020	5.3	13.3
October, 2020	8.5	7.7
November, 2020	15.9	5.2
December, 2020	17.7	4.6
January, 2021	1.0	0.4
Baseline Comorbidities		
Cardiovascular disease	38.5	15.9
Hypertension	34.5	13.1
Gastrointestinal disorders	23.7	8.6
Skin disorder	12.6	5.5
Cancer	7.6	5.8
Solid tumors	5.7	4.2
Hematologic malignancies	2.6	2.5
Chronic kidney disease	12.2	4.1
Chronic lung disease	12.8	6.8
Asthma	6	2.2
Chronic obstructive pulmonary disease	7.7	4.5
Pulmonary fibrosis	1	0.5
Diabetes mellitus		
Type I Diabetes	1.6	0.4
Type II Diabetes	20.8	6.7
Liver disease	2.5	5.6

Figure 1. Flow Diagram of US and ex-US Study Cohorts

A) US Cohort



*The counts in the exclusion criteria were not mutual exclusive.

B) ex-US Cohort

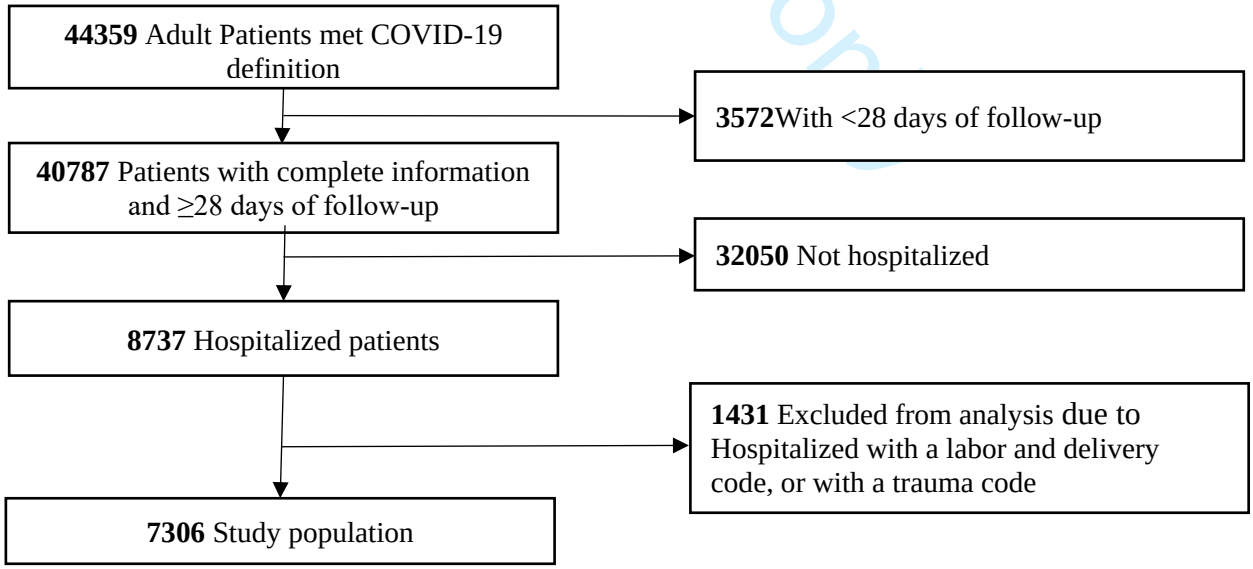
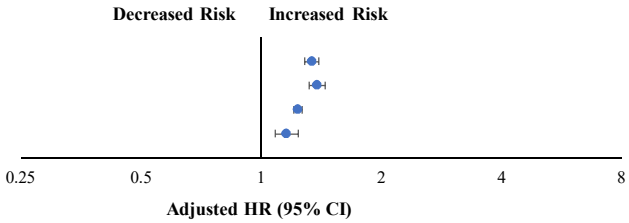


Figure 2. The Forest Plots of Model-adjusted Hazard Ratios among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month

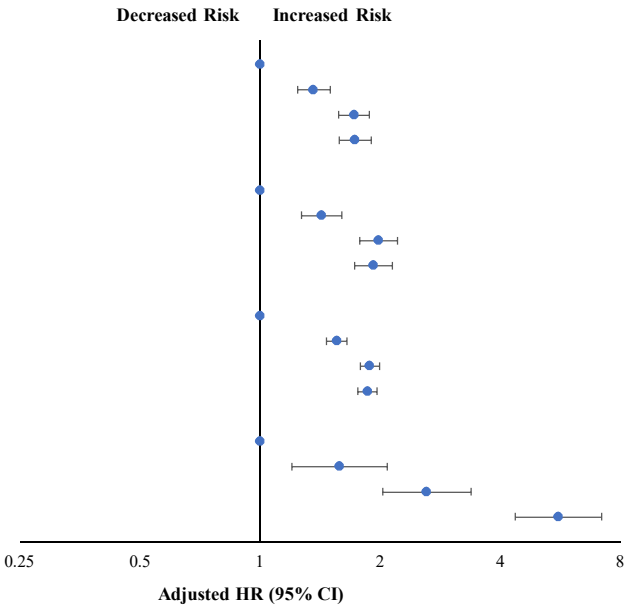
A) Gender

Characteristics	Adjusted HR (95%CI)	Pr > ChiSq
Male (Reference : Female)		
ICU Admission	1.34 (1.29-1.39)	<.0001
IMV	1.38 (1.32-1.45)	<.0001
ARDS/Respiratory Failure	1.24 (1.21-1.27)	<.0001
All-Cause Mortality	1.16 (1.08-1.24)	<.0001



B) Age

Characteristics	Adjusted HR (95%CI)	Pr > ChiSq
ICU Admission		
18-34	1 (ref)	
35-49	1.36 (1.24-1.50)	<.0001
50-64	1.72 (1.57-1.88)	<.0001
65+	1.73 (1.58-1.90)	<.0001
IMV		
18-34	1 (ref)	
35-49	1.43 (1.27-1.60)	<.0001
50-64	1.98 (1.78-2.21)	<.0001
65+	1.93 (1.73-2.15)	<.0001
ARDS/Respiratory Failure		
18-34	1 (ref)	
35-49	1.56 (1.47-1.65)	<.0001
50-64	1.88 (1.78-1.99)	<.0001
65+	1.86 (1.76-1.96)	<.0001
All-Cause Mortality		
18-34	1 (ref)	
35-49	1.58 (1.20-2.09)	0.0012
50-64	2.62 (2.03-3.37)	<.0001
65+	5.60 (4.36-7.18)	<.0001



C) Calendar Month

Characteristics	Adjusted HR (95%CI)	Pr > ChiSq
ICU Admission		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.67 (0.64-0.71)	<.0001
Aug, 2020 - Oct, 2020	0.58 (0.55-0.62)	<.0001
Nov, 2020 - Jan, 2021	0.51 (0.49-0.54)	<.0001
IMV		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.56 (0.53-0.60)	<.0001
Aug, 2020 - Oct, 2020	0.49 (0.45-0.52)	<.0001
Nov, 2020 - Jan, 2021	0.43 (0.40-0.45)	<.0001
ARDS/Respiratory Failure		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.78 (0.76-0.81)	<.0001
Aug, 2020 - Oct, 2020	0.83 (0.80-0.87)	<.0001
Nov, 2020 - Jan, 2021	0.84 (0.81-0.87)	<.0001
All-Cause Mortality		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.87 (0.80-0.96)	0.0056
Aug, 2020 - Oct, 2020	0.75 (0.67-0.83)	<.0001
Nov, 2020 - Jan, 2021	0.80 (0.73-0.88)	<.0001

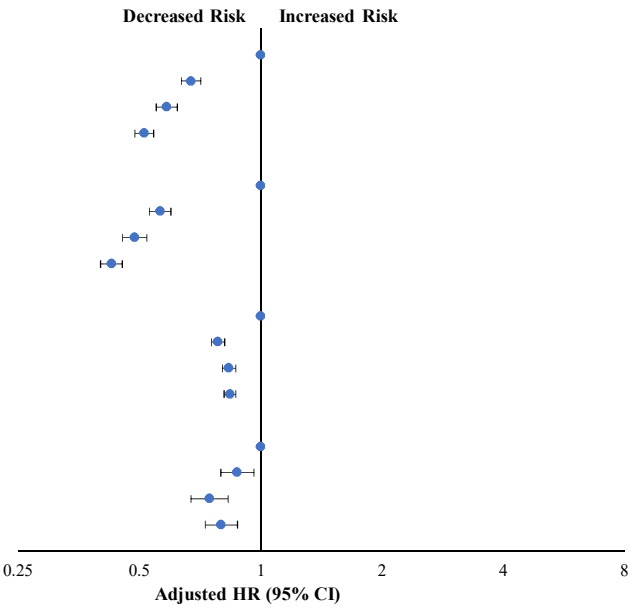
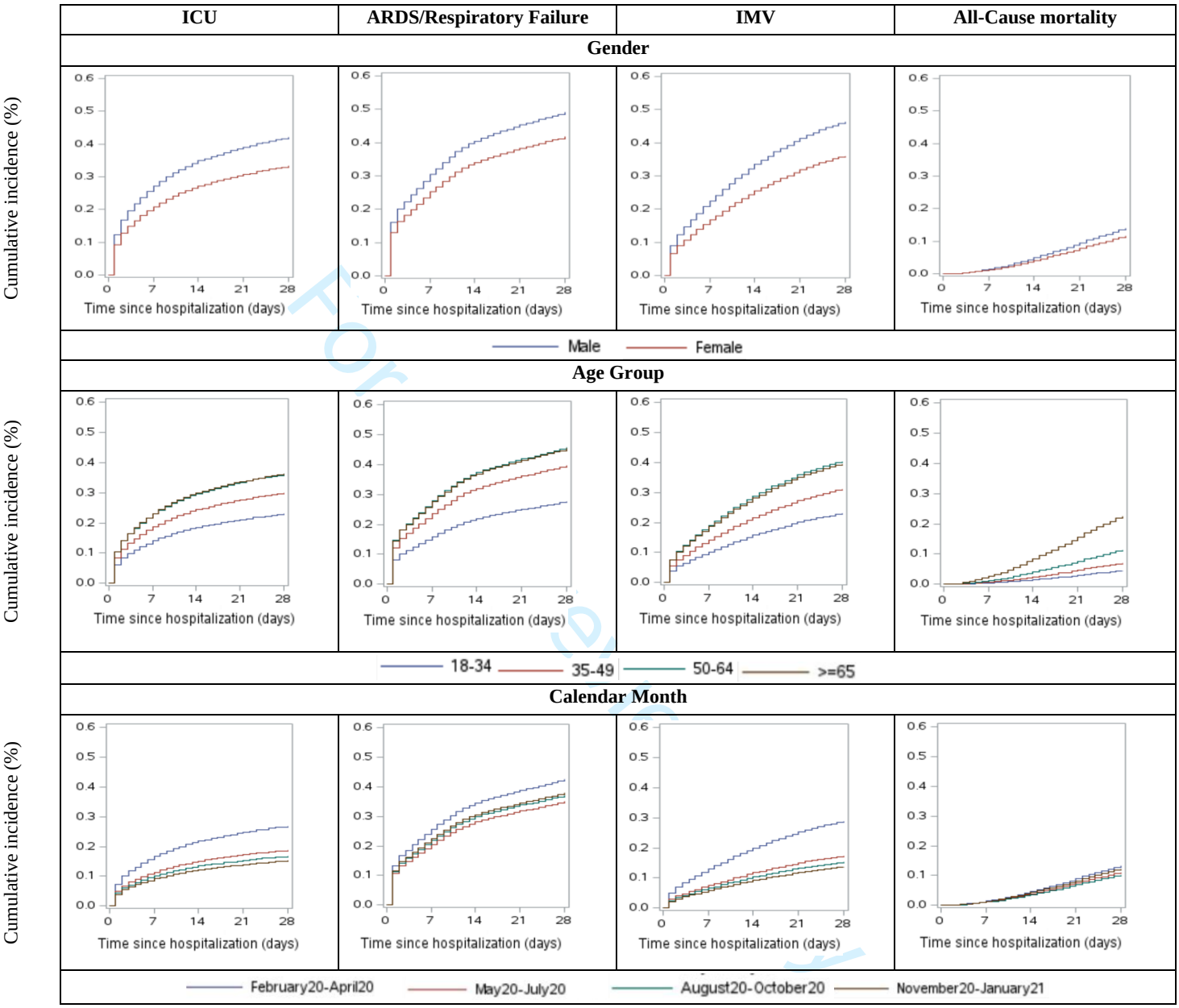
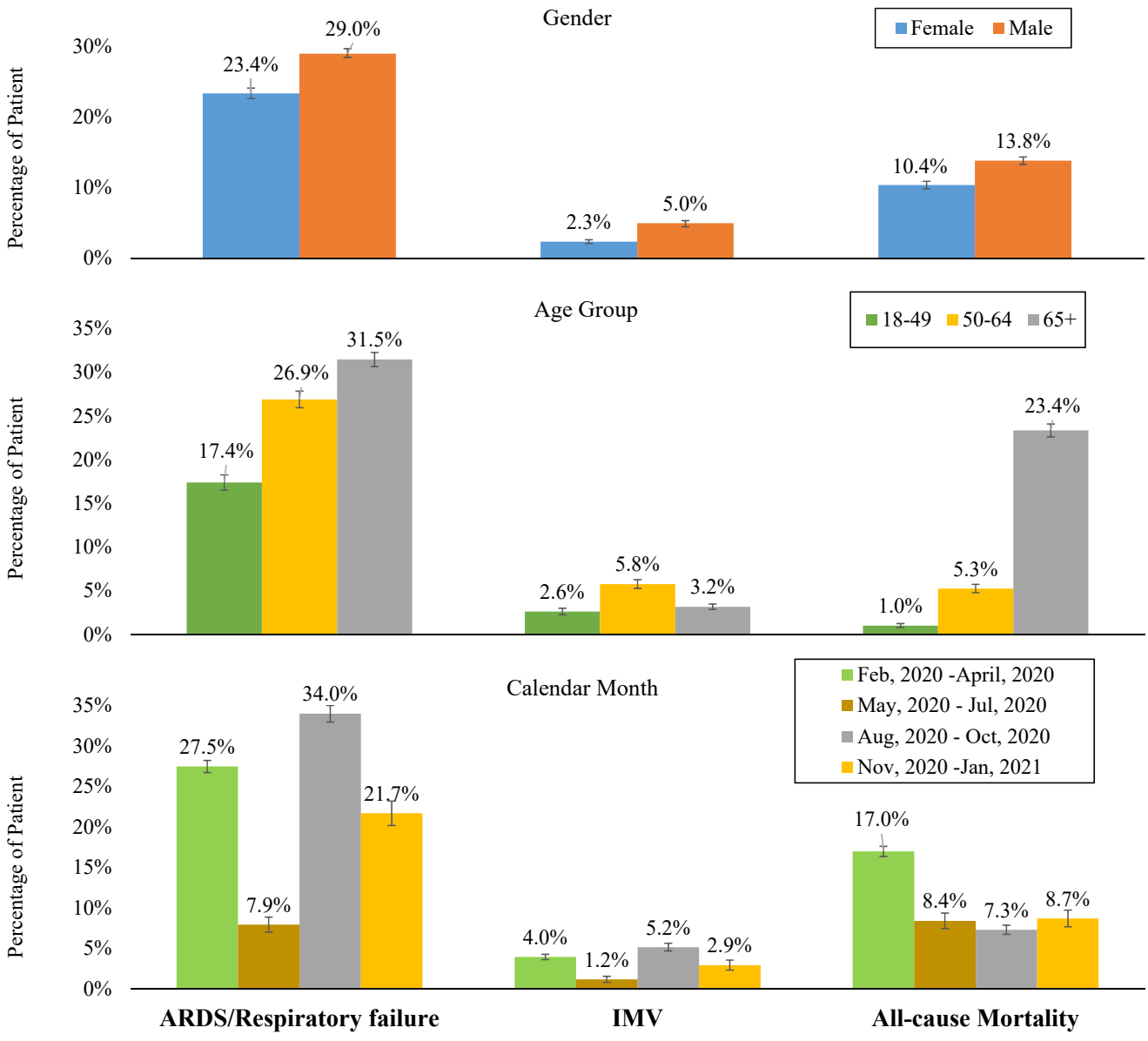


Figure 3. Model-adjusted Cumulative Incidence Plots of Selected Outcomes among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month



ARDS: the abbreviation of acute respiratory distress syndrome; ICU: the abbreviation of intensive care unit; IMV: the abbreviation of invasive mechanical ventilation

Figure 4. The Selected Outcomes among ex-US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month



Error bars reflect standard errors. ARDS: the abbreviation of acute respiratory distress syndrome; ICU: the abbreviation of intensive care unit; IMV: the abbreviation of invasive mechanical ventilation

Supplement

eTable 1 Medical Codes of Outcome Measures (ARDS/respiratory failure or IMV)

Criterion Name	Code Type	Code
ARDS	ICD-10-CM diagnosis	J80
respiratory failure	ICD-10-CM diagnosis	J96.0
respiratory failure	ICD-10-CM diagnosis	J96.01
respiratory failure	ICD-10-CM diagnosis	J96.02
respiratory failure	ICD-10-CM diagnosis	J96.20
respiratory failure	ICD-10-CM diagnosis	J96.21
respiratory failure	ICD-10-CM diagnosis	J96.22
Invasive Mechanical Ventilation	ICD-10-CM Diagnosis	Z99.12
Invasive Mechanical Ventilation	ICD-10-CM Diagnosis	Z99.11
Invasive Mechanical Ventilation	ICD-9-CM Diagnosis	V46.1
Invasive Mechanical Ventilation	ICD-9-CM Diagnosis	V46.11
Invasive Mechanical Ventilation	ICD-10-PCS	5A1955Z
Invasive Mechanical Ventilation	ICD-10-CM Procedure	5A1945Z
Invasive Mechanical Ventilation	ICD-10-CM Procedure	5A1935Z
Invasive Mechanical Ventilation	ICD-10-CM Procedure	0BH18EZ
Invasive Mechanical Ventilation	ICD-10-CM Procedure	0BH17EZ
Invasive Mechanical Ventilation	ICD-10-CM Procedure	0BH13EZ
Invasive Mechanical Ventilation	ICD-10-CM Procedure	0B21XEZ
Invasive Mechanical Ventilation	CPT	99504
Invasive Mechanical Ventilation	CPT	94004
Invasive Mechanical Ventilation	CPT	94003
Invasive Mechanical Ventilation	CPT	94002
Invasive Mechanical Ventilation	CPT	31730
Invasive Mechanical Ventilation	CPT	31502
Invasive Mechanical Ventilation	CPT	31500
Invasive Mechanical Ventilation	ICD-9-CM Procedure	97.23
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.72
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.71
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.70
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.7
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.05
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.04
Invasive Mechanical Ventilation	ICD-10-CM Diagnosis	Z99.1

eTable 2. Baseline Characteristics of US Hospitalized Adult COVID-19 Patients by Gender – Overall Cohort

Characteristic	Patient, No. (%)		
	All (n=67456)	Male (n=34518)	Female (n=32938)
Age, Mean[SD], y	58.3(17.3)	58.8(16.4)	57.6(18.1)
Race			
White	56.1	57.6	54.6
Black or African American	23.7	21.3	26.1
Asian	3.2	3.3	3.1
American Indian or Alaska Native	0.6	0.5	0.6
Native Hawaiian or Other Pacific Islander	0.3	0.3	0.3
Unknown	16.1	16.9	15.3
Ethnicity			
Hispanic	16.2	16.9	15.5
Site of diagnosis at inpatient setting	85.3	86.5	84.1
Mode of diagnosis			
Both	48.0	48.2	47.9
Clinical	41.8	42.2	41.4
Lab	10.2	9.7	10.7
Month of index			
February, 2020	1.2	1.4	1.1
March, 2020	6.7	7.1	6.3
April, 2020	11.1	11.4	10.7
May, 2020	7.3	7.2	7.3
June, 2020	7.8	7.7	7.8
Jul, 2020	11.1	10.9	11.3
August, 2020	6.5	6.2	6.8
September, 2020	5.3	5.1	5.4
October, 2020	8.5	8.4	8.6
November, 2020	15.9	15.6	16.1
December, 2020	17.7	17.8	17.6
January, 2021	1.0	1.1	1.0
US Census division			
Midwest	15.59	15.5	15.7
Northeast	13.10	13.2	13.0
South	45.44	44.1	46.8
West	3.95	4.1	3.8
Baseline Comorbidities			
Gastrointestinal disorders	27.3	24.7	30.0
Skin disorder	13.7	12.9	14.6
Cancer	7.9	8.3	7.6
Solid tumors	6.0	6.2	5.8
Hematologic malignancies	2.7	2.9	2.5
Cardiovascular disease	46.5	48.1	44.8
Chronic kidney diseas	14.1	15.5	12.7
Chronic dialysis	0.9	1.0	0.8
Chronic lung disease	16.2	14.3	18.2
Asthma	7.4	4.8	10.2
COPD	9.8	10.1	9.6
Pulmonary fibrosis	0.9	1.1	0.8

Diabetes Mellitus			
Type I	1.4	1.5	1.3
Type II, diabetic	25.4	26.1	24.5
Diabetes unknown	3.3	3.4	3.2
Liver disease	2.6	3.1	2.1
Hospitalization with infection in the past year	8.3	8.1	8.5

eTable 2. Baseline Characteristics of US Hospitalized Adult COVID-19 Patients by Age Group – Overall Cohort

Characteristic	Patient, %			
	Age 18-34 (n= 7859)	Age 35-49 (n= 12365)	Age 50-64 (n= 20382)	Age 65+ (n= 26850)
Age, Mean[SD],y	27.39(4.6)	42.64(4.4)	57.42(4.3)	75.10(6.9)
Sex (Males)	42.4	50.4	54.5	51.6
Race				
White	47.0	46.8	54.3	64.5
Black or African American	27.1	25.2	25.7	20.4
American Indian or Alaska Native	0.6	0.8	0.6	0.4
Asian	2.8	3.3	3.4	3.1
Native Hawaiian or Other Pacific Islander	0.3	0.5	0.4	0.2
Unknown	22.2	23.3	15.7	11.3
Ethnicity				
Hispanic	24.1	25.2	17.3	8.9
Month of index				
February, 2020	0.9	1.2	1.4	1.2
March, 2020	6.5	7.8	7.3	5.8
April, 2020	11.3	12.5	11.1	10.3
May, 2020	8.5	8.5	7.1	6.4
June, 2020	9.9	9.0	7.6	6.6
Jul, 2020	12.9	12.3	11.5	9.8
August, 2020	7.6	6.7	6.3	6.2
September, 2020	5.9	5.3	5.0	5.2
October, 2020	8.0	8.3	8.5	8.8
November, 2020	12.9	13.7	15.6	17.9
December, 2020	14.6	13.7	17.6	20.5
January, 2021	0.8	0.9	1.0	1.2
US Census division				
Midwest	12.0	12.2	15.0	18.7
Northeast	17.7	14.2	12.8	11.5
South	47.8	48.8	46.0	42.9
West	6.3	5.3	4.3	2.4
Baseline Comorbidities				
Gastrointestinal disorders	19.7	22.3	27.2	31.8
Skin disorder	10.9	11.4	12.7	16.4
Atopic dermatitis	0.3	0.3	0.2	0.2
Autoimmune diseases				
Systemic lupus erythematosus	0.7	0.8	0.7	0.4
Rheumatoid arthritis	0.3	0.7	1.5	2.0
Psoriasis, including psoriatic arthritis	0.3	0.6	0.7	0.6
Inflammatory bowel disease	0.3	0.2	0.2	0.1
Multiple sclerosis	0.3	0.5	0.6	0.4
Glomerulonephritis	0.6	0.5	0.4	0.2
Autoimmune thyroid disease	0.3	0.3	0.2	0.2
Cancer	2.5	3.9	7.4	11.7
Solid tumors	1.3	2.7	5.5	9.3
Breast	0.2	0.7	1.0	1.5

Prostate	0.0	0.1	0.6	2.4
Lung	0.2	0.3	1.0	1.7
Other	1.2	2.1	4.2	5.9
Hematologic malignancies	1.5	1.6	2.7	3.5
Leukemia	0.3	0.3	0.6	0.9
Lymphoma	0.4	0.4	0.6	0.8
Multiple myeloma (MM)	0.0	0.1	0.5	0.5
Other	0.9	0.8	1.3	1.6
Cardiovascular disease	11.9	28.2	47.5	64.2
Coronary artery disease	0.5	3.0	9.6	21.2
Peripheral vascular disease	0.4	1.2	3.6	7.3
Cerebrovascular disease	0.5	1.2	2.6	6.8
Hypertension	11.0	26.6	44.0	58.1
Congestive heart failure	1.5	4.4	8.7	17.4
Atrial Fibrillation	0.5	1.6	5.5	17.6
Chronic kidney disease	3.3	7.1	12.3	21.9
Stage I	0.1	0.1	0.1	0.2
Stage II	0.3	0.6	1.3	1.8
Stage III	0.8	1.9	4.1	9.5
Stage IV	0.5	1.0	1.7	3.3
Stage V (end stage renal disease)	1.3	2.8	3.5	3.3
Unknown	2.8	6.3	10.9	19.1
Chronic dialysis	0.4	0.9	15.2	21.5
Hemodialysis	0.4	0.8	1.0	1.0
Peritoneal dialysis	0.0	0.0	0.0	0.0
Chronic lung disease	9.9	10.5	15.2	21.4
Asthma	9.3	8.5	7.9	6.0
Chronic obstructive pulmonary disease	0.6	2.4	8.6	16.9
Pulmonary fibrosis	0.2	0.5	0.7	1.6
Diabetes mellitus				
Type I	2.5	1.8	1.3	1.0
Type II, diabetic	7.1	17.6	28.3	32.0
Diabetes mellitus_unknown	1.3	2.4	3.6	4.0
Human immunodeficiency virus	0.8	1.0	1.1	0.3
Liver disease	0.9	2.1	3.7	2.5
Chronic hepatitis	0.3	0.6	1.3	0.7
Cirrhosis	0.4	1.5	2.8	2.0
Non-alcoholic steatohepatitis	0.2	0.4	0.7	0.5
Major movement or cognitive disorder (excluding stroke)	0.8	1.5	3.7	15.0
Obstructive sleep apnea	2.5	5.9	8.8	8.3
Hospitalization with infection in the past year	6.3	7.0	7.9	9.8
Transplant history	0.4	0.6	0.5	0.2

eTable 3. Baseline Characteristics of US Hospitalized Adult COVID-19 Patients by Calendar Month – Overall Cohort

Characteristics	Patient, No. (%)			
	Feb, 2020 - Apr, 2020 (n= 12800)	May, 2020 - Jul, 2020 (n= 17634)	Aug, 2020 - Oct, 2020 (n= 13635)	Nov, 2020 - Jan, 2020 (n= 23326)
Age, Mean[SD], y	57.3(17.1)	56.1(17.3)	57.8(17.4)	60.6(17.0)
18-34	11.6	13.9	12.4	9.5
35-49	20.8	20.9	18.4	15.0
50-64	31.4	30.4	29.6	29.9
65+	36.3	34.8	39.7	45.6
Sex (Male)	53.4	50.7	49.9	51.0
Race				
White	44.4	50.0	61.9	63.8
Black or African American	27.7	26.9	20.8	20.7
American Indian or Alaska Native	0.5	0.9	0.5	0.4
Asian	2.6	4.4	3.2	2.6
Native Hawaiian or Other Pacific Islander	0.1	0.4	0.4	0.3
Unknown	24.6	17.4	0.0	12.3
Ethnicity				
Hispanic	16.5	24.8	15.9	9.6
US Census division				
Midwest	9.9	11.8	15.2	21.9
Northeast	27.7	6.6	5.2	14.7
South	35.9	58.1	51.4	37.9
West	6.3	4.3	5.1	1.7
Baseline Comorbidities				
Gastrointestinal disorders	27.8	23.7	27.9	29.4
Skin disorder	15.8	11.6	13.3	14.4
Atopic dermatitis	0.4	0.2	0.2	0.2
Autoimmune disease				
Systemic lupus erythematosus	0.7	0.5	0.6	0.6
Rheumatoid arthritis	1.5	1.0	1.3	1.7
Psoriasis, including psoriatic arthritis	0.6	0.5	0.6	0.7
Inflammatory bowel disease	0.2	0.1	0.2	0.2
Multiple sclerosis	0.5	0.4	0.4	0.5
Glomerulonephritis	0.4	0.4	0.3	0.3
Autoimmune thyroid disease	0.3	0.2	0.2	0.2
Cancer	8.2	6.8	8.0	8.5
Solid tumors	6.0	5.3	6.2	6.5
Breast	1.0	0.9	1.2	1.1
Prostate	1.1	0.9	1.1	1.3
Lung	1.2	0.9	1.0	1.1
Other	4.1	3.7	4.1	4.4

Hematologic malignancies	3.2	2.1	2.7	2.8
Leukemia	0.8	0.5	0.6	0.7
Lymphoma	0.9	0.4	0.5	0.7
Multiple myeloma (MM)	0.3	0.3	0.3	0.4
Other	1.6	1.0	1.3	1.3
Cardiovascular disease	45.8	39.2	45.8	52.7
Coronary artery disease	11.8	9.3	11.8	14.2
Peripheral vascular disease	4.9	3.7	3.9	4.5
Cerebrovascular disease	4.1	2.8	3.4	4.6
Hypertension	42.1	35.9	42.0	48.2
Congestive heart failure	11.0	9.1	9.6	11.9
Atrial Fibrillation	9.0	6.9	8.7	10.9
Chronic kidney disease	14.9	11.7	13.4	15.9
Stage I	0.3	0.1	0.2	0.1
Stage II	1.5	1.1	1.2	1.3
Stage III	6.6	4.8	5.4	5.3
Stage IV	2.2	1.6	2.0	2.4
Stage V (end stage renal disease)	3.3	2.9	2.7	3.2
Unknown	12.8	10.3	11.9	14.0
Chronic dialysis	1.0	0.8	0.8	1.0
Hemodialysis	1.0	0.8	0.8	1.0
Peritoneal dialysis	0.0	0.0	0.0	0.0
Chronic lung disease	16.9	12.5	16.3	18.6
Asthma	8.0	6.0	7.4	8.1
COPD	10.1	7.3	9.8	11.7
Pulmonary fibrosis	1.2	0.7	0.9	1.0
Diabetes mellitus				
Type I	1.8	1.3	1.2	1.4
Type II, diabetic	25.3	22.5	24.6	27.9
Diabetes mellitus_unknown	4.1	2.6	2.5	3.8
Human immunodeficiency virus	1.0	0.7	0.7	0.6
Liver disease	3.0	2.4	2.6	2.5
Chronic hepatitis	1.2	0.8	0.7	0.6
Cirrhosis	2.0	1.8	2.1	1.9
Non-alcoholic steatohepatitis	0.5	0.4	0.6	0.5
Major movement or cognitive disorder (excluding stroke)	8.5	6.4	6.9	8.1
Obstructive sleep apnea	7.1	5.7	7.2	8.8
Hospitalization with infection in the past year	11.1	7.1	7.8	8.0
Transplant history	0.3	0.3	0.4	0.5

eTable 4 The Percentage of Hospitalized Adult COVID-19 Patient by Region in ex-US Analysis

Region	% of Hospitalized Adult COVID-19 Patients
Europe	91.4%
LATAM	8.5%
APAC	0.1%

LATAM: Latin America; APAC: Asia-Pacific

eTable 5. Drug Treatment receipt among US Adult Hospitalized COVID-19 patients – Overall Cohort

Treatment	Patient,% (N=67456)
Acetaminophen	67.11%
Enoxaparin	49.47%
Dexamethasone	37.69%
Insulin	32.74%
Opioids	31.44%
Aspirin	26.69%
Azithromycin	23.72%
Atorvastatin	21.44%
Remdesivir	20.26%
Methylprednisolone	19.82%
Heparin	14.77%
Melatonin	13.42%
Zinc	13.00%
Prednisone	11.91%
Ibuprofen	11.78%
Doxycycline	8.83%
Apixaban	8.72%
Hydroxychloroquine	7.18%
Chloroquine	7.16%
Vitamin D	6.89%
Thiamine	5.63%
Levofloxacin	5.54%
Rosuvastatin	5.41%
Clopidogrel	5.21%
Hydrocortisone	4.92%
Amoxicillin	4.25%
Budesonide	4.25%
Rivaroxaban	3.95%
Amiodarone	3.91%
Montelukast	3.46%
Formoterol	3.26%
Alteplase	3.17%
Pravastatin	2.83%
Simvastatin	2.62%
Trimethoprim	2.33%
Tacrolimus	1.68%
Warfarin	1.60%
Hemodialysis	1.42%

eTable 6. Drug Treatment receipt among ex-US Adult Hospitalized COVID-19 patients

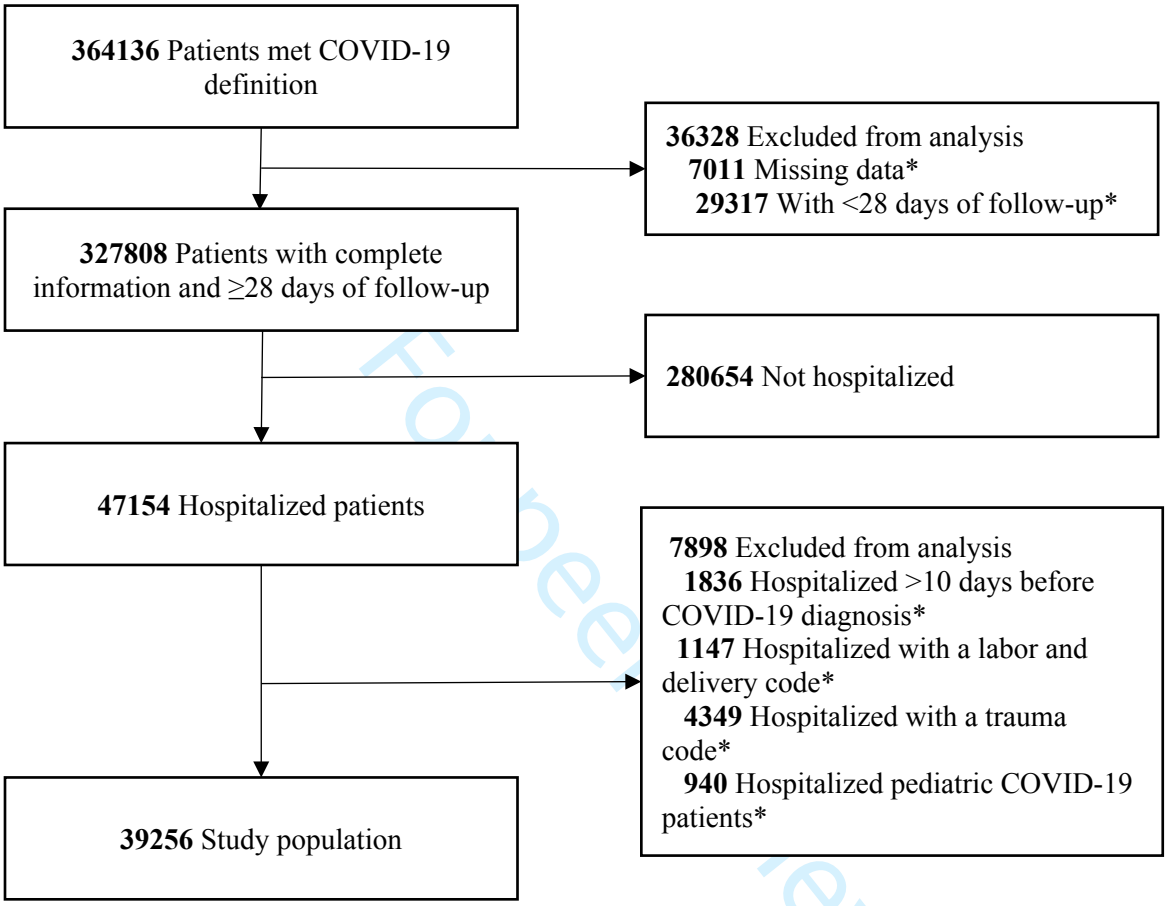
Treatment	Patient,% (N=67456)
Acetaminophen	64.6%
Azithromycin	38.9%
Hydroxychloroquine	29.0%
Methylprednisolone	21.4%
Insulin	20.2%
Dexamethasone	19.9%
Amoxicillin	18.9%
Other Bronchodilators	14.0%
Tocilizumab	8.3%
Atorvastatin	7.9%
Aspirin	7.9%
Formoterol	6.3%
Prednisone	5.5%
Levofloxacin	5.4%
Simvastatin	5.3%
Clopidogrel	1.8%
Thiamine	1.4%
Apixaban	1.2%
Rivaroxaban	1.2%
Amiodarone	1.1%
Montelukast	0.9%
Rosuvastatin	0.7%
Remdesivir	0.5%
Pravastatin	0.2%
Other Antihypertensives	0.2%
Warfarin	0.1%

eTable 7: Selected Outcomes Percentage of US Adult Hospitalized COVID-19 Patients – Overall Cohort

Category	ICU Admission		ARDS/Respiratory Failure		IMV		All-Cause Mortality	
	N	%	N	%	N	%	N	%
Gender								
Male	34518	16.89%	32560	40.98%	34518	13.65%	34518	6.14%
Female	32938	12.33%	30946	32.78%	32938	9.36%	32938	4.56%
Age								
18-34	7859	7.23%	7678	18.26%	7859	5.06%	7859	0.83%
35-49	12365	11.23%	11957	30.96%	12365	8.63%	12365	1.78%
50-64	20382	15.71%	19240	40.31%	20382	12.82%	20382	3.79%
65+	26850	17.62%	24631	43.14%	26850	13.84%	26850	9.55%
Calendar Month								
Feb, 2020 - Apr, 2020	12800	20.88%	11924	41.11%	12800	17.89%	12800	6.52%
May, 2020 - Jul, 2020	17634	14.46%	16805	33.04%	17634	11.53%	17634	5.33%
Aug, 2020 - Oct, 2020	13635	13.19%	12890	36.97%	13635	10.21%	13635	4.73%
Nov, 2020 - Jan, 2021	23326	12.21%	21837	37.73%	23326	8.82%	23326	5.16%

Sensitivity Analysis

eFigure 1. Patient Flow Diagram of US Adult Hospitalized COVID-19 Patients – Confirmed Cohort



*The counts were not mutual exclusive.

eTable 8. Baseline Characteristics of US Hospitalized Adult COVID-19 Patient Overall and by Gender – Confirmed Cohort

Characteristic	Patients, %		
	All (n=39256)	Male (n=19965)	Female (n=19291)
Age, Mean[SD], y	57(17.54)	58.4(16.7)	57.2(18.4)
18-34	12.6	10.4	14.8
35-49	18.5	18.5	18.6
50-64	29.8	31.7	27.9
65+	39.1	39.4	38.7
Race			
White	54.9	56.3	53.5
Black or African American	25.5	23.1	28.0
American Indian or Alaska Native	0.5	0.5	0.5
Asian	2.8	2.9	2.6
Native Hawaiian or Other Pacific Islander	0.3	0.3	0.2
Unknown	16.0	16.9	15.1
Ethnicity			
Hispanic	18.9	19.7	18.0
Site of Diagnosis			
Inpatient	83.5	84.8	82.2
Other	16.5	15.2	17.8
Mode of Diagnosis			
Both Diagnosis and lab	81.2	81.9	80.5
Lab	18.8	18.1	19.5
Month of Index			
Feb-20	0.8	1.0	0.6
Mar-20	6.6	7.1	6.2
Apr-20	11.3	11.8	10.7
May-20	7.5	7.6	7.3
Jun-20	8.0	8.1	8.0
Jul-20	11.3	11.0	11.7
Aug-20	6.3	6.0	6.7
Sep-20	5.0	4.8	5.2
Oct-20	8.5	8.4	8.5
Nov-20	16.4	16.0	16.8
Dec-20	17.3	17.2	17.3
Jan-21	1.1	1.1	1.1
US Census Division			
Midwest	19.9	19.8	20.0
Northeast	14.8	14.7	14.9
South	46.6	45.5	47.8
West	4.9	5.1	4.7
Unknown	13.8	14.91	12.58
Baseline Comorbidities			
Gastrointestinal disorders	25.1	22.3	28.0
Skin disorder	13.7	12.5	14.8
Atopic dermatitis (AD)	0.3	0.2	0.3
Autoimmune disease			

Systemic lupus erythematosus	0.5	0.2	0.9
Rheumatoid arthritis	1.2	0.7	1.7
Psoriasis, including psoriatic arthritis	0.6	0.5	0.6
Inflammatory bowel disease	0.2	0.1	0.2
Multiple sclerosis	0.4	0.3	0.5
Glomerulonephritis	0.3	0.3	0.4
Autoimmune thyroid disease	0.2	0.1	0.3
Cancer	7.0	7.4	6.6
Solid tumors	5.4	5.7	5.0
Breast	1.0	0.0	1.9
Prostate	1.1	2.1	0.0
Lung	0.9	1.0	0.8
Other	3.6	3.9	3.3
Hematologic malignancies	2.4	2.4	2.3
Leukemia	0.5	0.6	0.5
Lymphoma	0.6	0.6	0.5
Multiple myeloma (MM)	0.4	0.4	0.3
Other	1.1	1.1	1.1
Cardiovascular disease	41.5	42.5	40.3
Coronary artery disease	10.9	13.5	8.1
Peripheral vascular disease	3.9	4.4	3.4
Cerebrovascular disease	3.8	3.9	3.7
Hypertension	37.6	38.0	37.2
Congestive heart failure	9.1	9.5	8.7
Atrial Fibrillation	7.8	9.0	6.6
Chronic kidney disease	12.4	13.3	11.4
Stage I	0.1	0.1	0.1
Stage II	1.3	1.5	1.0
Stage III	5.3	5.5	5.1
Stage IV	1.9	1.9	2.0
Stage V (End stage renal disease)	2.5	2.8	2.2
Unknown	10.7	11.5	9.9
Chronic dialysis	0.7	0.7	0.7
Hemodialysis	0.7	0.7	0.7
Chronic lung disease	13.9	11.9	15.9
Asthma	6.7	4.2	9.3
COPD	8.0	8.1	8.0
Pulmonary fibrosis	0.7	0.8	0.6
Diabetes mellitus			
Type I	1.2	1.2	1.2
Type II, diabetic	22.2	22.5	21.9
Diabetes unknown	4.0	4.0	4.0
Human immunodeficiency virus	0.6	0.8	0.3
Liver disease	2.3	2.8	1.8
Chronic hepatitis	0.8	1.2	0.5
Cirrhosis	1.6	1.9	1.3
Non-alcoholic steatohepatitis	0.5	0.4	0.6
Major movement or cognitive disorder (excluding stroke)	6.2	6.0	6.4
Obstructive sleep apnea	7.1	7.4	6.8

Hospitalization with infection in the past year	7.5	7.0	7.9
Transplant history	0.4	0.5	0.3

eTable 9: Selected Outcomes Percentage of US Adult Hospitalized COVID-19 Patients – Confirmed Cohort

Category	ICU Admission		ARDS/Respiratory Failure		IMV		All-Cause Mortality	
	N	%	N	%	N	%	N	%
Gender								
Male	19965	15.65%	18946	36.41%	19965	12.19%	19965	4.94%
Female	19291	10.86%	18222	28.20%	19291	7.74%	19291	3.66%
Age								
18-34	4931	5.21%	4849	14.04%	4931	3.45%	4931	0.34%
35-49	7275	9.33%	7070	26.08%	7275	6.83%	7275	0.93%
50-64	11713	14.07%	11156	35.50%	11713	10.84%	11713	2.68%
65+	15337	17.19%	14093	39.40%	15337	12.98%	15337	8.43%
Calendar Month								
Feb, 2020 - Apr, 2020	7332	15.71%	6978	35.05%	7332	13.86%	7332	4.69%
May, 2020 - Jul, 2020	10530	14.32%	10089	28.98%	10530	10.53%	10530	4.72%
Aug, 2020 - Oct, 2020	7757	13.23%	7373	33.45%	7757	9.62%	7757	3.66%
Nov, 2020 - Jan, 2021	13626	11.24%	12718	33.02%	13626	7.75%	13626	4.16%

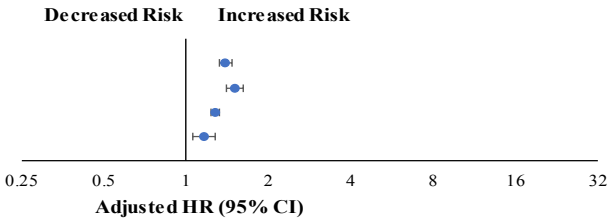
eTable 10. Treatment receipt among COVID-19 patients – Confirmed Cohort

Treatment	Patient, % (N=39256)
Acetaminophen	74.38%
Enoxaparin	54.41%
Dexamethasone	41.50%
Insulin	34.72%
Opioids	32.31%
Aspirin	28.66%
Azithromycin	23.60%
Atorvastatin	23.33%
Remdesivir	22.84%
Methylprednisolone	22.38%
Heparin	16.14%
Melatonin	14.06%
Zinc	13.73%
Ibuprofen	12.17%
Prednisone	12.06%
Apixaban	9.63%
Doxycycline	8.95%
Vitamin D	7.88%
Hydroxychloroquine	7.42%
Chloroquine	7.41%
Rosuvastatin	6.97%
Thiamine	6.34%
Clopidogrel	5.40%
Rivaroxaban	5.08%
Levofloxacin	4.99%
7Hydrocortisone	4.75%
Amoxicillin	4.21%
Budesonide	3.83%
Amiodarone	3.81%
Montelukast	3.64%
Pravastatin	3.14%
Alteplase	3.11%
Formoterol	3.05%
Simvastatin	2.36%
Trimethoprim	2.21%
Warfarin	1.82%
Tacrolimus	1.77%
Hemodialysis	0.93%

S2 Figure. The Forest Plots of Model-adjusted Hazard Ratios among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month – Confirmed

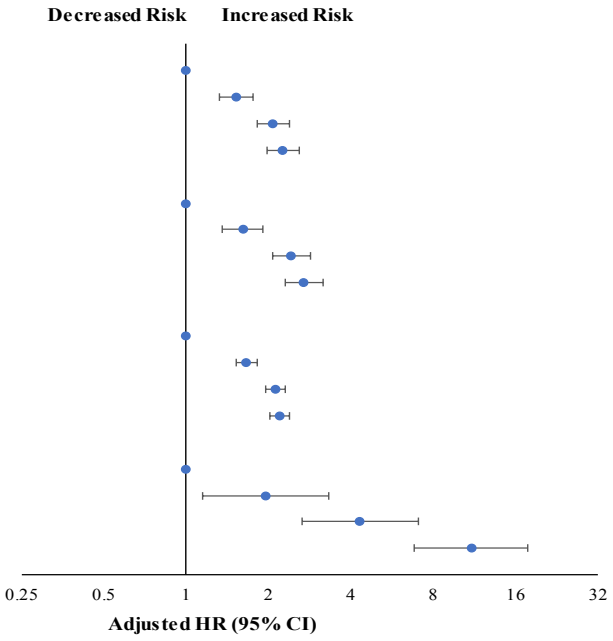
A) Gender

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
Male (Reference : Female)		
ICU Admission	1.39 (1.32-1.47)	<.0001
IMV	1.51 (1.41-1.61)	<.0001
ARDS/Respiratory Failure	1.28 (1.23-1.32)	<.0001
All-cause Mortality	1.16 (1.06-1.28)	0.0025



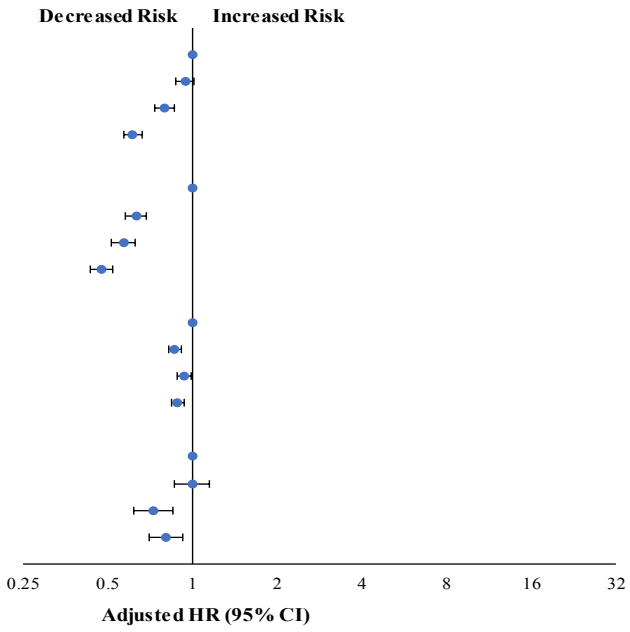
B) Age

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
ICU Admission		
18-34	1 (ref)	
35-49	1.53 (1.33-1.76)	<.0001
50-64	2.08 (1.82-2.37)	<.0001
65+	2.26 (1.98-2.58)	<.0001
IMV		
18-34	1 (ref)	
35-49	1.61 (1.35-1.91)	<.0001
50-64	2.42 (2.06-2.85)	<.0001
65+	2.69 (2.29-3.17)	<.0001
ARDS/Respiratory Failure		
18-34	1 (ref)	
35-49	1.66 (1.53-1.81)	<.0001
50-64	2.12 (1.96-2.30)	<.0001
65+	2.19 (2.02-2.38)	<.0001
All-cause Mortality		
18-34	1 (ref)	
35-49	1.95 (1.14-3.31)	0.0141
50-64	4.32 (2.65-7.03)	<.0001
65+	10.99 (6.79-17.78)	<.0001

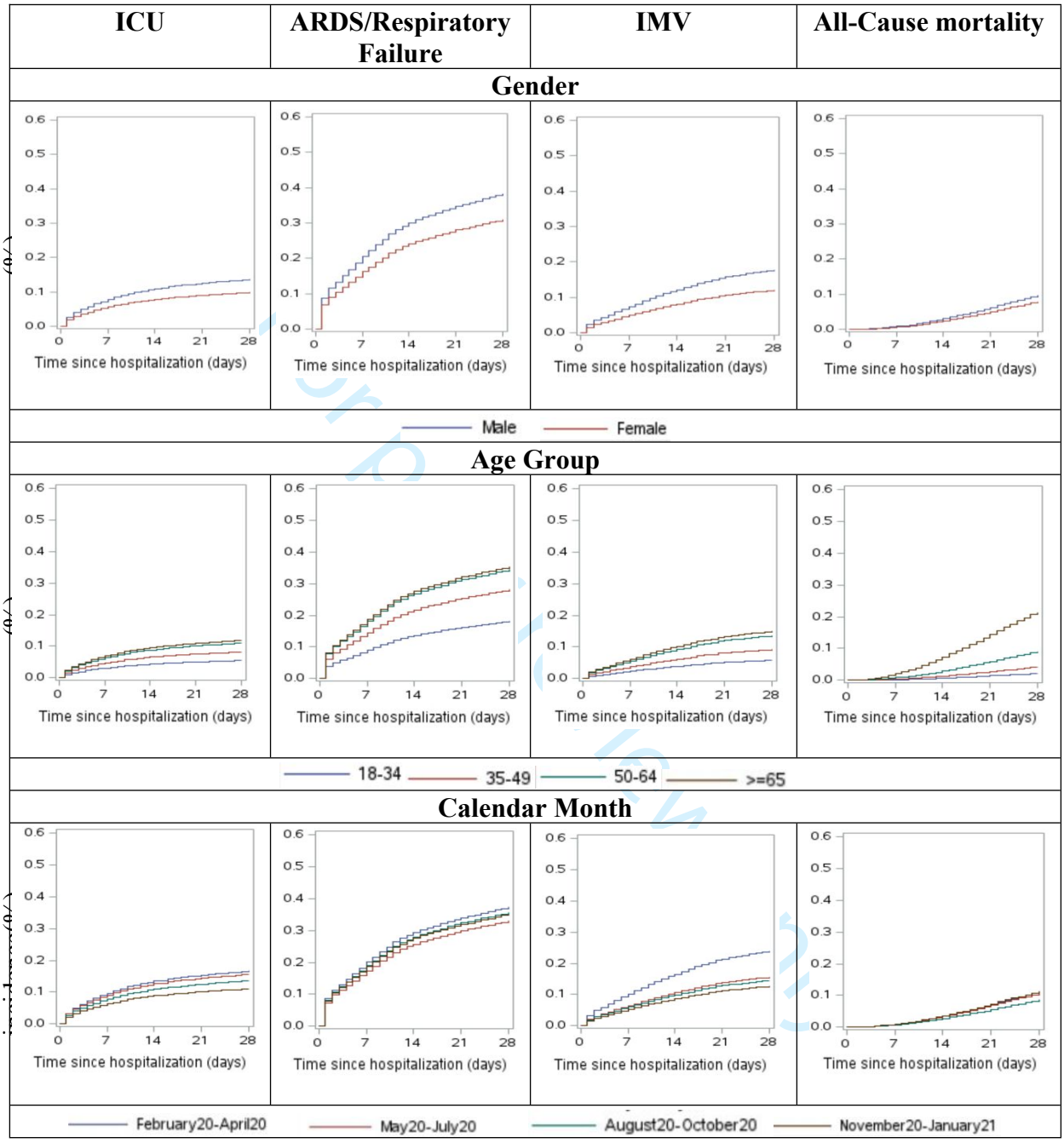


C) Calendar Month

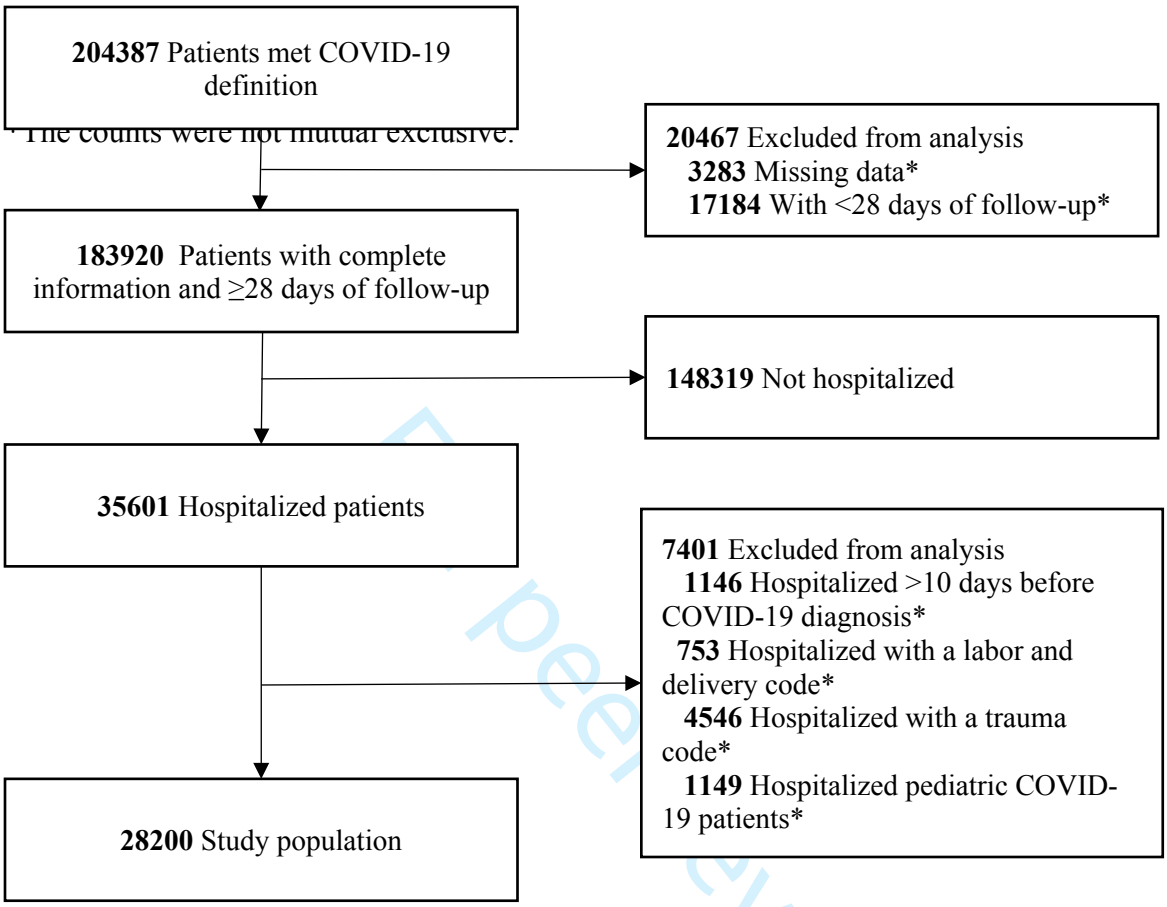
Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
ICU Admission		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.94 (0.87-1.02)	0.1208
Aug, 2020 - Oct, 2020	0.79 (0.73-0.87)	<.0001
Nov, 2020 - Jan, 2021	0.61 (0.57-0.66)	<.0001
IMV		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.63 (0.58-0.69)	<.0001
Aug, 2020 - Oct, 2020	0.57 (0.52-0.63)	<.0001
Nov, 2020 - Jan, 2021	0.47 (0.43-0.52)	<.0001
ARDS/Respiratory Failure		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.86 (0.82-0.91)	<.0001
Aug, 2020 - Oct, 2020	0.93 (0.88-0.99)	0.0117
Nov, 2020 - Jan, 2021	0.88 (0.84-0.93)	<.0001
All-cause Mortality		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.99 (0.86-1.14)	0.929
Aug, 2020 - Oct, 2020	0.72 (0.62-0.85)	<.0001
Nov, 2020 - Jan, 2021	0.80 (0.70-0.92)	0.0022



S3 Figure. Model-adjusted Cumulative Incidence of Selected Outcomes among Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month – Confirmed Cohort



eFigure 4. Patient Flow Diagram of US Adults Hospitalized with COVID-19 – Probable Cohort



eTable 11. Baseline Characteristics among US Hospitalized Adult COVID-19 Patients Overall and by Gender– Probable Cohort

Characteristic	Patient, %		
	All (n= 28200)	Male (n= 14553)	Female (n= 13647)
Age, Mean[SD], y	58.8(16.9)	59.5(16.2)	58.2(17.7)
18-34	10.4	8.6	12.3
35-49	18.0	17.5	18.7
50-64	30.7	32.8	28.6
65+	40.8	41.1	40.5
Race			
White	57.8	59.5	56.0
Black or African American	21.1	18.9	23.6
American Indian or Alaska Native	0.7	0.6	0.8
Asian	3.8	3.8	3.8
Native Hawaiian or Other Pacific Islander	0.4	0.4	0.4
Unknown	16.2	16.9	15.4
Ethnicity			
Hispanic	12.4	12.9	11.9
Month of Index			
February, 2020	1.8	1.0	0.6
March, 2020	6.8	7.1	6.2
April, 2020	10.8	11.8	10.7
May, 2020	7.0	7.6	7.3
June, 2020	7.4	8.1	8.0
Jul, 2020	10.8	11.0	11.7
August, 2020	6.7	6.0	6.7
September, 2020	5.6	4.8	5.2
October, 2020	8.5	8.4	8.5
November, 2020	15.1	16.0	16.8
December, 2020	18.3	17.2	17.3
January, 2021	1.0	1.1	1.1
US Census division			
Midwest	9.6	9.7	9.6
Northeast	10.8	11.1	10.4
South	44.0	42.1	45.8
West	33.0	2.6	2.6
Baseline Comorbidities			
Gastrointestinal disorders	30.4	28.0	32.9
Skin disorder	13.8	13.3	14.3
Atopic dermatitis	0.2	0.1	0.2
Autoimmune disease			
Systemic lupus erythematosus	0.7	0.2	1.3
Rheumatoid arthritis	1.7	1.0	2.5
Psoriasis, including psoriatic arthritis	0.7	0.7	0.7
Inflammatory bowel disease	0.2	0.2	0.2

Multiple sclerosis	0.5	0.3	0.8
Glomerulonephritis	0.4	0.4	0.3
Autoimmune thyroid disease	0.2	0.1	0.4
Cancer	9.2	9.5	8.9
Solid Tumors	7.0	6.9	7.0
Breast	1.2	0.0	2.4
Prostate	1.2	2.4	0.0
Lung	1.3	1.2	1.4
Other	4.8	4.8	4.8
Hematologic malignancies	3.2	3.5	2.8
Leukemia	0.8	1.1	0.5
Lymphoma	0.7	0.9	0.6
Multiple myeloma (MM)	0.4	0.4	0.3
Other	1.5	1.5	1.5
Cardiovascular disease	53.4	55.6	51.1
Coronary artery disease	13.5	16.6	10.2
Peripheral vascular disease	4.7	5.6	3.8
Cerebrovascular disease	3.8	3.8	3.8
Hypertension	49.5	51.1	47.8
Congestive heart failure	12.5	13.6	11.4
Atrial Fibrillation	10.7	12.5	8.8
Chronic kidney disease	16.5	18.5	14.4
Stage I	0.2	0.2	0.2
Stage II	1.2	1.5	0.9
Stage III	5.7	6.0	5.3
Stage IV	2.3	2.4	2.2
Stage V (end stage renal disease)	3.8	4.4	3.1
Unknown	14.7	16.7	12.7
Chronic dialysis	1.2	1.5	1.0
Hemodialysis	1.2	1.5	1.0
Peritoneal dialysis	0.0	0.0	0.0
Chronic lung disease	19.5	17.7	21.4
Asthma	8.3	5.5	11.4
Chronic obstructive pulmonary disease	12.4	12.8	11.9
Pulmonary fibrosis	1.3	1.5	1.1
Diabetes mellitus			
Type I	1.6	1.8	1.5
Type II, diabetic	29.7	31.1	28.2
Diabetes mellitus_unknown	2.3	2.6	2.1
Human immunodeficiency virus	1.7	2.3	1.1
Liver disease	3.0	3.5	2.5
Chronic hepatitis	0.8	1.0	0.6
Cirrhosis	2.4	2.8	1.9
Non-alcoholic steatohepatitis	0.5	0.5	0.6
Major movement or cognitive disorder (excluding stroke)	9.3	9.4	9.1
Obstructive sleep apnea	7.6	8.5	6.7

Hospitalization with infection in the past year	9.5	9.6	9.4
Transplant history	0.4	0.4	0.3

eTable 12: Selected Outcomes Percentage of US Adult Hospitalized COVID-19 Patients – Probable

Category	ICU Admission		ARDS/Respiratory Failure		IMV		All-Cause Mortality	
	N	%	N	%	N	%	N	%
Gender								
Male	14,553	18.59%	13,614	47.34%	14,553	15.64%	14,553	7.79%
Female	13,647	14.40%	12,724	39.34%	13,647	11.64%	13,647	5.84%
Age								
18-34	2,928	10.62%	2,829	25.49%	2,928	7.79%	2,928	1.64%
35-49	5,090	13.95%	4,887	38.02%	5,090	11.20%	5,090	2.99%
50-64	8,669	17.94%	8,084	46.96%	8,669	15.49%	8,669	5.29%
65+	11,513	18.19%	10,538	48.16%	11,513	14.97%	11,513	11.05%
Calendar Month								
Feb-20,Mar-20,Apr-20	5,468	27.82%	4,946	49.66%	5,468	23.30%	5,468	8.96%
May-20,Jun-20,Jul-20	7,104	14.65%	6,716	39.13%	7,104	13.02%	7,104	6.24%
Aug-20,Sept-20Oct-20	5,878	13.13%	5,517	41.67%	5,878	10.99%	5,878	6.14%
Nov-20,Dec-20,Jan-21	9,700	13.56%	9,119	44.31%	9,700	10.33%	9,700	6.56%

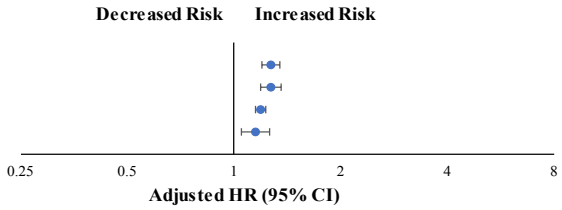
eTable 13. Treatment receipt among COVID-19 patients – Probable Cohort

Treatment	Patient, % (N=28200)
Acetaminophen	57.01%
Enoxaparin	42.59%
Dexamethasone	32.39%
Opioids	30.24%
Insulin	29.99%
Aspirin	23.95%
Azithromycin	23.89%
Atorvastatin	18.80%
Remdesivir	16.66%
Methylprednisolone	16.25%
Heparin	12.87%
Melatonin	12.53%
Zinc	11.99%
Prednisone	11.69%
Ibuprofen	11.23%
Doxycycline	8.67%
Apixaban	7.47%
Hydroxychloroquine	6.85%
Chloroquine	6.80%
Levofloxacin	6.29%
Vitamin D	5.51%
Hydrocortisone	5.16%
Clopidogrel	4.94%
Budesonide	4.83%
Thiamine	4.66%
Amoxicillin	4.29%
Amiodarone	4.04%
Formoterol	3.55%
Alteplase	3.26%
Rosuvastatin	3.24%
Montelukast	3.22%
Simvastatin	2.97%
Trimethoprim	2.51%
Pravastatin	2.40%
Rivaroxaban	2.39%
Hemodialysis	2.10%
Tacrolimus	1.55%
Warfarin	1.31%

S5 Figure. The Forest Plots of Model-adjusted Hazard Ratios among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month – Probable Cohort

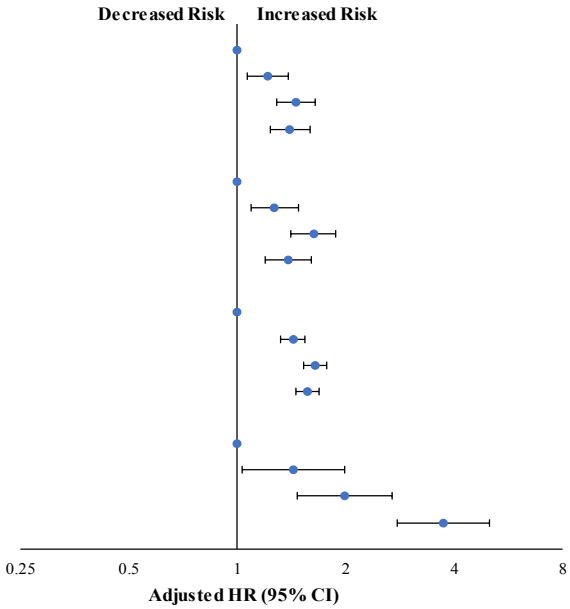
A) Gender

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
Male (Reference : Female)		
ICU Admission	1.27 (1.20-1.35)	<.0001
IMV	1.27 (1.19-1.36)	<.0001
ARDS/Respiratory Failure	1.19 (1.16-1.23)	<.0001
All-cause Mortality	1.15 (1.05-1.26)	0.0026



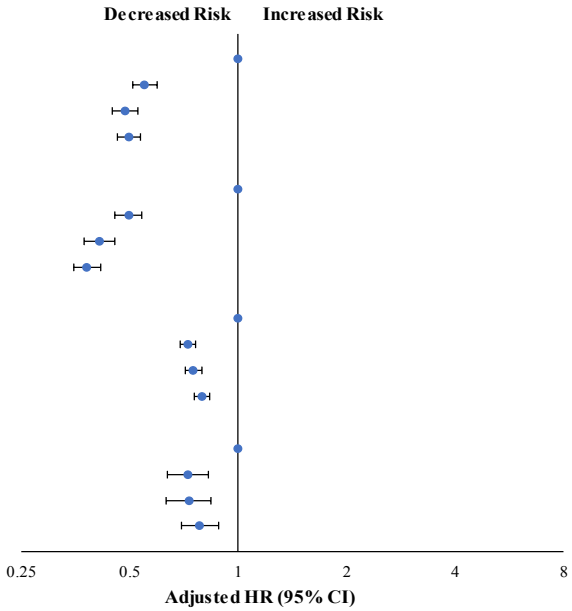
B) Age

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
ICU Admission		
18-34	1 (ref)	
35-49	1.22 (1.07-1.39)	0.0036
50-64	1.45 (1.29-1.64)	<.0001
65+	1.40 (1.24-1.58)	<.0001
IMV		
18-34	1 (ref)	
35-49	1.27 (1.09-1.48)	0.0026
50-64	1.63 (1.41-1.88)	<.0001
65+	1.38 (1.19-1.60)	<.0001
ARDS/Respiratory Failure		
18-34	1 (ref)	
35-49	1.42 (1.32-1.54)	<.0001
50-64	1.64 (1.53-1.77)	<.0001
65+	1.57 (1.45-1.69)	<.0001
All-cause Mortality		
18-34	1 (ref)	
35-49	1.43 (1.03-1.98)	0.0313
50-64	1.99 (1.47-2.69)	<.0001
65+	3.72 (2.77-4.99)	<.0001

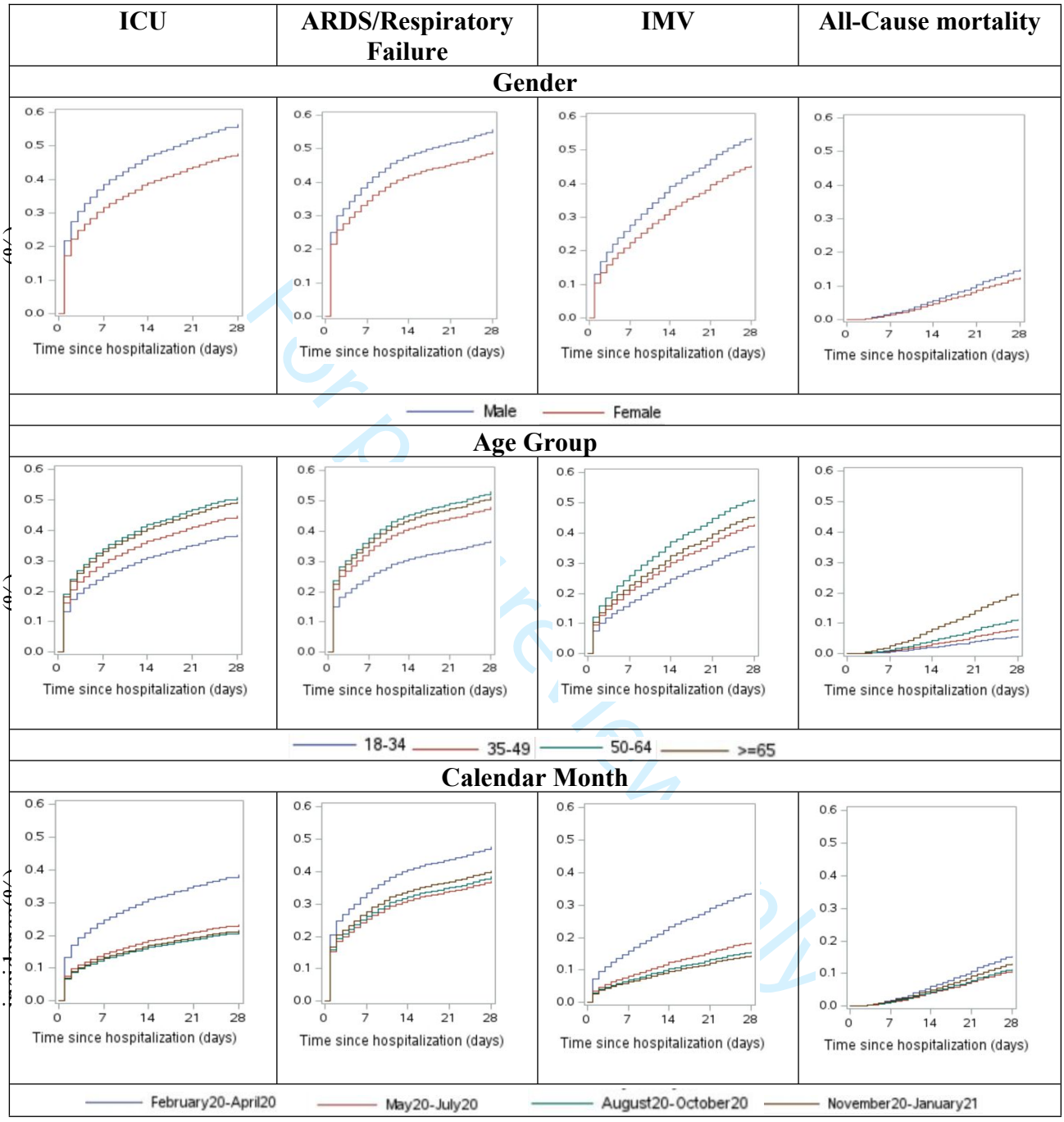


C) Calendar Month

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
ICU Admission		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.55 (0.51-0.60)	<.0001
Aug, 2020 - Oct, 2020	0.49 (0.45-0.53)	<.0001
Nov, 2020 - Jan, 2021	0.50 (0.46-0.54)	<.0001
IMV		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.50 (0.46-0.54)	<.0001
Aug, 2020 - Oct, 2020	0.41 (0.37-0.45)	<.0001
Nov, 2020 - Jan, 2021	0.38 (0.35-0.41)	<.0001
ARDS/Respiratory Failure		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.72 (0.69-0.76)	<.0001
Aug, 2020 - Oct, 2020	0.75 (0.71-0.79)	<.0001
Nov, 2020 - Jan, 2021	0.79 (0.76-0.83)	<.0001
All-cause Mortality		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.72 (0.63-0.82)	<.0001
Aug, 2020 - Oct, 2020	0.73 (0.63-0.84)	<.0001
Nov, 2020 - Jan, 2021	0.78 (0.69-0.88)	<.0001



S6 Figure. Model-adjusted Cumulative Incidence of Selected Outcomes among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Calendar Month – Probable Cohort



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	17-18
Study size	10	Explain how the study size was arrived at	11,12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11-12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11-12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-14

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-14 and supplement materials
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Abstract

Objective To examine age, gender, and temporal differences in baseline characteristics and clinical outcomes of adult patients hospitalized with COVID-19.

Design A cohort study using de-identified EMR from a global research network.

Setting/Participants 67,456 adult patients hospitalized with COVID-19 from the US;7,306 from Europe, Latin America, and Asia-Pacific between February 2020 and January 2021.

Results In the US cohort, compared to patients 18 to 34 years old, patients ≥ 65 had a greater risk of ICU admission (adjusted hazard ratio (aHR) 1·73, 95% CI 1·58-1·90), acute respiratory distress syndrome(ARDS)/Respiratory failure (aHR 1·86, 95% CI 1·76-1·96), invasive mechanical ventilation (IMV, aHR 1·93, 95% CI, 1·73-2·15), and all-cause mortality (aHR 5·6, 95% CI 4·36-7·18). Men appeared to be at a greater risk for ICU admission (aHR 1·34, 95% CI 1·29-1·39), ARDS/respiratory failure (aHR 1·24, 95% CI1·21-1·27), IMV (aHR 1·38, 95% CI 1·32-1·45), and all-cause mortality (aHR 1·16, 95% CI 1·08-1·24) compared to women. Moreover, we observed a greater risk of adverse outcomes during the early pandemic (i.e., February - April 2020) compared to later periods. In the ex-US cohort, the age and gender trends were similar; as for the temporal trend, the highest proportion of patients with all-cause mortality were also in February - April 2020; however, the highest percentages of patients with IMV and ARDS/Respiratory failure were in August - October 2020 followed by February - April 2020.

Conclusions This study provided valuable information on the temporal trend of characteristics and outcomes of hospitalized adult COVID-19 patients in both US and ex-US. It also described the population at a potentially greater risk for worse clinical outcomes by identifying the age and gender differences. Together, the information could inform the prevention and treatment

strategies of COVID-19. Furthermore, it can be used to raise public awareness of COVID-19's impact on vulnerable populations.

Strengths and limitations of this study

- This study investigated characteristics and clinical outcomes of COVID-19 patients using data from a global health research network, which includes COVID-19 test results and a wide range of clinical measures.
- The long follow-up (February 2020 to January 2021) allowed a thorough examination of the temporal trend of the COVID-19 clinical outcomes.
- The large sample size allowed extensive sensitivity analyses to test the robustness of the study.
- As with other observational studies using electronic health records, random measurement error is inevitable and may bias the results towards the null.

Introduction

The novel coronavirus disease 2019 (COVID-19) is a newly discovered infectious viral disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The virus not only affects the respiratory system but also causes damage to other systems, and may act as a precipitating factor to worsen existing conditions, potentially leading to death.[1,2] The first human case was reported in December 2019 in Wuhan City, China.[3] World Health Organization declared the COVID-19 outbreak a public health emergency of international concern on January 30, 2020 and a pandemic on March 11, 2020.[4] As of June 20, 2021, the pandemic has resulted in over 178·4 million cases and 3·8 million deaths worldwide.[5] The first case of COVID-19 in the United States (US) was reported on January 20, 2020 in Washington State.[6,7] As of June 20, 2021, the US had the highest number of reported infections, with more than 33·5 million confirmed cases and more than 0·6 million deaths.[5] A study conducted in China found higher cases of COVID-19 among men compared to women with higher case fatality in men compared to women (2·8% vs. 1·7%).[8] Similar gender disparity in mortality has been seen in reports from Italy[9], England, and Wales.[10] The Centers for Disease Control and Prevention also reported higher fatality among older adults with 80% of all COVID-19 deaths reported in the US occurring in adults ≥65 years.[11]

As COVID-19 cases have risen exponentially around the world since the start of the pandemic, there is a necessity to document the temporal changes in patient characteristics, and the impact of real-world clinical practice on outcomes including ICU admissions (US cohort only), ARDS/respiratory failure, invasive mechanical ventilation (IMV), and all-cause mortality over time among COVID-19 patients. The objectives of this study were to provide real-world

evidence on gender and age differences in COVID-19 outcomes and to understand temporal trends in outcomes among patients with COVID-19 in the US and outside of the US.

Methods

Data Source

This study used TriNetX® (www.trinetx.com), a global federated research network. The TriNetX database has been described in detail in other published papers.[12-16] TriNetX network provides a dataset of electronic medical records (EMR, diagnoses, procedures, medications, laboratory values, and genomic information) from different healthcare organizations (HCOs). The HCOs contributing EMR data to the TriNetX network are large academic medical institutions, specialty physician services, and community hospitals providing on average, seven years of historical patient data from both inpatient and outpatient facilities. The US analysis was conducted utilizing EMR data download from 44 different HCOs covering over 61 million patients that reside predominantly in the US; the data is de-identified based on the standard defined in Section §164·514(a) of the HIPAA Privacy Rule. The process by which Data Sets are de-identified is attested to through a formal determination by a qualified expert as defined in Section §164·514(b)(1) of the HIPAA Privacy Rule. The ex-US analysis used the federated cloud-based TriNetX network, representing 6·6 million patients from 12 HCOs in Spain, the United Kingdom (UK), Brazil, Australia, India, Malaysia, and Taiwan, as of January 31, 2021. The ex-US TriNetX platform provides aggregated counts and statistical summaries of de-identified information. Protected Health Information or Personal Data is not available to the users of the platform. As TriNetX allows real-time access to the data, the platform was queried to generate results for this study. The network contains data that is provided by participating HCOs, each of which represents and warrants that it has all necessary rights, consents, approvals, and authority

to provide the data to TriNetX so long as their name remains anonymous as a data source and their data are utilized for research purposes. The data shared through the TriNetX platform are attenuated to ensure that they do not include sufficient information to facilitate re-identification nor allow for the determination of which HCO contributed specific information about a patient. Within HIPAA, TriNetX has a business associate agreement with each of the HCOs. Overall, the TriNetX EMR database includes COVID-19 patients from mixed payer types, geographies, and demographic backgrounds, representing a geographically and socioeconomically diverse population both in and outside of the US.

Study Design, Setting, and Participants

This was an observational cohort study that identified patients at their earliest episode of COVID-19 and subsequently followed up to describe their disease progression, treatment received, and outcomes using EMR. This study included adults (aged ≥18 years) who were hospitalized with COVID-19. COVID-19 diagnosis was defined as the first occurrence from February 1, 2020 to January 31, 2021 of any of the following: 1) positive SARS-CoV-2 ribonucleic acid (RNA) or antigen test; 2) ICD-10-CM diagnosis code U07·1, J12·81, J12·89, or J80 on or after February 2020; 3) ICD-10-CM code B97·29 or B34·2 occurring between February 1, 2020 and April 30, 2020.

Patients were excluded, if 1) first COVID-19 diagnosis occurring within the last 28 days of the available data; 2) missing data on age or gender; 3) continuous hospitalization starting > 10 days before COVID-19 diagnosis date; 4) with diagnosis or procedure codes for labor and delivery during the index hospitalization; or 5) with diagnosis codes for trauma, injury, fracture, or poisoning during the first two days of the earliest hospitalization. See Figures 1a and 1b for the patient flow diagram for the US and ex-US analyses respectively. If a patient had multiple

hospitalizations that met the study criteria, only the earliest hospitalization was included in this study.

The index date was defined as the first COVID-19 diagnosis date or hospital admission date, whichever comes earlier; the follow-up window was from the index date to the earliest of the following: the end of data availability, discharge date, or death date. Health outcomes were assessed within the duration from the first COVID-19 related hospital admission date to the earliest of the following events: hospital discharge, death, end of data, or 28 days after hospital admission.

For temporal trend analysis, patients were stratified into four time periods based on their month of index date (February - April 2020, May - July 2020, August - October 2020, and November 2020 - January 2021) for all analyses.

Variables

The primary outcomes of interest were ICU admission, ARDS/respiratory failure, IMV, and all-cause mortality (please see medical codes in eAppendix Table 1). For ex-US, ICU admission was not reported given the consideration of potential misclassification. To comply with the data privacy agreement, only the patient's death month is available in the US data. Thus, the patient death date was inferred from a patient's last physically present/recorded date using the following: procedure (date), diagnosis (date), encounter (end date), vital signs (date), and medication (prescribing date).[17] In the ex-US analysis, the death date was used as reported in the platform.

Patient characteristics such as demographics (age, sex, race, geographic region, and ethnicity), and calendar month of index COVID-19 hospitalization were reported. The baseline comorbid conditions were evaluated using 12-month data prior to the index date (excluding index date).

Statistical methods

The demographic and clinical characteristics of the primary cohort and sub-cohorts at the index date are summarized using descriptive statistics. Mean, standard deviation (SD), standard error (SE), and 95% confidence interval (CI) were reported for continuous variables, and counts and percentages were reported for categorical variables.

For the US cohort, the proportional sub-distribution hazard model by Fine and Gray was used for estimating the hazard ratios (HRs) and cumulative incidence function (CIF) for all four outcomes; the hospital discharge date was treated as a competing risk in estimating HRs and CIF for mortality, whereas hospital discharge and death were treated as competing risks in estimating HRs and CIF for other outcomes.[18,19] Three separate Fine and Gray models were developed stratified by age group, gender, and time period; each model used the other two main categories of risk exposure (for example, gender and time period in the age group model) as covariates. The other covariates in each model were race, ethnicity, US region, hypertension, Type I/II diabetes, active cancer, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea. The cumulative incidence of selected outcomes was plotted against time from the day of admission through 28 days assuming censoring at the study end date (i.e., January 31, 2021) and stratified by gender, age, and time period respectively. All US analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) with a two-tailed *P*-value of <0·05 considered statistically significant. As for the ex-US cohort, the analysis was performed using a cloud-based TriNetX analytical

platform. The platform provided aggregated counts and statistical summaries but did not allow the estimation of adjusted hazard ratios and model-adjusted cumulative incidences.

As some diagnosis codes used to identify US COVID-19 patients in the study were not specific to COVID-19, we performed sensitivity analyses that include only patients with "confirmed" (at least one positive SARS-CoV-2 RNA or antigen test within 21 days of their index date) and "probable" COVID-19 diagnosis (no documented positive lab test for COVID-19 within 21 days following the index date). In the sensitivity analyses, we also examined patients' baseline characteristics, treatment during hospitalization, and selected outcomes in 'confirmed' and 'probable' cohorts in the US, respectively. The sensitivity analysis was not available for the ex-US study due to the limitation of the TriNetX ex-US analytical platform.

Patient and Public Involvement

No patient involved.

Results

A total of 67,456 patients hospitalized with COVID-19 were identified from February 2020 to January 2021 in the US (Figure 1a), with a mean (SD) age of 58·3(17·3) years old; 51·2% (n=34,518) were men (Table 1). The highest proportion of patients in the US cohort had their index hospitalization in November 2020 and December 2020 (15·9% and 17·7%, respectively). The most common comorbid condition was cardiovascular disease (n=25,970, 38·5%) including patients with hypertension (n=23,272, 34·5%), followed by gastrointestinal disorders (n=15,987, 23·7%), and type II diabetes (n=14,031, 20·8%) (Table 1). The proportion of patients with chronic lung diseases was higher in women compared to men, driven by a higher proportion of asthma in women (eAppendix Table 2). The burden of comorbidities increased with age (eAppendix Table 3). In the US, the proportion of White patients with index COVID-19

hospitalization increased over subsequent months with the highest proportion seen during November 2020 - January 2021; whereas the proportion of African American and Hispanic patients with index COVID-19 hospitalizations decreased over months, with the lowest seen during November 2020 - January 2021. The index COVID-19 hospitalizations in the Northeast region were highest at the beginning of the pandemic (27·7%), followed by a subsequent drop in infection rates between May - October 2020 then a sharp rise in November 2020 - January 2021 (14·7%). The Midwest region saw a gradual uptick in the infection rates over the course of the pandemic with the highest rates (21·9%) seen from November 2020 - January 2021. The US patients hospitalized with COVID-19 during November 2020 - January 2021 had more cardiovascular diseases compared to the patients in earlier months (eAppendix Table 3).

The ex-US cohort included a total of 7,306 patients hospitalized with COVID-19 (Figure 1b), with 91.4% of them from Europe (eAppendix Table 4). The mean (SD) age, 61·0 (16·9), was greater than that in the US cohort, 55·1% of the cohort were men, and the 48·5% patients had their index hospitalization in February - April 2020. A detailed description of the ex-US cohort was presented in Table 1.

In the US cohort, the most commonly used medications post index were acetaminophen 45,269 (67·1%) followed by enoxaparin 33,370 (49·5%), insulin (32·7%), heparin (14·8%), aspirin (26·7%), azithromycin (23·7%), and methylprednisolone (19·8%). The most commonly-used antiviral among the US cohort was remdesivir 13,667 (20·3%). Among the ex-US cohort, the most frequently used medication post index was also acetaminophen 4,719 (64·6%), followed by azithromycin 2,842 (38·9%), hydroxychloroquine 2,119 (29·0%), methylprednisolone 1,563 (21·4%), insulin 1,476 (20·2%), dexamethasone 1,454 (19·9%), and amoxicillin 1,381 (18·9%). For additional details refer to eAppendix Tables 5 and 6 in the Supplement.

Among US patients, this study showed that outcomes worsened with increased age, with the highest aHR in the age groups of 50-64 and 65+ compared to those aged 18-39 (reference group). In particular, patients ≥65 years had higher aHRs compared to the reference group for ICU admission (17·6% vs 7·2%; aHR 1·73, 95% CI 1·58-1·90, p<0.0001), ARDS/respiratory failure (43·1% vs 18·3%; aHR 1·86, 95% CI 1·76 - 1·96, p<0.0001), IMV (13·8% vs 5·1%; aHR 1·93, 95% CI, 1·73-2·15, p<0.0001), and all-cause mortality (9·6% vs. 0·8%; aHR 5·6, 95% CI 4·36-7·18, p<0.0001). In contrast to women, men were more often admitted to the ICU (16·9% vs 12·3%; aHR 1·34, 95% CI 1·29-1·39, p<0.0001), and were at higher risk for ARDS/respiratory failure (41·0% vs 32·8%; aHR 1·24, 95% CI 1·21-1·27, p<0.0001), IMV (13·7% vs 9·4%; aHR 1·35, 95% CI 1·32-1·45, p<0.0001), and all-cause mortality (6·1% vs 4·6%; aHR 1·16, 95% CI 1·08-1·24, p<0.0001). Moreover, we observed the highest risk of worse outcomes during the early pandemic (i.e., February - April 2020) compared to the later three time periods (May - July 2020, August - October 2020, and November 2020 - January 2021), with significantly higher aHRs for all four outcomes. The risk of ICU admission and IMV decreased across the four time periods. The risk of ARDS/respiratory failure during the summer period of May - July 2020 were lowest among all four periods, while the all-cause mortality of August - October 2020 and November 2020 - January 2021 were lower, compared to the periods of February - April 2020, or May - July 2020. (Figure 2 and eAppendix Table 7)

In the US analysis, the model-adjusted cumulative incidence for all four outcomes measures at 7, 14, and 28 days were consistently higher among men compared to women, and among patients over 50 years of age compared to 18 - 49 years old. With respect to time periods, the adjusted cumulative incidence for ICU admission, ARDS/respiratory failure, and IMV was markedly

greater among patients with index date in February - April 2020 as compared to patients having their index COVID-19 hospital admission during the other three time periods. (Figure 3)

The ex-US analysis demonstrated similar age, and gender trends, although the data format and availability did not allow for similarly detailed analyses. Patients≥65 years, compared to the age group of 18-39, had a higher incidence of ARDS/respiratory failure (31·5% vs 17·4%) and all-cause mortality (23·4% vs. 1·0%). A higher percentage of patients aged between 50-64 years old had IMV compared to the other two age groups. The differences in adverse clinical events were also evident across gender; with higher proportions of men experienced ARDS/respiratory failure (29·0% vs 23·4%), IMV (5·0% vs 2·3%), and all-cause mortality (13·8% vs 10·4%) compared to women. The proportion of patients with ARDS/respiratory failure and IMV were highest in August - October 2020 and lowest in May - July 2020. As for the temporal trend, though the highest all-cause mortality was also observed in the period of February - April 2020, the highest and lowest percentages of patients with IMV and ARS/respiratory failure were found in August - October 2020 and May - July 2020, respectively (Figure 4).

In the US analysis, the sensitivity analyses among subgroups of patients with confirmed COVID-19 diagnosis showed similar distributions of baseline characteristics, as well as comparable trends in adjusted cumulative incidence and adjusted hazard ratios for the primary outcomes of interest across age, gender, and time periods. Similar trends were also observed in the probable cohort. Details of sensitivity analysis results are presented in eAppendix Tables 8 - 12 and Figures 1 - 6 in the supplement.

Discussion

The COVID-19 pandemic has been rapidly evolving in the US and other countries. It is critical to understand the demographic distribution and temporal trends in adverse clinical events associated with the disease such as ICU admissions, ARDS/respiratory failure, IMV, and all-cause mortality across the globe. The evidence generated from this study showed that patients ≥ 65 years seemed to have an approximately 2-fold increased risk of ICU admission, ARDS/respiratory failure, and IMV; and about a 5·6-fold increase in all-cause mortality. The 7, 14, and 28 day (post hospital admission date) adjusted cumulative incidence of these adverse clinical events was consistently higher in patients ≥ 65 years compared to those aged 18 - 49 years, suggesting elevated risk throughout the course of disease among older patients. Similar trends were observed in ex-US patients for ARDS/respiratory failure and all-cause mortality, while the risk of IMV was similar among patients aged 18 - 49 and aged 65 or over. These results were in accordance with prior reports from studies across the globe.[6,20-23] As shown in eTable 2, elderly patients had a higher prevalence of pre-existing comorbidities, which could have undermined patients' ability to fight against infections.[24] In addition, Iwasaki et al. found that declined T-cell response is associated with increased age,[25] which could lead to lower efficacy in viral clearance and a higher likelihood of inflammatory cytokine storm, resulting in poor health outcomes.

Men had an approximate 20% - 41% increased risk of all-cause mortality, ARDS/respiratory failure, IMV, and ICU admissions compared to women. The increased risk of these clinical outcomes remained consistently higher in men over 7 - 28 days post index suggesting worse disease prognosis in men. These results were also in line with prior reports.[6,21,26-31] For example, Fried et al. showed increased mortality and morbidity associated with older age and male sex

using medical claims data.[6] Palaiodimos *et al*., reported increasing age and male sex were independently associated with worse in-hospital outcomes.[21] However, Fried's study only covered the period from February - April 2020 while the study by Palaiodimos *et al.* only included 200 patients from one medical center in New York. Our study included longitudinal data from thousands of patients lives in the US and outside of the US, thereby providing further support for the observation that gender seemed to be a differential factor in adverse clinical outcomes. Studies from national statistical agencies across England and Wales, France, Germany, Italy, Netherlands, Portugal, Korea, and Spain also observed that men had twice the risk of death from COVID-19 using data collated by the National Institute for Demographic Studies.[20] Many factors might contribute to the observed gender difference in adverse clinical outcomes. For example, Iwasaki *et al.* showed that immune responses to SARS-CoV-2 differed between men and women, possibly resulting from men having higher plasma levels of innate immune cytokines and poorer T cell activation.[25] Protein angiotensin-converting enzyme 2 (ACE2), a key protein involved in the entry of SARS-CoV-2 into cell and the protection from lung injury, was also higher in women than men.[32] Moreover, women were more likely to follow healthy behaviors, such as better hygiene practices and lower level of smoking and alcohol use, which could also explain better outcomes in women.[33,34]

Results of this study found a significantly higher cumulative rate and adjusted HR for ARDS/respiratory failure, and IMV among patients ≥ 65 years and men, in line with prior reports of hospitalized COVID-19 patients showing greater risk among these demographic subgroups.[35,36] Analysis of the trends of ICU admissions in the US and all-cause mortality over time periods in both US and ex-US revealed that patients with index date in February - April 2020 were at increased risk of death compared to patients diagnosed in the later time period. This

could potentially be due to healthcare facilities being overwhelmed with the volume of COVID-19 admissions at the onset of the pandemic in some areas. In addition, limited information about COVID-19, and lack of experience in the clinical management of the disease leading to a trial and error approach using different pharmaceutical and non-pharmaceutical interventions to manage disease progression and spread, and inexperience in resource management of the healthcare staff in the early stage of COVID-19 pandemic[37-39] could have resulted in poorer outcomes among patients diagnosed at the beginning of the pandemic. Besides, the lack of SARS-CoV-2 diagnosis kits in the early pandemic could play an important role. Thus, the diagnosis kits were likely to have been reserved for the sickest patients, with the consequence that rates of ICU admission, ARDS/respiratory failure, IMV, and death will appear higher at earlier time points. It was also possible that these trends were confounded by other unobserved patient-related or environmental risk factors.

This study was not meant to compare the US and ex-US cohorts; however, there are some differences between ARDS/Respiratory failure and IMV in temporal trend. For example, ex-US patients seemed to have a much lower ARDS/Respiratory failure and IMV in May - July 2020, compared to the US cohort. Additionally, ARDS/Respiratory failure and IMV proportion in November 2020 - January 2021 were much lower compared to August - October 2020 in the ex-US cohort; while the proportions of these two outcomes during these two periods were closer in the US cohort. This is very likely due to different non-pharmaceutical interventions for the COVID-19 pandemic (e.g., lockdown policies) implemented by each country within the ex-US cohorts as well as different response strategies each country's HCO took. In addition, the baseline characteristics of the US and ex-US cohorts differed, which may reflect the differences in the underlying demographic distribution and healthcare systems across countries. Of note, the

prevalence of some comorbidities in the ex-US cohort was lower than the prevalence in previous studies conducted in non-US countries. For example, in the current study, the prevalence of hypertension was 13·1% in the ex-US cohort, whereas a recent meta-analysis of COVID-19 studies showed that the prevalence of hypertension was 39·5% in China, 35·9% in Italy, and 27·8% in the UK.[40] The difference might be due to different compositions of the patient populations across studies. For example, the ex-US cohort in the current study had 55·1% men, while the studies included in the meta-analysis had a male to female ratio of 1·57 on average. Moreover, the current study had a longer follow-up than previous studies, which might also explain different patient characteristics across studies.

Our study has certain limitations. First, there is often a trade-off between sensitivity and specificity in defining a representative real-world cohort of COVID-19 patients. We performed a sensitivity analysis using only patients with COVID-19 specific clinical diagnosis, and patients with lab confirmation of disease. The results from our sensitivity analyses were similar to those from our primary analyses, suggesting that the potential effect of misclassification was minimal and did not impact the study conclusion. Second, compared to claims data, the EMR database may provide more timely, detailed, and accurate patient health information, but it only reflects the patient experience in the participating healthcare systems within the research network[41,42], and the information from medical encounters before the COVID-19 hospitalization or with other doctors/providers outside the research network is not captured.[42]Third, among deceased patients, as the death information was available at a monthly level, the patients' last physically present date in the database was used to infer the death date, but this measurement error should be non-differential and bias the results towards null. Fourth, for the ex-US analysis, the statistical analysis has been built into the platform and does not allow customization, which has limited the

ability to calculate statistics such as standard error, confidence interval, and model the risk. Moreover, due to data privacy, the number of COVID-19 patients contributed by each country could not be specified. Finally, though COVID-19 patients included in this study were from multiple participating HCOs in the US and outside of the US, it may not fully represent the wider population across the globe.

Conclusions

Temporal trends in adverse clinical outcomes among patients with COVID-19 from this multinational EMR database comprising of patients from diverse demographic backgrounds suggest that older age, male gender, and diagnosis in earlier months of the pandemic conferred greater risk for ICU admissions, ARDS/respiratory failure, IMV, and all-cause mortality over 7 - 28 days post index hospital admission. This evidence may be helpful in identifying patients at greater risk of these adverse clinical events, and in so doing, inform clinical interventions, and increase public awareness.

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Competing Interests:

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Patient consent for publication: Not required.

Ethical approval: This study was approved by Observational Protocol Review Committee at Bristol-Myers Squibb Co.. This work used existing de-identified data which does not constitute research with human subjects because there is no interaction with any individual and no identifiable private information were used. No ethical approval was considered necessary.

Data sharing: Data for this study are not publicly available; access to which is restricted on commercial terms. Please contact authors for information on data availability.

Supplemental materials: This content has been supplied by the author(s).

Figure Caption

Figure 1. Flow Diagram of US and ex-US Study Cohorts

Figure 2. The Forest Plots of Model-adjusted Hazard Ratios among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period

Figure 3. Model-adjusted Cumulative Incidence Plots of Selected Outcomes among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period

Figure 4. The Selected Outcomes among ex-US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period

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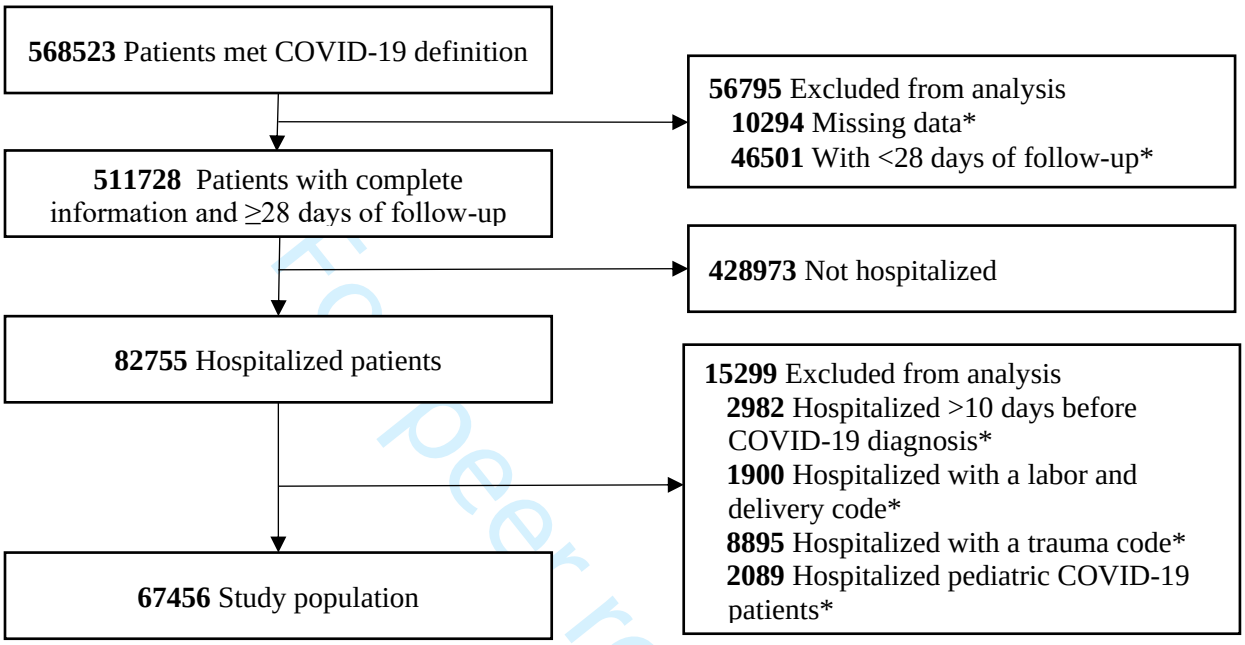
Table 1. Baseline Characteristics of US and ex-US Hospitalized Adult Patients with COVID-19

Characteristic	Patient, %	
	US Cohort (n=67456)	**Ex-US Cohort** (n=7306)
Age, Mean[SD], y	58.3(17.3)	61.0 (16.9)
Male	51.2	55.1
Race		
White	56.1	19.4
Black or African American	23.7	0.8
Asian	3.2	0.8
American Indian or Other Pacific Islander	0.9	NA
Unknown	16.1	79.0
Ethnicity		
Hispanic	24.8	NA
Month of index		
February, 2020	1.2	0.3
March, 2020	6.7	30.1
April, 2020	11.1	18.4
May, 2020	7.3	6.0
June, 2020	7.8	3.2
July, 2020	11.1	2.4
August, 2020	6.5	8.5
September, 2020	5.3	13.3
October, 2020	8.5	7.7
November, 2020	15.9	5.2
December, 2020	17.7	4.6
January, 2021	1.0	0.4
Baseline Comorbidities		
Cardiovascular disease	38.5	15.9
Hypertension	34.5	13.1
Gastrointestinal disorders	23.7	8.6
Skin disorder	12.6	5.5
Cancer	7.6	5.8
Solid tumors	5.7	4.2
Hematologic malignancies	2.6	2.5
Chronic kidney disease	12.2	4.1
Chronic lung disease	12.8	6.8
Asthma	6	2.2
Chronic obstructive pulmonary disease	7.7	4.5
Pulmonary fibrosis	1	0.5
Diabetes mellitus		
Type I Diabetes	1.6	0.4
Type II Diabetes	20.8	6.7
Liver disease	2.5	5.6

Figure 1. Flow Diagram of US and ex-US Study Cohorts

A) US Cohort



*The counts in the exclusion criteria were not mutual exclusive.

B) ex-US Cohort

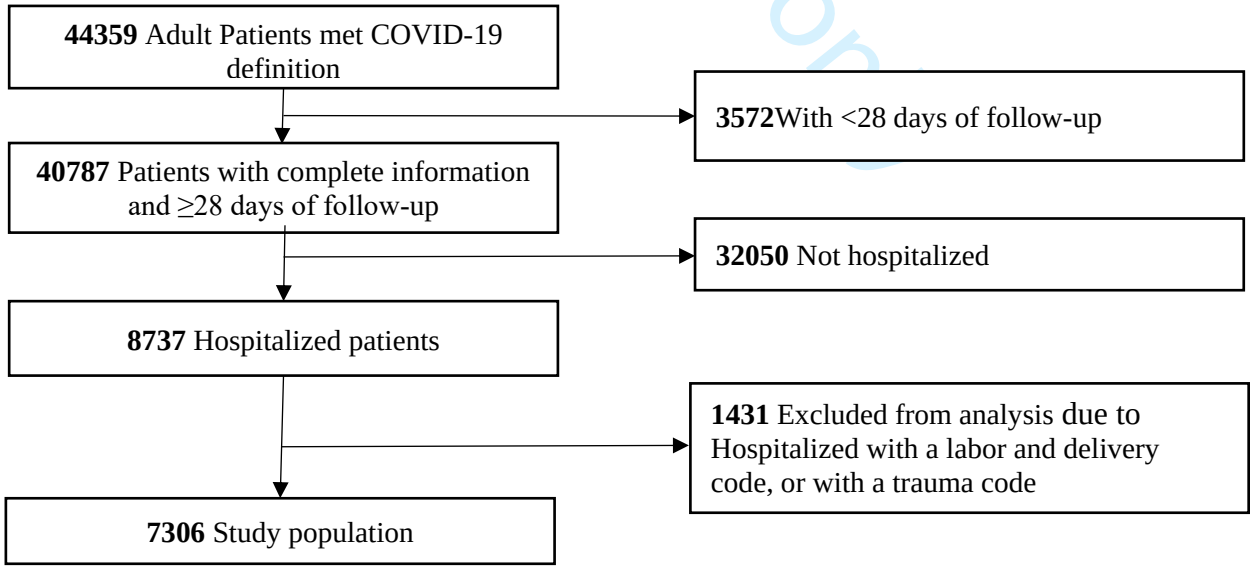
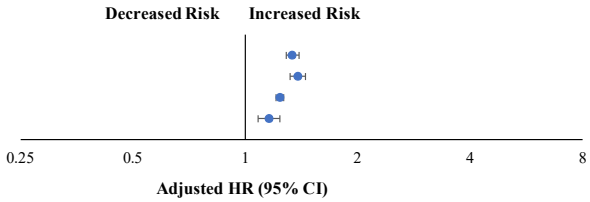


Figure 2 The Forest Plots of Adjusted Hazard Ratios among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period

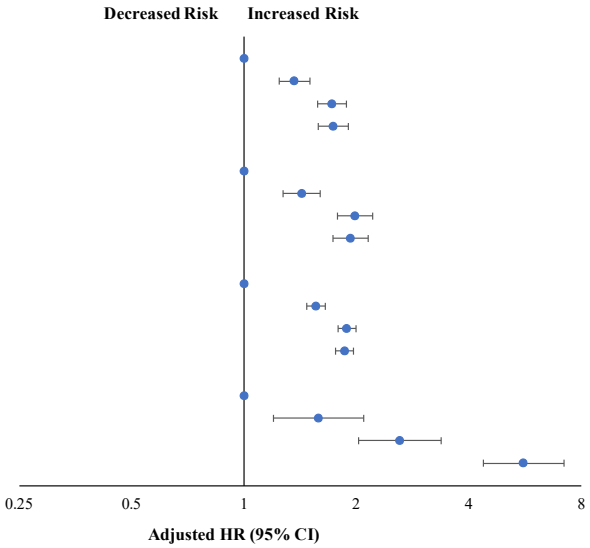
A) Gender

Characteristics	Adjusted HR (95%CI)	Pr > ChiSq
Male (Reference : Female)		
ICU Admission	1.34 (1.29-1.39)	<.0001
IMV	1.38 (1.32-1.45)	<.0001
ARDS/Respiratory Failure	1.24 (1.21-1.27)	<.0001
All-Cause Mortality	1.16 (1.08-1.24)	<.0001



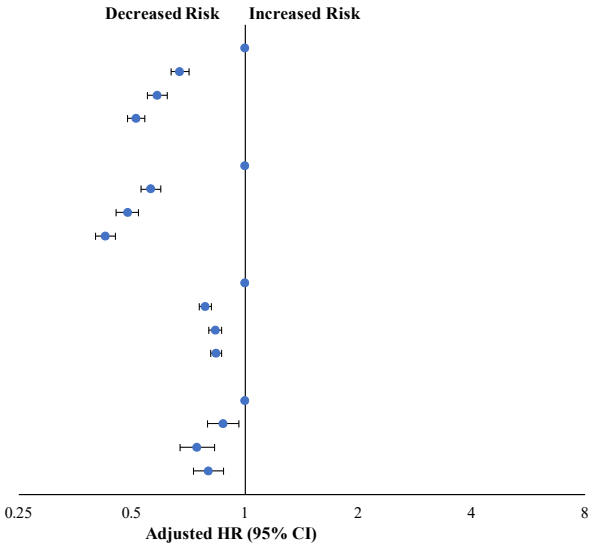
B) Age

Characteristics	Adjusted HR (95%CI)	Pr > ChiSq
ICU Admission		
18-34	1 (ref)	
35-49	1.36 (1.24-1.50)	<.0001
50-64	1.72 (1.57-1.88)	<.0001
65+	1.73 (1.58-1.90)	<.0001
IMV		
18-34	1 (ref)	
35-49	1.43 (1.27-1.60)	<.0001
50-64	1.98 (1.78-2.21)	<.0001
65+	1.93 (1.73-2.15)	<.0001
ARDS/Respiratory Failure		
18-34	1 (ref)	
35-49	1.56 (1.47-1.65)	<.0001
50-64	1.88 (1.78-1.99)	<.0001
65+	1.86 (1.76-1.96)	<.0001
All-Cause Mortality		
18-34	1 (ref)	
35-49	1.58 (1.20-2.09)	0.0012
50-64	2.62 (2.03-3.37)	<.0001
65+	5.60 (4.36-7.18)	<.0001



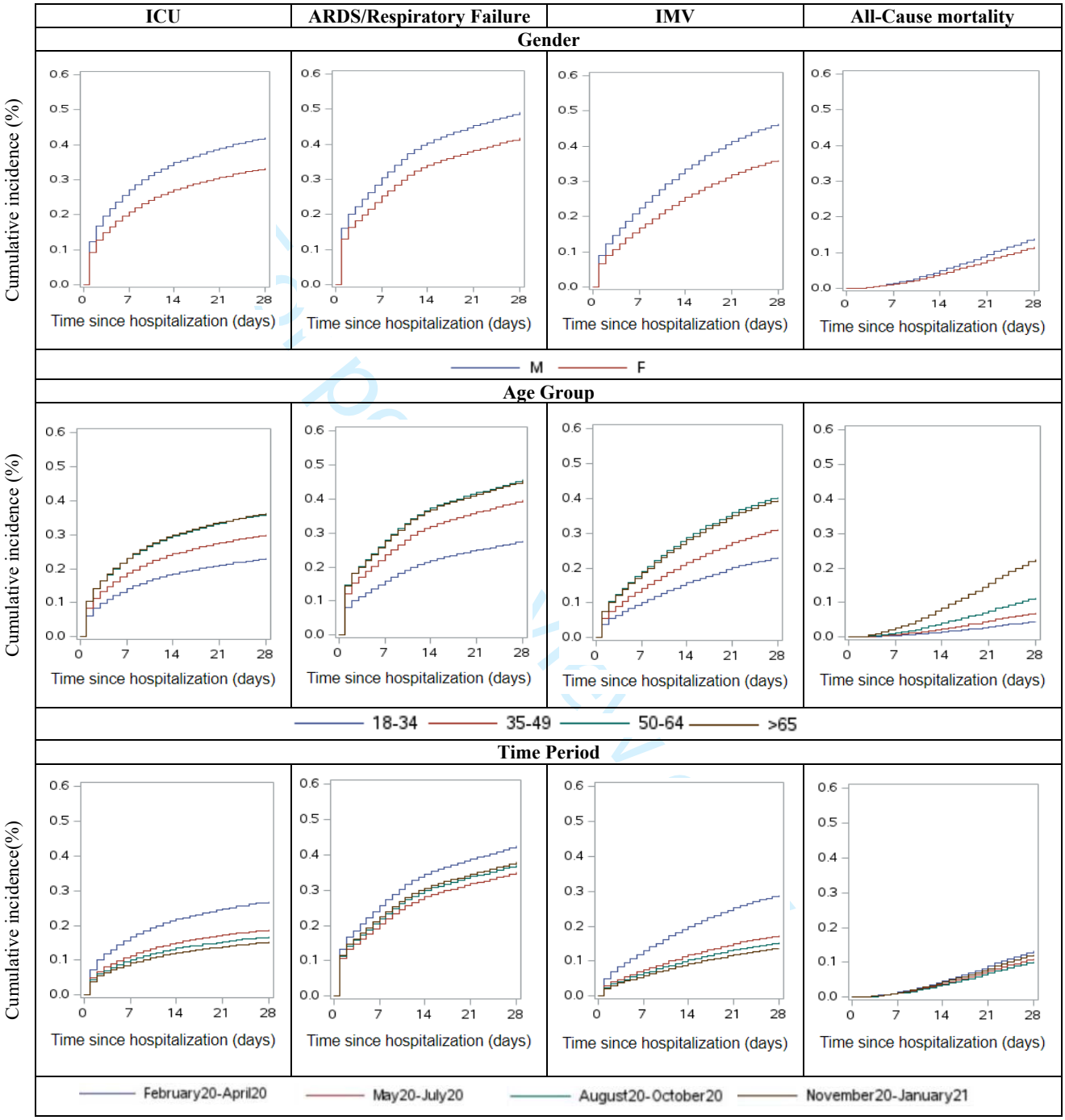
C) Calendar Month

Characteristics	Adjusted HR (95%CI)	Pr > ChiSq
ICU Admission		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.67 (0.64-0.71)	<.0001
Aug, 2020 - Oct, 2020	0.58 (0.55-0.62)	<.0001
Nov, 2020 - Jan, 2021	0.51 (0.49-0.54)	<.0001
IMV		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.56 (0.53-0.60)	<.0001
Aug, 2020 - Oct, 2020	0.49 (0.45-0.52)	<.0001
Nov, 2020 - Jan, 2021	0.43 (0.40-0.45)	<.0001
ARDS/Respiratory Failure		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.78 (0.76-0.81)	<.0001
Aug, 2020 - Oct, 2020	0.83 (0.80-0.87)	<.0001
Nov, 2020 - Jan, 2021	0.84 (0.81-0.87)	<.0001
All-Cause Mortality		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.87 (0.80-0.96)	0.0056
Aug, 2020 - Oct, 2020	0.75 (0.67-0.83)	<.0001
Nov, 2020 - Jan, 2021	0.80 (0.73-0.88)	<.0001



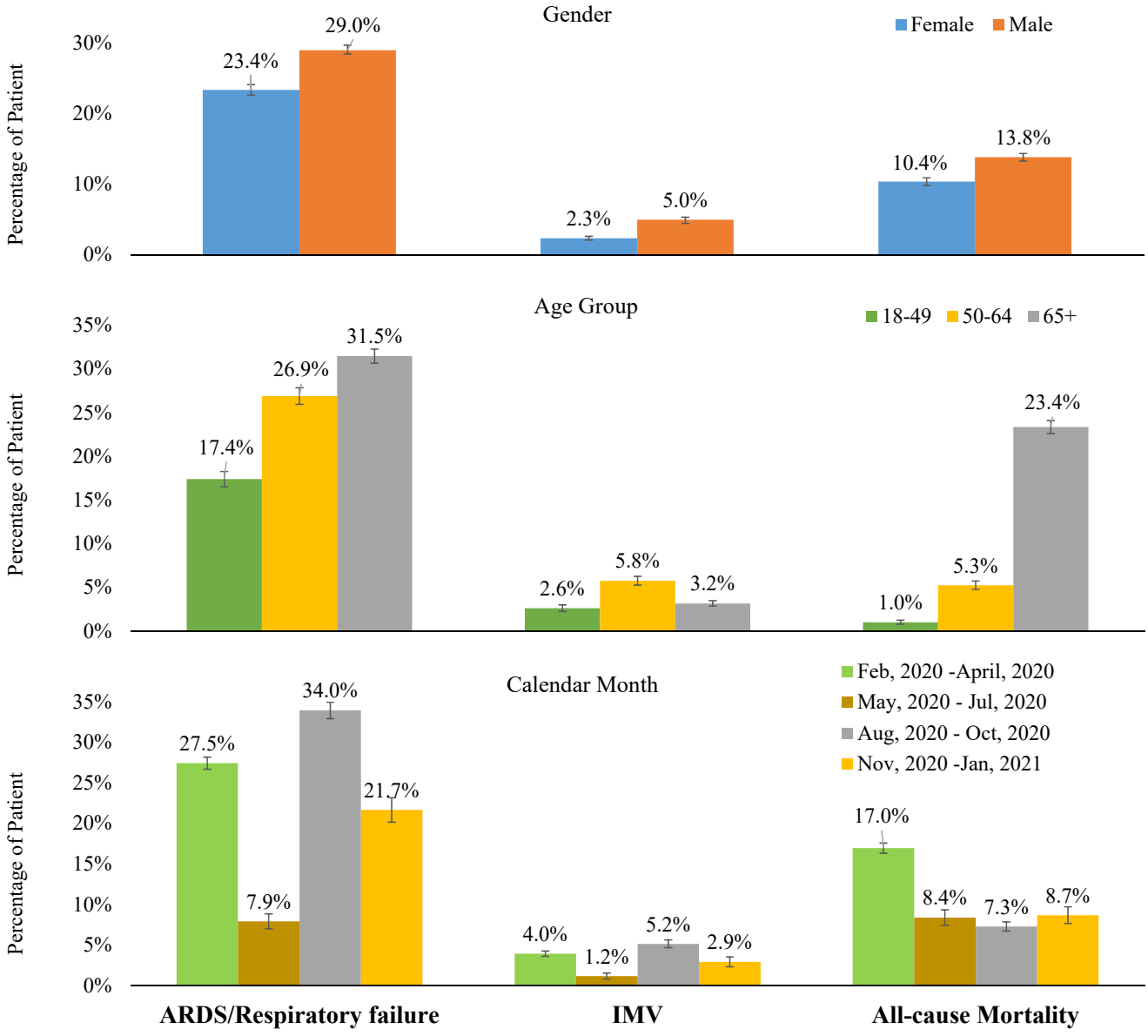
HR: the abbreviation of Hazard Ratio; ARDS: the abbreviation of acute respiratory distress syndrome; ICU: the abbreviation of intensive care unit; IMV: the abbreviation of invasive mechanical ventilation. Three separate Fine and Gray models were developed stratified by age group, gender, and time period; each model used the other two main categories of risk exposure (for example, gender and calendar month in the age group model) as covariates. The other covariates in each model were race, ethnicity, US region, hypertension, diabetes (Type I and II), active cancer, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea.

Figure 3 Regression-adjusted Cumulative Incidence Plots of Selected Outcomes among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period



ARDS: the abbreviation of acute respiratory distress syndrome; ICU: the abbreviation of intensive care unit; IMV: the abbreviation of invasive mechanical ventilation; Three separate Fine and Gray models were developed stratified by age group, gender, and time period; each model used the other two main categories of risk exposure (for example, gender and calendar month in the age group model) as covariates. The other covariates in each model were race, ethnicity, US region, hypertension, diabetes (Type I and II), active cancer, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea.

Figure 4 The Selected Outcomes among ex-US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period



Error bars reflect standard errors. ARDS: the abbreviation of acute respiratory distress syndrome; ICU: the abbreviation of intensive care unit; IMV: the abbreviation of invasive mechanical ventilation

Supplement

eTable 1 Medical Codes of Outcome Measures (ARDS/respiratory failure or IMV)

Criterion Name	Code Type	Code
ARDS	ICD-10-CM diagnosis	J80
respiratory failure	ICD-10-CM diagnosis	J96.0
respiratory failure	ICD-10-CM diagnosis	J96.01
respiratory failure	ICD-10-CM diagnosis	J96.02
respiratory failure	ICD-10-CM diagnosis	J96.20
respiratory failure	ICD-10-CM diagnosis	J96.21
respiratory failure	ICD-10-CM diagnosis	J96.22
Invasive Mechanical Ventilation	ICD-10-CM Diagnosis	Z99.12
Invasive Mechanical Ventilation	ICD-10-CM Diagnosis	Z99.11
Invasive Mechanical Ventilation	ICD-9-CM Diagnosis	V46.1
Invasive Mechanical Ventilation	ICD-9-CM Diagnosis	V46.11
Invasive Mechanical Ventilation	ICD-10-PCS	5A1955Z
Invasive Mechanical Ventilation	ICD-10-CM Procedure	5A1945Z
Invasive Mechanical Ventilation	ICD-10-CM Procedure	5A1935Z
Invasive Mechanical Ventilation	ICD-10-CM Procedure	0BH18EZ
Invasive Mechanical Ventilation	ICD-10-CM Procedure	0BH17EZ
Invasive Mechanical Ventilation	ICD-10-CM Procedure	0BH13EZ
Invasive Mechanical Ventilation	ICD-10-CM Procedure	0B21XEZ
Invasive Mechanical Ventilation	CPT	99504
Invasive Mechanical Ventilation	CPT	94004
Invasive Mechanical Ventilation	CPT	94003
Invasive Mechanical Ventilation	CPT	94002
Invasive Mechanical Ventilation	CPT	31730
Invasive Mechanical Ventilation	CPT	31502
Invasive Mechanical Ventilation	CPT	31500
Invasive Mechanical Ventilation	ICD-9-CM Procedure	97.23
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.72
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.71
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.70
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.7
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.05
Invasive Mechanical Ventilation	ICD-9-CM Procedure	96.04
Invasive Mechanical Ventilation	ICD-10-CM Diagnosis	Z99.1

eTable 2. Baseline Characteristics of US Hospitalized Adult COVID-19 Patients by Gender – Overall Cohort

Characteristic	Patient, No. (%)		
	All (n=67456)	Male (n=34518)	Female (n=32938)
Age, Mean[SD], y	58.3(17.3)	58.8(16.4)	57.6(18.1)
Race			
White	56.1	57.6	54.6
Black or African American	23.7	21.3	26.1
Asian	3.2	3.3	3.1
American Indian or Alaska Native	0.6	0.5	0.6
Native Hawaiian or Other Pacific Islander	0.3	0.3	0.3
Unknown	16.1	16.9	15.3
Ethnicity			
Hispanic	16.2	16.9	15.5
Site of diagnosis at inpatient setting	85.3	86.5	84.1
Mode of diagnosis			
Both	48.0	48.2	47.9
Clinical	41.8	42.2	41.4
Lab	10.2	9.7	10.7
Month of index			
February, 2020	1.2	1.4	1.1
March, 2020	6.7	7.1	6.3
April, 2020	11.1	11.4	10.7
May, 2020	7.3	7.2	7.3
June, 2020	7.8	7.7	7.8
Jul, 2020	11.1	10.9	11.3
August, 2020	6.5	6.2	6.8
September, 2020	5.3	5.1	5.4
October, 2020	8.5	8.4	8.6
November, 2020	15.9	15.6	16.1
December, 2020	17.7	17.8	17.6
January, 2021	1.0	1.1	1.0
US Census division			
Midwest	15.59	15.5	15.7
Northeast	13.10	13.2	13.0
South	45.44	44.1	46.8
West	3.95	4.1	3.8
Baseline Comorbidities			
Gastrointestinal disorders	27.3	24.7	30.0
Skin disorder	13.7	12.9	14.6
Cancer	7.9	8.3	7.6
Solid tumors	6.0	6.2	5.8
Hematologic malignancies	2.7	2.9	2.5
Cardiovascular disease	46.5	48.1	44.8
Chronic kidney disease	14.1	15.5	12.7
Chronic dialysis	0.9	1.0	0.8
Chronic lung disease	16.2	14.3	18.2
Asthma	7.4	4.8	10.2
COPD	9.8	10.1	9.6
Pulmonary fibrosis	0.9	1.1	0.8

Diabetes Mellitus			
Type I	1.4	1.5	1.3
Type II, diabetic	25.4	26.1	24.5
Diabetes unknown	3.3	3.4	3.2
Liver disease	2.6	3.1	2.1
Hospitalization with infection in the past year	8.3	8.1	8.5

eTable 2. Baseline Characteristics of US Hospitalized Adult COVID-19 Patients by Age Group – Overall Cohort

Characteristic	Patient, %			
	Age 18-34 (n= 7859)	**Age 35-49 (n= 12365)**	**Age 50-64 (n= 20382)**	**Age 65+ (n= 26850)**
Age, Mean[SD],y	27.39(4.6)	42.64(4.4)	57.42(4.3)	75.10(6.9)
Sex (Males)	42.4	50.4	54.5	51.6
Race				
White	47.0	46.8	54.3	64.5
Black or African American	27.1	25.2	25.7	20.4
American Indian or Alaska Native	0.6	0.8	0.6	0.4
Asian	2.8	3.3	3.4	3.1
Native Hawaiian or Other Pacific Islander	0.3	0.5	0.4	0.2
Unknown	22.2	23.3	15.7	11.3
Ethnicity				
Hispanic	24.1	25.2	17.3	8.9
Month of index				
February, 2020	0.9	1.2	1.4	1.2
March, 2020	6.5	7.8	7.3	5.8
April, 2020	11.3	12.5	11.1	10.3
May, 2020	8.5	8.5	7.1	6.4
June, 2020	9.9	9.0	7.6	6.6
Jul, 2020	12.9	12.3	11.5	9.8
August, 2020	7.6	6.7	6.3	6.2
September, 2020	5.9	5.3	5.0	5.2
October, 2020	8.0	8.3	8.5	8.8
November, 2020	12.9	13.7	15.6	17.9
December, 2020	14.6	13.7	17.6	20.5
January, 2021	0.8	0.9	1.0	1.2
US Census division				
Midwest	12.0	12.2	15.0	18.7
Northeast	17.7	14.2	12.8	11.5
South	47.8	48.8	46.0	42.9
West	6.3	5.3	4.3	2.4
Baseline Comorbidities				
Gastrointestinal disorders	19.7	22.3	27.2	31.8
Skin disorder	10.9	11.4	12.7	16.4
Atopic dermatitis	0.3	0.3	0.2	0.2
Autoimmune diseases				
Systemic lupus erythematosus	0.7	0.8	0.7	0.4
Rheumatoid arthritis	0.3	0.7	1.5	2.0
Psoriasis, including psoriatic arthritis	0.3	0.6	0.7	0.6
Inflammatory bowel disease	0.3	0.2	0.2	0.1
Multiple sclerosis	0.3	0.5	0.6	0.4
Glomerulonephritis	0.6	0.5	0.4	0.2
Autoimmune thyroid disease	0.3	0.3	0.2	0.2
Cancer	2.5	3.9	7.4	11.7
Solid tumors	1.3	2.7	5.5	9.3
Breast	0.2	0.7	1.0	1.5

Prostate	0.0	0.1	0.6	2.4
Lung	0.2	0.3	1.0	1.7
Other	1.2	2.1	4.2	5.9
Hematologic malignancies	1.5	1.6	2.7	3.5
Leukemia	0.3	0.3	0.6	0.9
Lymphoma	0.4	0.4	0.6	0.8
Multiple myeloma (MM)	0.0	0.1	0.5	0.5
Other	0.9	0.8	1.3	1.6
Cardiovascular disease	11.9	28.2	47.5	64.2
Coronary artery disease	0.5	3.0	9.6	21.2
Peripheral vascular disease	0.4	1.2	3.6	7.3
Cerebrovascular disease	0.5	1.2	2.6	6.8
Hypertension	11.0	26.6	44.0	58.1
Congestive heart failure	1.5	4.4	8.7	17.4
Atrial Fibrillation	0.5	1.6	5.5	17.6
Chronic kidney disease	3.3	7.1	12.3	21.9
Stage I	0.1	0.1	0.1	0.2
Stage II	0.3	0.6	1.3	1.8
Stage III	0.8	1.9	4.1	9.5
Stage IV	0.5	1.0	1.7	3.3
Stage V (end stage renal disease)	1.3	2.8	3.5	3.3
Unknown	2.8	6.3	10.9	19.1
Chronic dialysis	0.4	0.9	15.2	21.5
Hemodialysis	0.4	0.8	1.0	1.0
Peritoneal dialysis	0.0	0.0	0.0	0.0
Chronic lung disease	9.9	10.5	15.2	21.4
Asthma	9.3	8.5	7.9	6.0
Chronic obstructive pulmonary disease	0.6	2.4	8.6	16.9
Pulmonary fibrosis	0.2	0.5	0.7	1.6
Diabetes mellitus				
Type I	2.5	1.8	1.3	1.0
Type II, diabetic	7.1	17.6	28.3	32.0
Diabetes mellitus_unknown	1.3	2.4	3.6	4.0
Human immunodeficiency virus	0.8	1.0	1.1	0.3
Liver disease	0.9	2.1	3.7	2.5
Chronic hepatitis	0.3	0.6	1.3	0.7
Cirrhosis	0.4	1.5	2.8	2.0
Non-alcoholic steatohepatitis	0.2	0.4	0.7	0.5
Major movement or cognitive disorder (excluding stroke)	0.8	1.5	3.7	15.0
Obstructive sleep apnea	2.5	5.9	8.8	8.3
Hospitalization with infection in the past year	6.3	7.0	7.9	9.8
Transplant history	0.4	0.6	0.5	0.2

eTable 3. Baseline Characteristics of US Hospitalized Adult COVID-19 Patients by Time Period – Overall Cohort

Characteristics	Patient, No. (%)			
	Feb, 2020 - Apr, 2020 (n= 12800)	May, 2020 - Jul, 2020 (n= 17634)	Aug, 2020 - Oct, 2020 (n= 13635)	Nov, 2020 - Jan, 2020 (n= 23326)
Age, Mean[SD], y	57.3(17.1)	56.1(17.3)	57.8(17.4)	60.6(17.0)
18-34	11.6	13.9	12.4	9.5
35-49	20.8	20.9	18.4	15.0
50-64	31.4	30.4	29.6	29.9
65+	36.3	34.8	39.7	45.6
Sex (Male)	53.4	50.7	49.9	51.0
Race				
White	44.4	50.0	61.9	63.8
Black or African American	27.7	26.9	20.8	20.7
American Indian or Alaska Native	0.5	0.9	0.5	0.4
Asian	2.6	4.4	3.2	2.6
Native Hawaiian or Other Pacific Islander	0.1	0.4	0.4	0.3
Unknown	24.6	17.4	0.0	12.3
Ethnicity				
Hispanic	16.5	24.8	15.9	9.6
US Census division				
Midwest	9.9	11.8	15.2	21.9
Northeast	27.7	6.6	5.2	14.7
South	35.9	58.1	51.4	37.9
West	6.3	4.3	5.1	1.7
Baseline Comorbidities				
Gastrointestinal disorders	27.8	23.7	27.9	29.4
Skin disorder	15.8	11.6	13.3	14.4
Atopic dermatitis	0.4	0.2	0.2	0.2
Autoimmune disease				
Systemic lupus erythematosus	0.7	0.5	0.6	0.6
Rheumatoid arthritis	1.5	1.0	1.3	1.7
Psoriasis, including psoriatic arthritis	0.6	0.5	0.6	0.7
Inflammatory bowel disease	0.2	0.1	0.2	0.2
Multiple sclerosis	0.5	0.4	0.4	0.5
Glomerulonephritis	0.4	0.4	0.3	0.3
Autoimmune thyroid disease	0.3	0.2	0.2	0.2
Cancer	8.2	6.8	8.0	8.5
Solid tumors	6.0	5.3	6.2	6.5
Breast	1.0	0.9	1.2	1.1
Prostate	1.1	0.9	1.1	1.3
Lung	1.2	0.9	1.0	1.1
Other	4.1	3.7	4.1	4.4

Hematologic malignancies	3.2	2.1	2.7	2.8
Leukemia	0.8	0.5	0.6	0.7
Lymphoma	0.9	0.4	0.5	0.7
Multiple myeloma (MM)	0.3	0.3	0.3	0.4
Other	1.6	1.0	1.3	1.3
Cardiovascular disease	45.8	39.2	45.8	52.7
Coronary artery disease	11.8	9.3	11.8	14.2
Peripheral vascular disease	4.9	3.7	3.9	4.5
Cerebrovascular disease	4.1	2.8	3.4	4.6
Hypertension	42.1	35.9	42.0	48.2
Congestive heart failure	11.0	9.1	9.6	11.9
Atrial Fibrillation	9.0	6.9	8.7	10.9
Chronic kidney disease	14.9	11.7	13.4	15.9
Stage I	0.3	0.1	0.2	0.1
Stage II	1.5	1.1	1.2	1.3
Stage III	6.6	4.8	5.4	5.3
Stage IV	2.2	1.6	2.0	2.4
Stage V (end stage renal disease)	3.3	2.9	2.7	3.2
Unknown	12.8	10.3	11.9	14.0
Chronic dialysis	1.0	0.8	0.8	1.0
Hemodialysis	1.0	0.8	0.8	1.0
Peritoneal dialysis	0.0	0.0	0.0	0.0
Chronic lung disease	16.9	12.5	16.3	18.6
Asthma	8.0	6.0	7.4	8.1
COPD	10.1	7.3	9.8	11.7
Pulmonary fibrosis	1.2	0.7	0.9	1.0
Diabetes mellitus				
Type I	1.8	1.3	1.2	1.4
Type II, diabetic	25.3	22.5	24.6	27.9
Diabetes mellitus_unknown	4.1	2.6	2.5	3.8
Human immunodeficiency virus	1.0	0.7	0.7	0.6
Liver disease	3.0	2.4	2.6	2.5
Chronic hepatitis	1.2	0.8	0.7	0.6
Cirrhosis	2.0	1.8	2.1	1.9
Non-alcoholic steatohepatitis	0.5	0.4	0.6	0.5
Major movement or cognitive disorder (excluding stroke)	8.5	6.4	6.9	8.1
Obstructive sleep apnea	7.1	5.7	7.2	8.8
Hospitalization with infection in the past year	11.1	7.1	7.8	8.0
Transplant history	0.3	0.3	0.4	0.5

eTable 4 The Percentage of Hospitalized Adult COVID-19 Patient by Region in ex-US Analysis

Region	% of Hospitalized Adult COVID-19 Patients
Europe	91.4%
LATAM	8.5%
APAC	0.1%

LATAM: Latin America; APAC: Asia-Pacific

eTable 5. Drug Treatment receipt among US Adult Hospitalized COVID-19 patients – Overall Cohort

Treatment	Patient,% (N=67456)
Acetaminophen	67.11%
Enoxaparin	49.47%
Dexamethasone	37.69%
Insulin	32.74%
Opioids	31.44%
Aspirin	26.69%
Azithromycin	23.72%
Atorvastatin	21.44%
Remdesivir	20.26%
Methylprednisolone	19.82%
Heparin	14.77%
Melatonin	13.42%
Zinc	13.00%
Prednisone	11.91%
Ibuprofen	11.78%
Doxycycline	8.83%
Apixaban	8.72%
Hydroxychloroquine	7.18%
Chloroquine	7.16%
Vitamin D	6.89%
Thiamine	5.63%
Levofloxacin	5.54%
Rosuvastatin	5.41%
Clopidogrel	5.21%
Hydrocortisone	4.92%
Amoxicillin	4.25%
Budesonide	4.25%
Rivaroxaban	3.95%
Amiodarone	3.91%
Montelukast	3.46%
Formoterol	3.26%
Alteplase	3.17%
Pravastatin	2.83%
Simvastatin	2.62%
Trimethoprim	2.33%
Tacrolimus	1.68%
Warfarin	1.60%
Hemodialysis	1.42%

eTable 6. Drug Treatment receipt among ex-US Adult Hospitalized COVID-19 patients

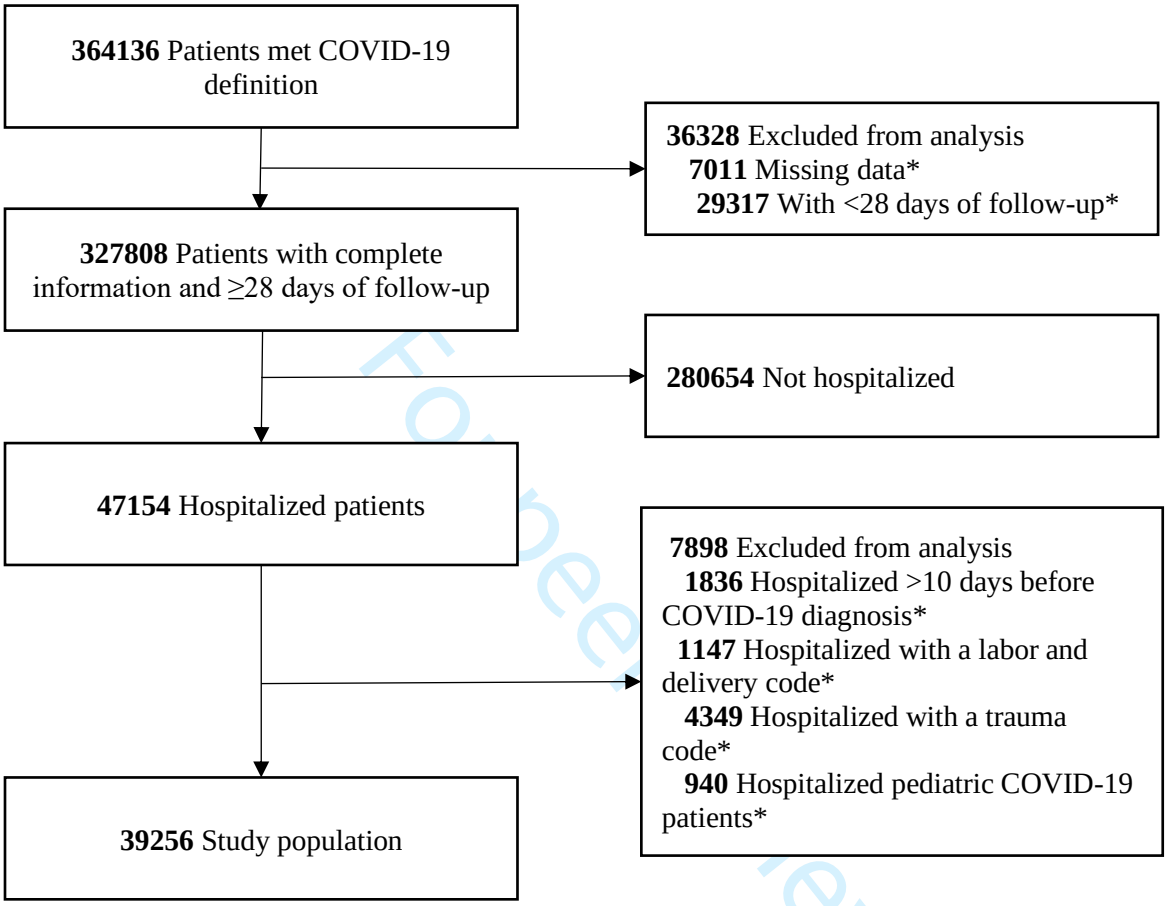
Treatment	Patient,% (N=67456)
Acetaminophen	64.6%
Azithromycin	38.9%
Hydroxychloroquine	29.0%
Methylprednisolone	21.4%
Insulin	20.2%
Dexamethasone	19.9%
Amoxicillin	18.9%
Other Bronchodilators	14.0%
Tocilizumab	8.3%
Atorvastatin	7.9%
Aspirin	7.9%
Formoterol	6.3%
Prednisone	5.5%
Levofloxacin	5.4%
Simvastatin	5.3%
Clopidogrel	1.8%
Thiamine	1.4%
Apixaban	1.2%
Rivaroxaban	1.2%
Amiodarone	1.1%
Montelukast	0.9%
Rosuvastatin	0.7%
Remdesivir	0.5%
Pravastatin	0.2%
Other Antihypertensives	0.2%
Warfarin	0.1%

eTable 7: Selected Outcomes Percentage of US Adult Hospitalized COVID-19 Patients – Overall Cohort

Category	ICU Admission		ARDS/Respiratory Failure		IMV		All-Cause Mortality	
	N	%	N	%	N	%	N	%
Gender								
Male	34518	16.89%	32560	40.98%	34518	13.65%	34518	6.14%
Female	32938	12.33%	30946	32.78%	32938	9.36%	32938	4.56%
Age								
18-34	7859	7.23%	7678	18.26%	7859	5.06%	7859	0.83%
35-49	12365	11.23%	11957	30.96%	12365	8.63%	12365	1.78%
50-64	20382	15.71%	19240	40.31%	20382	12.82%	20382	3.79%
65+	26850	17.62%	24631	43.14%	26850	13.84%	26850	9.55%
Time Period								
Feb, 2020 - Apr, 2020	12800	20.88%	11924	41.11%	12800	17.89%	12800	6.52%
May, 2020 - Jul, 2020	17634	14.46%	16805	33.04%	17634	11.53%	17634	5.33%
Aug, 2020 - Oct, 2020	13635	13.19%	12890	36.97%	13635	10.21%	13635	4.73%
Nov, 2020 - Jan, 2021	23326	12.21%	21837	37.73%	23326	8.82%	23326	5.16%

Sensitivity Analysis

eFigure 1. Patient Flow Diagram of US Adult Hospitalized COVID-19 Patients – Confirmed Cohort



*The counts were not mutual exclusive.

eTable 8. Baseline Characteristics of US Hospitalized Adult COVID-19 Patient Overall and by Gender – Confirmed Cohort

Characteristic	Patients, %		
	All (n=39256)	Male (n=19965)	Female (n=19291)
Age, Mean [SD], y	57(17.54)	58.4(16.7)	57.2(18.4)
18-34	12.6	10.4	14.8
35-49	18.5	18.5	18.6
50-64	29.8	31.7	27.9
65+	39.1	39.4	38.7
Race			
White	54.9	56.3	53.5
Black or African American	25.5	23.1	28.0
American Indian or Alaska Native	0.5	0.5	0.5
Asian	2.8	2.9	2.6
Native Hawaiian or Other Pacific Islander	0.3	0.3	0.2
Unknown	16.0	16.9	15.1
Ethnicity			
Hispanic	18.9	19.7	18.0
Site of Diagnosis			
Inpatient	83.5	84.8	82.2
Other	16.5	15.2	17.8
Mode of Diagnosis			
Both Diagnosis and lab	81.2	81.9	80.5
Lab	18.8	18.1	19.5
Month of Index			
Feb-20	0.8	1.0	0.6
Mar-20	6.6	7.1	6.2
Apr-20	11.3	11.8	10.7
May-20	7.5	7.6	7.3
Jun-20	8.0	8.1	8.0
Jul-20	11.3	11.0	11.7
Aug-20	6.3	6.0	6.7
Sep-20	5.0	4.8	5.2
Oct-20	8.5	8.4	8.5
Nov-20	16.4	16.0	16.8
Dec-20	17.3	17.2	17.3
Jan-21	1.1	1.1	1.1
US Census Division			
Midwest	19.9	19.8	20.0
Northeast	14.8	14.7	14.9
South	46.6	45.5	47.8
West	4.9	5.1	4.7
Unknown	13.8	14.91	12.58
Baseline Comorbidities			
Gastrointestinal disorders	25.1	22.3	28.0
Skin disorder	13.7	12.5	14.8
Atopic dermatitis (AD)	0.3	0.2	0.3
Autoimmune disease			

Systemic lupus erythematosus	0.5	0.2	0.9
Rheumatoid arthritis	1.2	0.7	1.7
Psoriasis, including psoriatic arthritis	0.6	0.5	0.6
Inflammatory bowel disease	0.2	0.1	0.2
Multiple sclerosis	0.4	0.3	0.5
Glomerulonephritis	0.3	0.3	0.4
Autoimmune thyroid disease	0.2	0.1	0.3
Cancer	7.0	7.4	6.6
Solid tumors	5.4	5.7	5.0
Breast	1.0	0.0	1.9
Prostate	1.1	2.1	0.0
Lung	0.9	1.0	0.8
Other	3.6	3.9	3.3
Hematologic malignancies	2.4	2.4	2.3
Leukemia	0.5	0.6	0.5
Lymphoma	0.6	0.6	0.5
Multiple myeloma (MM)	0.4	0.4	0.3
Other	1.1	1.1	1.1
Cardiovascular disease	41.5	42.5	40.3
Coronary artery disease	10.9	13.5	8.1
Peripheral vascular disease	3.9	4.4	3.4
Cerebrovascular disease	3.8	3.9	3.7
Hypertension	37.6	38.0	37.2
Congestive heart failure	9.1	9.5	8.7
Atrial Fibrillation	7.8	9.0	6.6
Chronic kidney disease	12.4	13.3	11.4
Stage I	0.1	0.1	0.1
Stage II	1.3	1.5	1.0
Stage III	5.3	5.5	5.1
Stage IV	1.9	1.9	2.0
Stage V (End stage renal disease)	2.5	2.8	2.2
Unknown	10.7	11.5	9.9
Chronic dialysis	0.7	0.7	0.7
Hemodialysis	0.7	0.7	0.7
Chronic lung disease	13.9	11.9	15.9
Asthma	6.7	4.2	9.3
COPD	8.0	8.1	8.0
Pulmonary fibrosis	0.7	0.8	0.6
Diabetes mellitus			
Type I	1.2	1.2	1.2
Type II, diabetic	22.2	22.5	21.9
Diabetes unknown	4.0	4.0	4.0
Human immunodeficiency virus	0.6	0.8	0.3
Liver disease	2.3	2.8	1.8
Chronic hepatitis	0.8	1.2	0.5
Cirrhosis	1.6	1.9	1.3
Non-alcoholic steatohepatitis	0.5	0.4	0.6
Major movement or cognitive disorder (excluding stroke)	6.2	6.0	6.4
Obstructive sleep apnea	7.1	7.4	6.8

Hospitalization with infection in the past year	7.5	7.0	7.9
Transplant history	0.4	0.5	0.3

eTable 9: Selected Outcomes Percentage of US Adult Hospitalized COVID-19 Patients – Confirmed Cohort

Category	ICU Admission		ARDS/Respiratory Failure		IMV		All-Cause Mortality	
	N	%	N	%	N	%	N	%
Gender								
Male	19965	15.65%	18946	36.41%	19965	12.19%	19965	4.94%
Female	19291	10.86%	18222	28.20%	19291	7.74%	19291	3.66%
Age								
18-34	4931	5.21%	4849	14.04%	4931	3.45%	4931	0.34%
35-49	7275	9.33%	7070	26.08%	7275	6.83%	7275	0.93%
50-64	11713	14.07%	11156	35.50%	11713	10.84%	11713	2.68%
65+	15337	17.19%	14093	39.40%	15337	12.98%	15337	8.43%
Time Period								
Feb, 2020 - Apr, 2020	7332	15.71%	6978	35.05%	7332	13.86%	7332	4.69%
May, 2020 - Jul, 2020	10530	14.32%	10089	28.98%	10530	10.53%	10530	4.72%
Aug, 2020 - Oct, 2020	7757	13.23%	7373	33.45%	7757	9.62%	7757	3.66%
Nov, 2020 - Jan, 2021	13626	11.24%	12718	33.02%	13626	7.75%	13626	4.16%

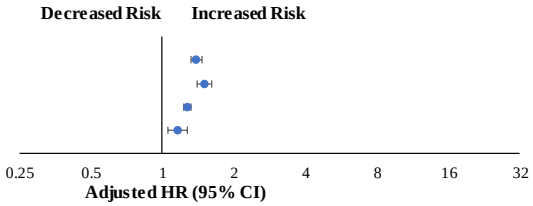
eTable 10. Treatment receipt among COVID-19 patients – Confirmed and Probable Cohorts

Treatment	Patient, %	
	Confirmed Cohort (N=39256)	Probable Cohort (N=28200)
Acetaminophen	74.4%	57.0%
Enoxaparin	54.4%	42.6%
Dexamethasone	41.5%	32.4%
Insulin	34.7%	30.0%
Opioids	32.3%	30.2%
Aspirin	28.7%	24.0%
Azithromycin	23.6%	23.9%
Atorvastatin	23.3%	18.8%
Remdesivir	22.8%	16.7%
Methylprednisolone	22.4%	16.3%
Heparin	16.1%	12.9%
Melatonin	14.1%	12.5%
Zinc	13.7%	12.0%
Ibuprofen	12.2%	11.2%
Prednisone	12.1%	11.7%
Apixaban	9.6%	7.5%
Doxycycline	9.0%	8.7%
Vitamin D	7.9%	5.5%
Hydroxychloroquine	7.4%	6.9%
Chloroquine	7.4%	6.8%
Rosuvastatin	7.0%	3.2%
Thiamine	6.3%	4.7%
Clopidogrel	5.4%	4.9%
Rivaroxaban	5.1%	2.4%
Levofloxacin	5.0%	6.3%
Hydrocortisone	4.8%	5.2%
Amoxicillin	4.2%	4.3%
Budesonide	3.8%	4.8%
Amiodarone	3.8%	4.0%
Montelukast	3.6%	3.2%
Pravastatin	3.1%	2.4%
Alteplase	3.1%	3.3%
Formoterol	3.1%	3.6%
Simvastatin	2.4%	3.0%
Trimethoprim	2.2%	2.5%
Warfarin	1.8%	1.3%
Tacrolimus	1.8%	1.6%
Hemodialysis	0.9%	2.1%

S2 Figure. The Forest Plots of Model-adjusted Hazard Ratios among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period – Confirmed Cohort

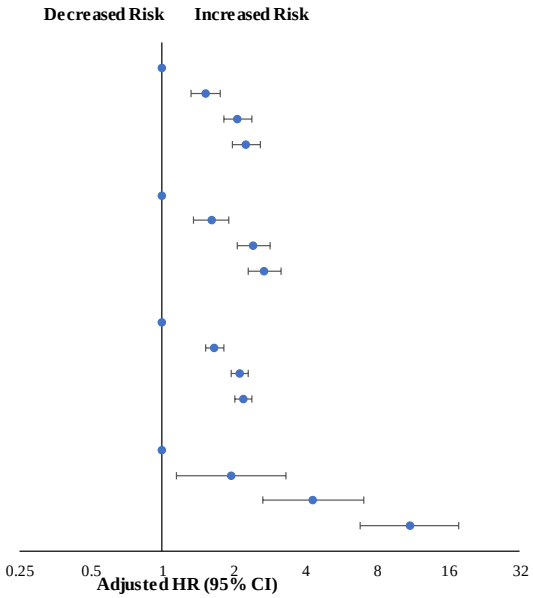
A) Gender

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
Male (Reference : Female)		
ICU Admission	1.39 (1.32-1.47)	<.0001
IMV	1.51 (1.41-1.61)	<.0001
ARDS/Respiratory Failure	1.28 (1.23-1.32)	<.0001
All-cause Mortality	1.16 (1.06-1.28)	0.0025



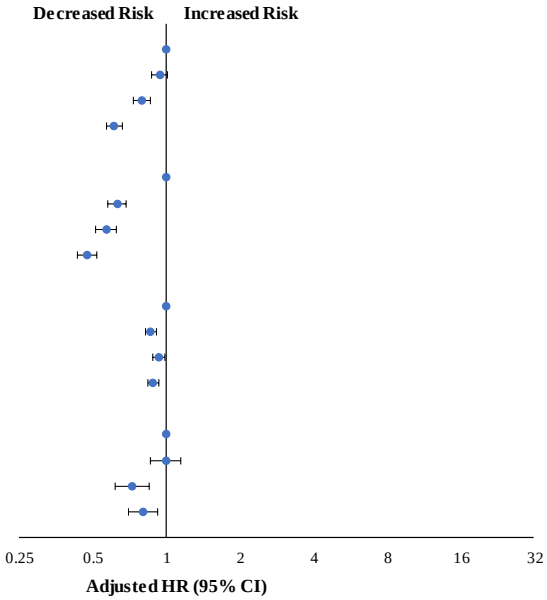
B) Age

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
ICU Admission		
18-34	1 (ref)	
35-49	1.53 (1.33-1.76)	<.0001
50-64	2.08 (1.82-2.37)	<.0001
65+	2.26 (1.98-2.58)	<.0001
IMV		
18-34	1 (ref)	
35-49	1.61 (1.35-1.91)	<.0001
50-64	2.42 (2.06-2.85)	<.0001
65+	2.69 (2.29-3.17)	<.0001
ARDS/Respiratory Failure		
18-34	1 (ref)	
35-49	1.66 (1.53-1.81)	<.0001
50-64	2.12 (1.96-2.30)	<.0001
65+	2.19 (2.02-2.38)	<.0001
All-cause Mortality		
18-34	1 (ref)	
35-49	1.95 (1.14-3.31)	0.0141
50-64	4.32 (2.65-7.03)	<.0001
65+	10.99 (6.79-17.78)	<.0001



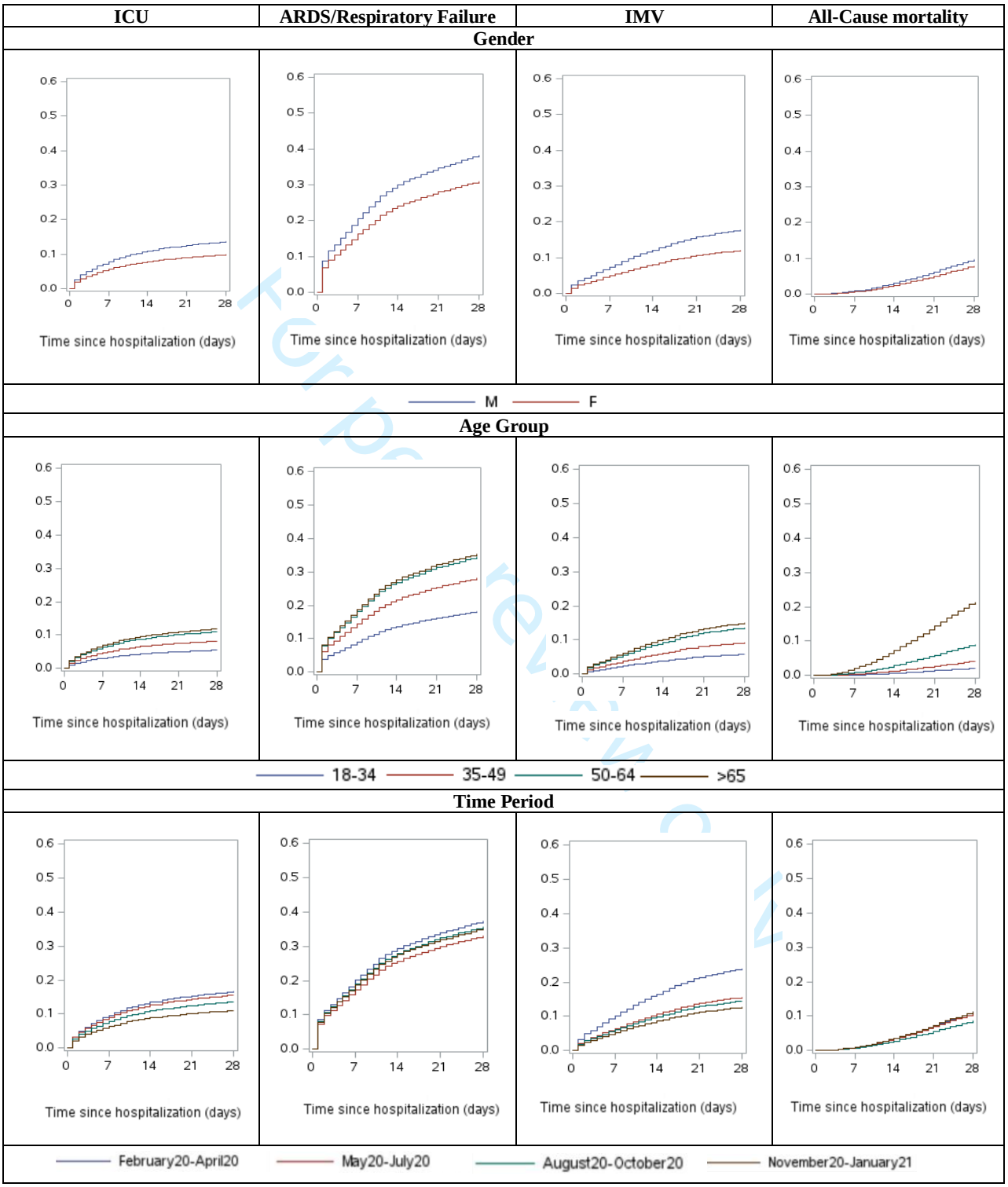
C) Time Period

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
ICU Admission		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.94 (0.87-1.02)	0.1208
Aug, 2020 - Oct, 2020	0.79 (0.73-0.87)	<.0001
Nov, 2020 - Jan, 2021	0.61 (0.57-0.66)	<.0001
IMV		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.63 (0.58-0.69)	<.0001
Aug, 2020 - Oct, 2020	0.57 (0.52-0.63)	<.0001
Nov, 2020 - Jan, 2021	0.47 (0.43-0.52)	<.0001
ARDS/Respiratory Failure		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.86 (0.82-0.91)	<.0001
Aug, 2020 - Oct, 2020	0.93 (0.88-0.99)	0.0117
Nov, 2020 - Jan, 2021	0.88 (0.84-0.93)	<.0001
All-cause Mortality		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.99 (0.86-1.14)	0.929
Aug, 2020 - Oct, 2020	0.72 (0.62-0.85)	<.0001
Nov, 2020 - Jan, 2021	0.80 (0.70-0.92)	0.0022



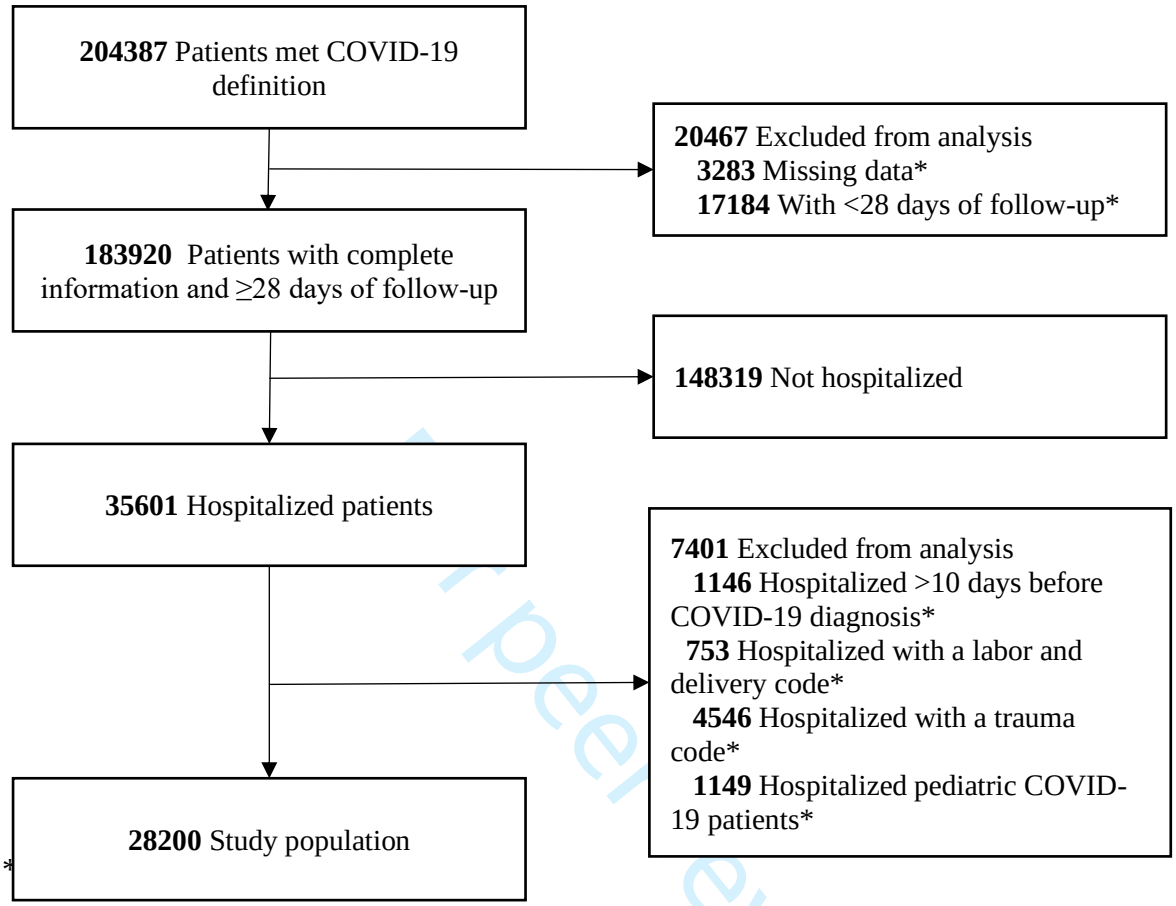
HR: the abbreviation of Hazard Ratio; ARDS: the abbreviation of acute respiratory distress syndrome; ICU: the abbreviation of intensive care unit; IMV: the abbreviation of invasive mechanical ventilation. Three separate Fine and Gray models were developed stratified by age group, gender, and time period; each model used the other two main categories of risk exposure (for example, gender and time period in the age group model) as covariates. The other covariates in each model were race, ethnicity, US region, hypertension, diabetes (Type I and II), active cancer, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea.

S3 Figure. Model-adjusted Cumulative Incidence of Selected Outcomes among Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period – Confirmed Cohort



HR: the abbreviation of Hazard Ratio; ARDS: the abbreviation of acute respiratory distress syndrome; ICU: the abbreviation of intensive care unit; IMV: the abbreviation of invasive mechanical ventilation. Three separate Fine and Gray models were developed stratified by age group, gender, and time period; each model used the other two main categories of risk exposure (for example, gender and time period in the age group model) as covariates. The other covariates in each model were race, ethnicity, US region, hypertension, diabetes (Type I and II), active cancer, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea.

eFigure 4. Patient Flow Diagram of US Adults Hospitalized with COVID-19 – Probable Cohort



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eTable 11. Baseline Characteristics among US Hospitalized Adult COVID-19 Patients Overall and by Gender– Probable Cohort

Characteristic	Patient, %		
	All (n= 28200)	Male (n= 14553)	Female (n= 13647)
Age, Mean[SD], y	58.8(16.9)	59.5(16.2)	58.2(17.7)
18-34	10.4	8.6	12.3
35-49	18.0	17.5	18.7
50-64	30.7	32.8	28.6
65+	40.8	41.1	40.5
Race			
White	57.8	59.5	56.0
Black or African American	21.1	18.9	23.6
American Indian or Alaska Native	0.7	0.6	0.8
Asian	3.8	3.8	3.8
Native Hawaiian or Other Pacific Islander	0.4	0.4	0.4
Unknown	16.2	16.9	15.4
Ethnicity			
Hispanic	12.4	12.9	11.9
Month of Index			
February, 2020	1.8	1.0	0.6
March, 2020	6.8	7.1	6.2
April, 2020	10.8	11.8	10.7
May, 2020	7.0	7.6	7.3
June, 2020	7.4	8.1	8.0
Jul, 2020	10.8	11.0	11.7
August, 2020	6.7	6.0	6.7
September, 2020	5.6	4.8	5.2
October, 2020	8.5	8.4	8.5
November, 2020	15.1	16.0	16.8
December, 2020	18.3	17.2	17.3
January, 2021	1.0	1.1	1.1
US Census division			
Midwest	9.6	9.7	9.6
Northeast	10.8	11.1	10.4
South	44.0	42.1	45.8
West	33.0	2.6	2.6
Baseline Comorbidities			
Gastrointestinal disorders	30.4	28.0	32.9
Skin disorder	13.8	13.3	14.3
Atopic dermatitis	0.2	0.1	0.2
Autoimmune disease			
Systemic lupus erythematosus	0.7	0.2	1.3
Rheumatoid arthritis	1.7	1.0	2.5
Psoriasis, including psoriatic arthritis	0.7	0.7	0.7
Inflammatory bowel disease	0.2	0.2	0.2

Multiple sclerosis	0.5	0.3	0.8
Glomerulonephritis	0.4	0.4	0.3
Autoimmune thyroid disease	0.2	0.1	0.4
Cancer	9.2	9.5	8.9
Solid Tumors	7.0	6.9	7.0
Breast	1.2	0.0	2.4
Prostate	1.2	2.4	0.0
Lung	1.3	1.2	1.4
Other	4.8	4.8	4.8
Hematologic malignancies	3.2	3.5	2.8
Leukemia	0.8	1.1	0.5
Lymphoma	0.7	0.9	0.6
Multiple myeloma (MM)	0.4	0.4	0.3
Other	1.5	1.5	1.5
Cardiovascular disease	53.4	55.6	51.1
Coronary artery disease	13.5	16.6	10.2
Peripheral vascular disease	4.7	5.6	3.8
Cerebrovascular disease	3.8	3.8	3.8
Hypertension	49.5	51.1	47.8
Congestive heart failure	12.5	13.6	11.4
Atrial Fibrillation	10.7	12.5	8.8
Chronic kidney disease	16.5	18.5	14.4
Stage I	0.2	0.2	0.2
Stage II	1.2	1.5	0.9
Stage III	5.7	6.0	5.3
Stage IV	2.3	2.4	2.2
Stage V (end stage renal disease)	3.8	4.4	3.1
Unknown	14.7	16.7	12.7
Chronic dialysis	1.2	1.5	1.0
Hemodialysis	1.2	1.5	1.0
Peritoneal dialysis	0.0	0.0	0.0
Chronic lung disease	19.5	17.7	21.4
Asthma	8.3	5.5	11.4
Chronic obstructive pulmonary disease	12.4	12.8	11.9
Pulmonary fibrosis	1.3	1.5	1.1
Diabetes mellitus			
Type I	1.6	1.8	1.5
Type II, diabetic	29.7	31.1	28.2
Diabetes mellitus,unknown	2.3	2.6	2.1
Human immunodeficiency virus	1.7	2.3	1.1
Liver disease	3.0	3.5	2.5
Chronic hepatitis	0.8	1.0	0.6
Cirrhosis	2.4	2.8	1.9
Non-alcoholic steatohepatitis	0.5	0.5	0.6
Major movement or cognitive disorder (excluding stroke)	9.3	9.4	9.1
Obstructive sleep apnea	7.6	8.5	6.7

Hospitalization with infection in the past year	9.5	9.6	9.4
Transplant history	0.4	0.4	0.3

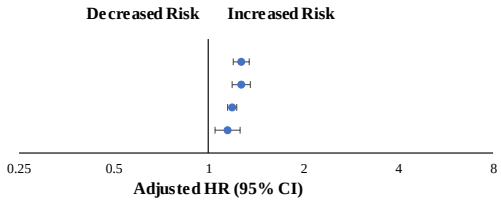
eTable 12: Selected Outcomes Percentage of US Adult Hospitalized COVID-19 Patients – Probable

Category	ICU Admission		ARDS/Respiratory Failure		IMV		All-Cause Mortality	
	N	%	N	%	N	%	N	%
Gender								
Male	14,553	18.59%	13,614	47.34%	14,553	15.64%	14,553	7.79%
Female	13,647	14.40%	12,724	39.34%	13,647	11.64%	13,647	5.84%
Age								
18-34	2,928	10.62%	2,829	25.49%	2,928	7.79%	2,928	1.64%
35-49	5,090	13.95%	4,887	38.02%	5,090	11.20%	5,090	2.99%
50-64	8,669	17.94%	8,084	46.96%	8,669	15.49%	8,669	5.29%
65+	11,513	18.19%	10,538	48.16%	11,513	14.97%	11,513	11.05%
Time Period								
Feb-20,Mar-20,Apr-20	5,468	27.82%	4,946	49.66%	5,468	23.30%	5,468	8.96%
May-20,Jun-20,Jul-20	7,104	14.65%	6,716	39.13%	7,104	13.02%	7,104	6.24%
Aug-20,Sept-20,Oct-20	5,878	13.13%	5,517	41.67%	5,878	10.99%	5,878	6.14%
Nov-20,Dec-20,Jan-21	9,700	13.56%	9,119	44.31%	9,700	10.33%	9,700	6.56%

S5 Figure. The Forest Plots of Model-adjusted Hazard Ratios among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period – Probable Cohort

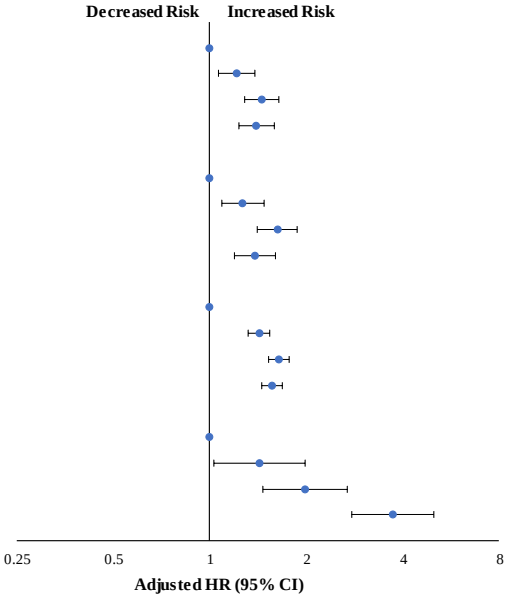
A) Gender

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
Male (Reference : Female)		
ICU Admission	1.27 (1.20-1.35)	<.0001
IMV	1.27 (1.19-1.36)	<.0001
ARDS/Respiratory Failure	1.19 (1.16-1.23)	<.0001
All-cause Mortality	1.15 (1.05-1.26)	0.0026



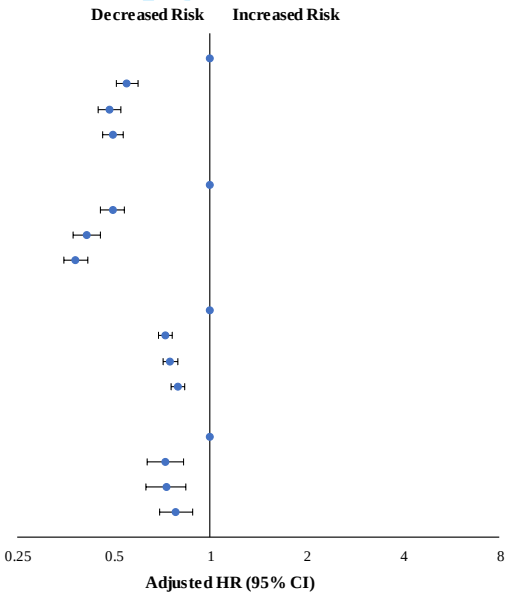
B) Age

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
ICU Admission		
18-34	1 (ref)	
35-49	1.22 (1.07-1.39)	0.0036
50-64	1.45 (1.29-1.64)	<.0001
65+	1.40 (1.24-1.58)	<.0001
IMV		
18-34	1 (ref)	
35-49	1.27 (1.09-1.48)	0.0026
50-64	1.63 (1.41-1.88)	<.0001
65+	1.38 (1.19-1.60)	<.0001
ARDS/Respiratory Failure		
18-34	1 (ref)	
35-49	1.42 (1.32-1.54)	<.0001
50-64	1.64 (1.53-1.77)	<.0001
65+	1.57 (1.45-1.69)	<.0001
All-cause Mortality		
18-34	1 (ref)	
35-49	1.43 (1.03-1.98)	0.0313
50-64	1.99 (1.47-2.69)	<.0001
65+	3.72 (2.77-4.99)	<.0001



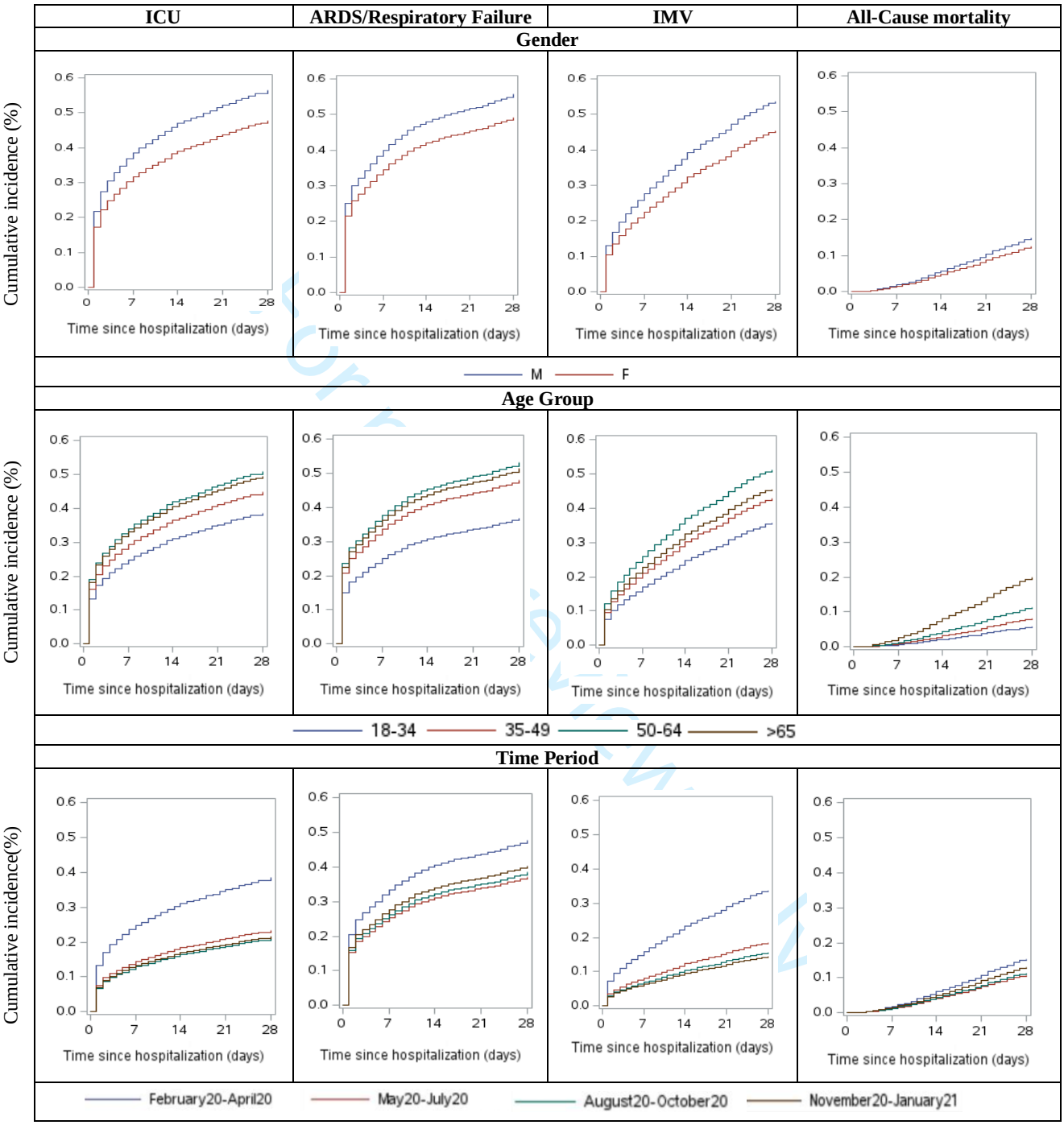
C) Time Period

Characteristics	Adjusted HR (95% CI)	Pr > ChiSq
ICU Admission		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.55 (0.51-0.60)	<.0001
Aug, 2020 - Oct, 2020	0.49 (0.45-0.53)	<.0001
Nov, 2020 - Jan, 2021	0.50 (0.46-0.54)	<.0001
IMV		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.50 (0.46-0.54)	<.0001
Aug, 2020 - Oct, 2020	0.41 (0.37-0.45)	<.0001
Nov, 2020 - Jan, 2021	0.38 (0.35-0.41)	<.0001
ARDS/Respiratory Failure		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.72 (0.69-0.76)	<.0001
Aug, 2020 - Oct, 2020	0.75 (0.71-0.79)	<.0001
Nov, 2020 - Jan, 2021	0.79 (0.76-0.83)	<.0001
All-cause Mortality		
Feb, 2020 - Apr, 2020	1 (ref)	
May, 2020 - Jul, 2020	0.72 (0.63-0.82)	<.0001
Aug, 2020 - Oct, 2020	0.73 (0.63-0.84)	<.0001
Nov, 2020 - Jan, 2021	0.78 (0.69-0.88)	<.0001



HR: the abbreviation of Hazard Ratio; ARDS: the abbreviation of acute respiratory distress syndrome; ICU: the abbreviation of intensive care unit; IMV: the abbreviation of invasive mechanical ventilation. Three separate Fine and Gray models were developed stratified by age group, gender, and time period; each model used the other two main categories of risk exposure (for example, gender and time period in the age group model) as covariates. The other covariates in each model were race, ethnicity, US region, hypertension, diabetes (Type I and II), active cancer, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea.

S6 Figure. Model-adjusted Cumulative Incidence of Selected Outcomes among US Hospitalized Adult Patients with COVID-19 by Gender, by Age Group, and by Time Period – Probable Cohort



HR: the abbreviation of Hazard Ratio; ARDS: the abbreviation of acute respiratory distress syndrome; ICU: the abbreviation of intensive care unit; IMV: the abbreviation of invasive mechanical ventilation. Three separate Fine and Gray models were developed stratified by age group, gender, and time period; each model used the other two main categories of risk exposure (for example, gender and time period in the age group model) as covariates. The other covariates in each model were race, ethnicity, US region, hypertension, diabetes (Type I and II), active cancer, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	18-19
Study size	10	Explain how the study size was arrived at	11,12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11-12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11-12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-14

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-14 and supplement materials
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.