Trends over time in the risk of adverse outcomes among patients with SARS-CoV-2 infection

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Summary:

The risk of adverse outcomes (hospitalization, ICU admission, ventilation, death) in patients with SARS-CoV-2 infection declined substantially from February to July 2020, and subsequently plateaued from July to September 2020. These trends may reflect changing treatment practices or viral pathogenicity.

Abstract

Background:

We aimed to describe trends in adverse outcomes among patients who tested positive for SARS-CoV-2 between February and September 2020 within a national healthcare system.

Methods:

We identified enrollees in the national U.S. Veterans Affairs healthcare system who tested positive for SARS-CoV-2 between 2/28/2020 and 9/30/2020 (n=55,952), with follow-up extending to 11/19/2020. We determined trends over time in incidence of the following outcomes that occurred within 30 days of testing positive: hospitalization, intensive care unit (ICU) admission, mechanical ventilation and death.

Results:

Between February and July 2020, there were marked downward trends in the 30-day incidence of hospitalization (44.2% to 15.8%), ICU admission (20.3% to 5.3%), mechanical ventilation (12.7% to 2.2%), and death (12.5% to 4.4%), which subsequently plateaued between July and September 2020. These trends persisted after adjustment for sociodemographic characteristics, comorbid conditions, documented symptoms and laboratory tests, including among subgroups of patients hospitalized, admitted to the ICU or treated with mechanical ventilation. From February to September, there were decreases in the use of hydroxychloroquine (56.5% to 0%), azithromycin (48.3% to 16.6%) vasopressors (20.6% to 8.7%), and dialysis (11.6% to 3.8%) and increases in the use of dexamethasone (3.4% to 53.1%), other corticosteroids (4.9% to 29.0%) and remdesivir (1.7% to 45.4%) among hospitalized patients.

Conclusions:

The risk of adverse outcomes in SARS-CoV-2-positive patients decreased markedly between February and July, with subsequent stabilization from July to September. These trends were not explained by changes in measured baseline patient characteristics and may reflect changing treatment practices or viral pathogenicity.

Keywords: COVID-19; NOVEL CORONAVIRUS; MORTALITY; REMDESIVIR; HYDROXYCHLOROQUINE;

Introduction

Infection with SARS-CoV-2 results in a broad spectrum of clinical severity ranging from asymptomatic infection to life-threatening illness.[1 2] Among individuals who test positive for SARS-CoV-2, there is substantial variation across different populations in rates of hospital admission (from 8% to 80.7%),[3-5] mechanical ventilation (from 2.3% of the Chinese population to 93.2% of critically ill admitted to New York area hospitals[5-12]), and mortality (from 2.8% of unselected patients in the US to 10.2-67% of hospitalized and high-risk patients).[3 5 11 13-17] To date, only a few studies have described trends in these measures over time within populations.[18-22]

Since the first case of SARS-CoV-2 was diagnosed in the US on January 19, 2020, there have been marked changes in the availability and approach to testing, in mitigation strategies both in the community and within health systems, in how symptomatic patients are managed medically, in the distribution of viral variants and most recently in the availability of vaccination. Some studies described improved outcomes among infected patients after the initial months of the pandemic. Improvements in mortality were reported for patients treated in an 8-hospital health system in Houston, Texas between mid-March and mid-July, in a 3-hospital system in New York between March and August, 2020, in a single hospital in Milano, Italy between late February and mid-May, 2020 and in the Hospital Clinic of Barcelona from March to September, 2020.[18 20 22 23] Improvements in in-hospital mortality were described between March and August in patients hospitalized in US medical centers using administrative data, without any adjustment for baseline characteristics or disease severity.[21] Also, improvements in outcomes were described among patients admitted to the ICU in England, Wales and Northern Ireland between February and May, 2020 and among patients admitted to the ICU in England from March through June, 2020.[19 24]

To our knowledge, no prior studies have described temporal trends in the risk of severe complications of COVID-19 in a national US health care system extending beyond the first wave of

the pandemic i.e. after June 2020. The Department of Veterans Affairs (VA) healthcare system supports the largest, integrated, comprehensive national healthcare system in the US, providing a unique view of national trends in outcomes among those infected with SARS-CoV-2. We used national data from the VA to measure trends in hospitalization, ICU admission, mechanical ventilation, dialysis, medication use and death among individuals who tested positive for SARS-CoV-2 between February 28 and September 30, 2020, with follow-up extending through November 19, 2020.

Methods

Data source and study population

The VA provides care for more than six million Veterans annually and uses a single, national comprehensive electronic healthcare information network. We used data from the VA's Corporate Data Warehouse (CDW), a relational database of VA enrollees' electronic health records (EHR), developed by the VA Informatics and Computing Infrastructure (VINCI) to support research and clinical operations, including datasets and analytic variables specifically related to SARS-CoV-2 developed by VINCI as part of the "COVID-19 Shared Data Resource."[25]

This study was approved by the Institutional Review Board of the Veterans Affairs Puget Sound Healthcare System, which granted a waiver of informed consent. Patients or the public were not involved in the design, conduct, reporting, or dissemination of our research.

Study Population

We identified all VA enrollees (n=559,616) with available results of testing for SARS-CoV-2 using approved polymerase chain reaction (PCR) tests from 02/28/2020 (the date of the first SARS-CoV-2 test in the VA system) to 9/30/2020, including 55,952 (10.0%) who tested positive at least once. The

index date was the earliest date of a documented positive test or, in rare instances, if the patient was already hospitalized prior to testing positive, the date of hospitalization.

Adverse outcomes

We ascertained the following four outcomes within 30 days of the index date: 1) hospitalization, 2) ICU admission, 3) mechanical ventilation, and 4) all-cause mortality. Deaths that occurred both within and outside the VA are comprehensively captured in CDW through a variety of sources including VA inpatient files, VA Beneficiary Identification and Records Locator System (BIRLS), Social Security Administration (SSA) death files, and the Department of Defense.[26] However, episodes of mechanical ventilation, ICU admission and hospitalization that occurred outside the VA are captured only if these were paid for by the VA and thus do not include episodes of care covered by Medicare, Medicaid, the Department of Defense or private health insurance. Patients were followed through 11/19/2020 allowing for a minimum follow-up time of 50 days from the most recent index date (09/30/21), which was adequate for outcomes to be electronically recorded in CDW.

Baseline characteristics

Baseline *sociodemographic characteristics* associated with adverse SARS-CoV-2 outcomes,[5] included age, sex, race, ethnicity, body mass index (BMI), urban vs. rural residence (based on zip codes), and geographic location (divided into 10 US Federal Regions[27]) (**Table 2**).

Comorbid conditions were based on ICD-10 codes recorded in VA electronic health records during the 2-year period before the index date.[25] We used the Deyo modification[28] of the Charlson Comorbidity Index (CCI)[29] to estimate overall burden of comorbidity (**Table 2**). We also extracted the following individual comorbid condition which were associated with adverse outcomes among SARS-CoV-2 infected Veterans[5]: diabetes, chronic kidney disease, congestive heart failure, hypertension, obstructive sleep apnea, and obesity hypoventilation syndrome.

We identified *symptoms* potentially associated with SARS-CoV-2 documented on or within 30 days prior to the index date based on a combination of natural language processing to capture relevant documentation in the EHR and searching for relevant ICD-10 codes,[25] occurring on or within 30 days prior to the index date. In our multivariable models, we used only two symptoms (dyspnea and fever), previously found to be associated with adverse SARS0-CoV-2-related outcomes in Veterans. [5]

We extracted 5 routine *laboratory blood tests* (albumin, aspartate aminotransferase, creatinine, white blood cell count, neutrophil-to-lymphocyte ratio), which we recently showed to be associated with adverse outcomes in SARS-CoV-2[5]. For each test, we extracted the value closest to the index date, on or within 10 days before the index date, or if absent, within 5 days after the index date (93% of tests were performed within 2 days of the index date).

Pharmacotherapy, Noninvasive Ventilation and Dialysis

We identified inpatient and outpatient medications prescribed for SARS-CoV-2 and filled on or within 60 days after the index date, using VA electronic pharmacy records. We also report use of non-invasive ventilation (continuous (CPAP) or bilevel (BiPAP) positive airway pressure) and dialysis during the same time frame. Use of high-flow oxygen supplementation could not be reliably captured.

Statistical Analysis

We divided the observation period into monthly intervals. Using the Kaplan-Meier method, we calculated for the persons infected each month the 30-day cumulative incidence of hospitalization, ICU admission, mechanical ventilation, and mortality from the index date. Patients were censored at the time of death or after 30 days of follow-up. We used Cox proportional hazards regression, stratified by VA medical center, to compare the risk of each outcome among patients infected during each subsequent month relative to the earliest time period after adjusting for the following baseline

characteristics, which we found in a prior study to be associated with adverse outcomes among SARS-CoV-2-infected VA enrollees[5]: age, sex, race, ethnicity, BMI, geographical region, CCI, diabetes, chronic kidney disease, congestive heart failure, hypertension, obstructive sleep apnea, obesity hypoventilation, fever, and dyspnea. In analyses limited to hospitalized patients, we additionally adjusted for the 5 laboratory tests listed above[5]. The aim of these adjustments was to attempt to account for changes over time in baseline characteristics of SARS-CoV-2-positive patients that could have resulted in changes in the risk of adverse outcomes.

A non-parametric Wilcoxon-type test was used to test for trend over time across ordered groups. Interrupted time series (ITS) analysis of trends methods with adjustment for an auto-correlation lag of one month and robust variance estimators were used to test the difference in 30-day outcome rate slope before and after July 1, 2020[30]. We used July 1, 2020 as the transition point because it marked the end of the "first-wave" and beginning of the "second-wave" of the pandemic in the USA[31].

Results

Trends in baseline characteristics of patients with SARS-CoV-2 infection

Among 55,952 individuals who tested positive for SARS-CoV-2 during the study period, the majority were male (89.3%), mean age was 60.0 years, 58.2% were White, 31.0% were Black, 12.3% were Hispanic, 12.4% had a CCI≥5, 25.4% had documentation of fever and 11% had documentation of dyspnea (**Table 1**).

The number of patients testing positive each month ranged from 2504 in the earliest time period (2/28/20 to 03/31/20) to 16,273 in July. There were substantial trends in certain baseline socio-demographic characteristics, including a decrease over time in the proportion who were Black (from 51.9% before March 31 to 21.3% in September), an increase in the proportion who were white (from

51.9% to 68.2%) and an increase in the proportion who resided in rural/highly rural (vs. urban) areas (from 18.8% to 51.9% in September). The proportion of patients originating from each U.S. geographical region varied dramatically over time consistent with well-described changes in disease epicenters (e.g. 24.2% of positive patients from region 2 (NY, NJ, PR) in February/March versus only 2.8% in September).

The proportion of patients with severe comorbidity burden (CCI≥5) decreased over time (from 18.1% to 11%) as did the proportion with documented fever (from 57.7% to 20%) or dyspnea (from 26.6% to 8.9%). Among patients who were hospitalized, there were no clear temporal trends the proportion who had abnormalities in the five laboratory tests examined.

Trends in pharmacotherapy, dialysis and non-invasive ventilation in patients with SARS-CoV-2 infection

The proportion of hospitalized patients prescribed hydroxychloroquine on or after the index date decreased from 56.6% in February/March to 2.4% in May 2020 and ranged from 0-0.6% thereafter (**Table 2, Figure 1a**). The proportion of hospitalized patients prescribed azithromycin decreased from 48.3% in February/March to 16.6% in September and use of vasopressors decreased from 20.6% to 8.7%. Tocilizumab prescription rates in hospitalized patients ranged from a peak of 8.7% in April to 0.8% in September 2020. In contrast, remdesivir prescriptions increased from 1.7% to 45.4% of hospitalized patients from February/March to September. Dexamethasone prescriptions were low during the first three months (<4% for hospitalized patients) but from May to September increased from 3% to 53.1% among hospitalized patients and prescription of corticosteroids other than dexamethasone also increased during the same time from 7.8% to 29%. Prescription of anticoagulants among hospitalized patients did not change appreciably over time. The percentage of hospitalized patients who received dialysis decreased from 11.6% in the earliest time period to 3.8%

in August and use of non-invasive ventilation increased from a low of 8.4% in February/March to a high of 12.5% in August.

Analogous decreases in prescription of hydroxychloroquine, azithromycin and vasopressors and increases in prescription of remdesivir, dexamethasone and other corticosteroids were observed when presented as a proportion of all infected patients (rather than the hospitalized subgroup) – **Table 2**.

Trends in adverse outcomes: hospitalization, ICU admission, mechanical ventilation, death.

Between February and July 2020, there were downward trends in the 30-day incidence of hospitalization (44.2% to 15.8%, adjusted hazard ratio [AHR] 0.62, 95% CI 0.57-0.67), ICU admission (20.3% to 5.3%, AHR 0.49, 95% CI 0.43-0.55), mechanical ventilation (12.7% to 2.2%, AHR 0.25, 95% CI 0.21-0.29), and death (12.5% to 4.4%, AHR 0.40, 95% CI 0.34-0.46) among patients who tested positive for SARS-CoV-2, with relative stabilization from July through September, 2020 (**Table 3, Figure 1b, Figure 2a**).

Among hospitalized patients, the 30-day incidence of ICU admission decreased from 47.6% in February/March to 34.8% in July (AHR 0.74, 95% CI 0.64-0.84) then increased slightly between July and September (34.8% to 39.5%) (**Table 3, Figure 1c, Figure 2a**). The 30-day incidence of mechanical ventilation decreased from 29.2% in February/March to 11.4% in June and plateaued thereafter. The 30-day mortality decreased from 24.1% in February/March to 12.0% in July (AHR 0.39, 95% CI 0.31-0.48) and plateaued thereafter. Among those admitted to the ICU, the 30-day incidence of mechanical ventilation decreased from 57.0% in February/March to 22.0% in August (AHR 0.32, 95% CI 0.24-0.43), increasing slightly to 23.9% in September. The 30-day mortality among those admitted to the ICU decreased from 39.2% in February/March to 21.2% in July (AHR 0.48, 95% CI 0.36-0.63), plateauing thereafter. Among patients who received mechanical ventilation, 30-day mortality

decreased from 58.3% in February/March to 31.3% in May (AHR 0.48, 9% CI 0.30-0.76), increasing thereafter to between 39.8% to 46.7%. After adjustment for sociodemographic characteristics, comorbid conditions, symptoms and baseline laboratory characteristics, risk for all adverse outcomes decreased most markedly during the early months of the pandemic until July with stabilization after July (**Figure 2**) ($p<0.05$ for ITS test for difference in 30-day outcome rate slope before and after July 1 for all outcomes except for mortality among mechanically ventilated patients) (**Table 3 and Supplemental Figure**).

Discussion

In our study of 55,952 VA enrollees who tested positive for SARS-CoV-2 between February 28 and September 30, 2020, there were marked decreases in the 30-day incidence of hospitalization, ICU admission, mechanical ventilation and death during the first wave of the US pandemic from February/March through July, 2020 with stabilization during the late summer and early fall. Similar trends were noted in analyses adjusted for baseline sociodemographic characteristics, comorbid conditions, symptoms and laboratory tests (among hospitalized patients) and in all subgroups examined, including those admitted to the hospital, those admitted to the ICU and those who received mechanical ventilation

While there have been marked changes over time in the characteristics of Veterans infected with SARS-CoV-2, the trends in improved outcomes during the first wave of the US pandemic with subsequent stabilization persisted after adjustment for a wide range of measured sociodemographic characteristics, comorbid conditions and documented symptoms. Increased availability of testing over time would be expected to identify a greater number of asymptomatic or mildly symptomatic individuals infected with SARS-CoV-2; however, improvements in adverse outcomes during the initial months of the pandemic persisted after stratification by illness severity and among the sickest cohort members (i.e., those who were hospitalized, admitted to the ICU or received mechanical

ventilation) and after adjustment for documented symptoms and additional adjustment for a range of laboratory markers of illness acuity among hospitalized patients.

While it is possible that temporal trends in the frequency of adverse outcomes might reflect geographic variations as the pandemic moved across the country, multivariable models were stratified by VA facility and our results were robust to adjustment for geographic region. If criteria for hospitalization, ICU admission and mechanical ventilation of SARS-CoV-2-infected patients relaxed over time, this may have resulted in some of the decreases in adverse outcomes that we observed.

Our findings raise the question of whether marked improvements in outcomes among patients infected with SARS-CoV-2 during the first wave of the pandemic might reflect improvements in clinical management.[32] We did observe very substantial increases in the use of potentially effective pharmacotherapy (e.g. remdesivir and dexamethasone) and decreases in the use of ineffective (e.g. azithromycin) or potentially harmful (e.g. hydroxychloroquine) therapy toward the end of the first wave of the pandemic, although inflection points in the use of each of these agents did not exactly parallel those for adverse outcomes. The VA national Pharmacy Benefits Management (PBM) group issued numerous guidelines and criteria-for-use documents related to COVID-19 pharmacotherapies, while the VA national Antimicrobial Stewardship Task Force as well as antimicrobial stewardship programs at the facility and network level provided ongoing support and oversight of off-label use of agents such as hydroxychloroquine and azithromycin. Other shifts in clinical practice that occurred within the first months of the pandemic could not be captured reliably in the data sources available to us. Such shifts include high flow nasal canula [HFNC], pronation and noninvasive positive-pressure ventilation (NIPPV) which were increasingly used to avoid or delay intubation and may have resulted in improved outcomes.[33]

Another possible explanation for declining rates of adverse outcomes is that the severity of disease caused by SARS-CoV-2 infection may have declined. This might occur, for example, through reduction in inoculum related to physical distancing or wearing facemasks, which became more common.[34] Also, as an RNA virus, SARS-CoV-2 undergoes rapid mutation, which could impact its pathogenicity.[35 36] A SARS-CoV-2 variant carrying the spike protein amino acid change D614G became progressively more common after March 2020 throughout the world, including the United States, and was the dominant variant by July 2020[37]. This strain has enhanced replication and transmissibility compared to the wild-type strain but it is unclear if it has greater pathogenicity.[37-39] However, after the end of our study period, many viral variants have been described, such as the "United Kingdom variant" (B.1.1.7), the "South Africa variant" (B.1.351) and the "Brazil variant" (P.1), all of which have greater transmissibility. Emerging data suggests that the B.1.1.7 variant may actually be associated with higher mortality.[40 41] The transmissibility and pathogenicity of new variants will need to be closely monitored.

Limitations: While our Veteran cohort is racially diverse and nationally distributed, it includes relatively few women. We did not capture episodes of hospitalization, ICU admission or mechanical ventilation of VA patients in non-VA facilities (unless they were paid for by the VA), but there is no evidence that such non-VA care increased substantially over the course of our study. Also, this would not explain the temporal trends in adverse outcomes among hospitalized patients reported here. Finally, although we adjusted for a number of sociodemographic characteristics, comorbid conditions, symptoms and laboratory tests, some residual confounding by disease severity and other unmeasured factors likely persisted.

In conclusion, we identified marked improvements in outcomes of SARS-CoV-2 infection among Veterans infected during the first wave of the US pandemic with stabilization in late summer and early fall. These trends may reflect changing treatment practices, public health measures and viral

pathogenicity. Studies should continue to track trends in adverse outcomes, especially with the emergence of multiple new variants that may have different pathogenicity.

NOTES

Authors' Contributions and Authorship Statement

George Ioannou is the guarantor of this paper. All authors approved the final version of the manuscript.

Ioannou: Study concept and design, analysis of data, interpretation of results, drafting of manuscript, critical revision of manuscript, obtaining funding.

Locke: Study concept and design

Green: Extraction of data, creation of analytic variables, analysis of data, interpretation of results.

Berry: Study concept and design, analysis of data, interpretation of results, drafting of manuscript, critical revision of manuscript

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Declaration of Personal Interests:

None of the authors has any conflicts of interest to disclose.

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Figure Legends.

Figure 1. Trends over time in pharmacotherapy and adverse outcomes of SARS-CoV-2 infection in a national cohort of VA patients

a. Trends over time in pharmacotherapy among SARS-CoV-2-infected hospitalized patients

("Vasopressors" include Norepinephrine, Dobutamine, Vasopressin)

b. Trends over time in 30-day adverse outcomes among all SARS-CoV-2-infected patients

c. Trends over time in 30-day adverse outcomes among hospitalized SARS-CoV-2-infected patients

Figure 2. Trends over time in the adjusted hazards ratios (AHR) for adverse outcomes relative to the baseline time period before March 31, 2020.

a. **Adjusted hazard ratios for 30-day adverse outcomes among all SARS-CoV-2-infected patients**
b. **Adjusted hazard ratios for 30-day adverse outcomes among hospitalized SARS-CoV-2-infected patients**

Table 1. Baseline characteristics of VA patients who tested positive for SARS-CoV-2 between 2/28/20 and 9/30/20, by month

	All Patients N=55,952	Before March 31 N=2504	April N=7451	May N=5025	June N=7782	July N=16,273	August N=9284	September N=7633
Sex								
Female (%)	10.7	9	9.8	9.2	11.3	12.1	10.5	9.7
Male (%)	89.3	91	90.2	90.8	88.7	87.9	89.5	90.3
Age (years) mean (sd)	60.0±16.8	60.7±15.4	64.1±16.4	64.1±16.5	57.5±17.5	57.6±16.7	60.0±16.4	61.0±16.4
18-49 (%)	27	24.2	19	18.3	33.1	32.4	26.2	25.1
50-64 (%)	28.2	31.4	27.6	28.6	27.5	28.6	28.7	26.6
65-79 (%)	34.1	35.1	37.2	36.5	30	31.2	35.5	37.6
>=80 (%)	10.7	9.3	16.1	16.7	9.5	7.8	9.6	10.7
Race								
White (%)	58.2	39.2	51.9	55.8	58.1	57.9	61.9	68.2
Black (%)	31	51.9	39	34.3	29.9	30.3	27.5	21.3
Other (%)	2.8	2.2	2.3	2.7	3.2	3	2.9	2.9
Missing/Unknown (%)	8	6.7	6.9	7.2	8.8	8.8	7.7	7.6
Ethnicity								
Non-Hispanic (%)	84.3	86.3	88.1	88.1	80.1	80.8	85.3	88.3
Hispanic (%)	12.3	11.1	8.8	8.6	16.1	15.8	11.1	8.5
Missing/Unknown (%)	3.4	2.6	3.2	3.3	3.8	3.5	3.5	3.2
Geographical Region*								
1	3.3	3.9	11.3	7.8	2.4	0.9	1.1	1.3
2	7	24.2	23	11.4	3.4	2	2.4	2.8
3	7.2	7.6	11.5	13.4	5.8	4.7	6.4	6.3
4	29.8	14.1	14.7	20.1	31.9	36.8	36.5	30.6
5	11.8	16.7	16.5	19.6	8.1	7.6	11	14.5
6	18.7	18.3	9.3	10	22.9	25.1	18.5	16.1
7	5.4	2.5	3.5	5	3.1	3.8	7.6	11.5
8	2.9	3.4	2.9	3.9	2.1	1.8	2.7	5.5
9	11.5	7.2	5.3	6.9	18.4	14.8	10.7	8.7
10	2.4	2.1	2	1.9	1.9	2.5	3.2	2.7
Urban vs. Rural								
Rural/Highly rural (%)	36	18.8	21.4	28	32.6	36.9	45.1	51.9
Urban (%)	50.8	61.2	61	55.8	52.2	50	44.9	41.7
Missing (%)	13.1	19.9	17.6	16.2	15.2	13.1	10	6.4
BMI								
<18.5 (underweight) (%)	1.2	1.5	1.9	2.1	1.2	0.7	1.1	0.9
18.5-24.9 (normal weight) (%)	15.9	16.6	19.2	20.4	15.6	14.4	14.4	14.7
25.29.9 (overweight) (%)	31.5	31.9	31.1	31.1	32.1	31.7	30.8	32

30-34.9 (Obese I) (%)	27.6	27.1	25.2	24.9	27.8	28.5	28.9	28.5
≥35 (Obese II and III) (%)	21.6	21.8	20.1	18.7	21.2	22.5	22.8	21.7
Missing (%)	2.2	1	2.5	2.8	2.2	2.2	2.1	2.2
Charlson Comorbidity Index (CCI)								
0 (%)	39.3	32.2	31.4	32.7	43.7	43.2	39.8	40.4
1-2 (%)	33.6	34.2	32.4	33.7	32.7	34.1	34.4	33.5
3-4 (%)	14.6	15.5	17.9	17	12.6	12.9	14.8	15.1
≥5 (%)	12.4	18.1	18.3	16.6	11	9.7	11	11
Fever (%)	25.4	57.7	33.4	22.3	26.8	22.9	19.9	20
Dyspnea(%)	11	26.6	15.1	10.3	10.8	9.6	8.4	8.9
Albumin (g/dL)†								
> 3.9	24.6	29.1	19	18.7	28.1	25.7	26.2	25.7
>3.6 to 3.9	19.4	19.7	16.8	18	18.4	20.6	20.1	21.9
>3.1 to 3.6	30.4	30.2	31.9	27.9	30.9	31.2	29.5	29.3
>2.7 to 3.1	15.2	13.6	18.2	20.1	13.6	13.2	14.8	14.4
<= 2.7	10.4	7.5	14.2	15.4	9	9.3	9.4	8.6
Aspartate aminotransferase†								
<= 23	27	16.5	22.9	31.9	29.5	26.7	30.5	32.2
>23 to 33	24.1	23.6	22.3	21.1	27.8	25.2	24.5	23
>33 to 49	23.5	24.4	24.4	25.3	21.9	23.2	23.8	21.8
>49 to 78	15.3	21.1	17	13.3	13.1	14.8	13.2	15.2
> 78	10.1	14.4	13.4	8.4	7.8	10	8	7.8
Creatinine (mg/dL) †								
<= .95	25.3	20.3	23.4	28.3	27.3	25.4	26.3	26.9
>.95 to 1.2	25.6	27.7	24.5	24.7	25	25.3	26.1	26.6
>1.2 to 1.67	23.2	23.4	22.7	21	23	24.1	23.3	23.8
>1.67 to 2.99	15.4	17.4	16.1	14.8	14.4	15.5	15.6	13.8
> 2.99	10.5	11.3	13.3	11.3	10.3	9.7	8.7	8.9
White blood cell count (k/µL)†								
<= 4.7	25.3	30.1	23	24.1	26.2	26.5	23.5	24.1
>4.7 to 6.2	25.3	27.8	24.4	26.2	24.2	26.6	24.2	23.8
>6.2 to 8.32	24.5	23.7	25.3	24.4	25.3	23.2	24.6	25.5
>8.32 to 11.3	15	10.9	17.2	14.8	15.6	14.4	15.6	15.5
> 11.3	9.9	7.5	10.1	10.4	8.7	9.4	12.1	11.2
Neutrophil-to-lymphocyte ratio (sd) †								
<= 2.46	26	20.5	20.6	27.3	31.6	28.7	27.3	25.4
>2.46 to 4.2	25	26.3	23.5	25.5	25.2	25.6	23.2	26.1
>4.2 to 7.17	24.7	29.6	25.9	23.2	22	24.3	24.7	23.2
>7.17 to 12.25	14.7	15.4	18.7	14.6	12.9	13.2	13.3	15.1
> 12.25	9.6	8.3	11.3	9.4	8.2	8.2	11.5	10.2

*Categorized according to the 10 "Standard Federal Regions" drawn up by the Office of Management and Budget: 1 (CT, MA, ME, NH, RI, VT), 2 (NJ, NY, PR), 3 (DC, DE, MD, PA, VA, WV), 4 (AL, FL, GA, KY, MS, NC, SC, TN), 5 (IL, IN, MI, MN, OH, WI), 6 (AR, LA, NM, OK, TX), 7 (IA, KS, MO, NE), 8 (CO, MT, ND, SD, UT, WY), 9 (AZ, CA, GU, HI, NV), 10 (AK, ID, OR, WA from https://www.fema.gov/about/organization/regions).

†Laboratory tests are reported for hospitalized patients only and categorized according to percentiles for all patients: 0-25, 25-50, 50-75, 75-90 and 90-100

Table 2. Changes in pharmacotherapy, noninvasive ventilation and dialysis over time in patients with SARS-CoV-2 infection

	All Patients N=55,952	Before March 31 N=2504	April N=7451	May N=5025	June N=7782	July N=16,273	August N=9284	September N=7633
	ALL PATIENTS							
MEDICATIONS*								
Decreasing prescriptions								
Hydroxychloroquine (%)	2.6	26.2	9.5	0.5	0.1	0.2	0.2	0.1
Azithromycin (%)	7.9	26.5	9.5	5.9	7.2	6.9	6.5	5.9
Tocilizumab (%)	0.8	2.6	2.1	1.1	0.7	0.6	0.2	0.1
Vasopressors‡ (%)	2.8	9.3	4.4	3.2	2.4	1.8	1.9	1.9
Increasing prescriptions								
Remdesivir (%)	5.4	0.7	0.7	4.9	6.3	6.2	6.5	7.6
Dexamethasone (%)	7.0	1.6	0.5	0.8	6.7	9.5	9.8	10.5
Corticosteroids (%)††	5.8	4.6	3.4	2.8	5.4	6.9	6.7	7.7
Rare prescriptions								
Eculizumab (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ADT (%) †	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0
Degarelix (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Unchanged prescriptions								
Anticoagulants (%)	11.5	24.4	13.7	12.0	11.4	10.0	10.2	9.8
DIALYSIS** (%)	1.5	5.2	2.3	1.9	1.2	1.2	0.9	1.0
NON-INVASIVE VENTILATION (%)	3.0	4.5	2.9	2.9	3.0	2.9	3.1	2.8
	HOSPITALIZED PATIENTS							
	N= 9,294	N= 979	N= 1,581	N= 930	N= 1,203	N= 2,181	N= 1,314	N= 1,106
MEDICATIONS								
Decreasing prescriptions								
Hydroxychloroquine (%)	13.0	56.6	38.4	2.4	0.0	0.6	0.6	0.0
Azithromycin (%)	24.5	48.3	30.0	20.3	20.2	21.4	19.1	16.6
Tocilizumab (%)	4.4	5.6	8.7	5.1	4.0	4.4	1.1	0.8
Vasopressors ‡ (%)	11.9	20.6	16.4	12.4	10.3	8.9	9.1	8.7
Increasing prescriptions								
Remdesivir (%)	27.5	1.7	2.5	24.0	33.0	39.3	39.6	45.4
Dexamethasone (%)	30.7	3.4	2.1	3.0	30.8	52.1	50.9	53.1
Corticosteroids (%)††	17.9	4.9	7.3	7.8	16.0	26.6	25.6	29.0
Rare prescriptions								
Eculizumab (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ADT (%)†	0.2	0.0	0.1	0.1	0.0	0.3	0.3	0.2

Degarelix (%)	0.1	0.0	0.0	0.0	0.0	0.1	0.2	0.1
Unchanged prescriptions								
Anticoagulants (%)	51.8	52.5	50.0	49.7	51.6	54.8	51.5	50.3
DIALYSIS (%)	6.0	11.6	7.7	5.7	4.6	5.3	3.8	4.2
NON-INVASIVE VENTILATION (%)	10.7	8.4	9.4	9.5	10.6	12.2	12.5	11.2

*Medications refer to new prescriptions of medications on or within 60 days after the index date that were not prescribed before the index date.

†ADT = Androgen Deprivation Therapy

‡ Vasoressors: Norepinephrine, Dobutamine, Vasopressin

** Dialysis refers to new initiation of dialysis on or after the index date in patients who were not on dialysis before

†† Corticosteroids, other than dexamethasone

Table 3. Association between time period and adverse outcomes in patients with SARS-CoV-2 infection

Dates of SARS-CoV-2 testing	Number positive N=55,952	Number with Event	30-day Incidence	Unadjusted Hazard Ratio	Adjusted Hazard Ratio*	p-value for trends**/†
ALL PATIENTS						
		Hospitalization				
Before March 31	2,504	1,104	44.2	1	1	< 0.001/0.04
April	7,451	1,798	24.3	0.53(0.49-0.57)	0.66(0.61-0.71)	
May	5,025	1,057	21.2	0.47(0.43-0.51)	0.68(0.62-0.74)	
June	7,782	1,472	19.0	0.40(0.37-0.44)	0.68(0.63-0.75)	
July	16,273	2,567	15.8	0.35(0.32-0.37)	0.62(0.57-0.67)	
August	9,284	1,561	16.9	0.37(0.34-0.40)	0.64(0.59-0.70)	
September	7,633	1,305	17.1	0.38(0.35-0.41)	0.66(0.60-0.72)	
		ICU admission				
Before March 31	2,504	506	20.3	1	1	< 0.001/0.03
April	7,451	708	9.7	0.45(0.40-0.50)	0.56(0.49-0.63)	
May	5,025	446	9.0	0.41(0.36-0.47)	0.61(0.53-0.69)	
June	7,782	521	6.7	0.33(0.29-0.37)	0.56(0.49-0.64)	
July	16,273	863	5.3	0.27(0.24-0.31)	0.49(0.43-0.55)	
August	9,284	548	5.9	0.28(0.25-0.32)	0.50(0.44-0.57)	
September	7,633	499	6.6	0.32(0.28-0.36)	0.56(0.49-0.65)	
		Mechanical Ventilation				
Before March 31	2,504	316	12.7	1	1	< 0.001/0.04
April	7,451	376	5.2	0.38(0.33-0.45)	0.47(0.40-0.55)	
May	5,025	168	3.4	0.24(0.20-0.30)	0.36(0.29-0.44)	
June	7,782	189	2.5	0.16(0.13-0.19)	0.26(0.21-0.32)	
July	16,273	351	2.2	0.15(0.12-0.17)	0.25(0.21-0.29)	
August	9,284	191	2.1	0.14(0.11-0.17)	0.23(0.19-0.28)	
September	7,633	164	2.2	0.15(0.12-0.18)	0.25(0.20-0.31)	
		Mortality				
Before March 31	2,504	312	12.5	1	1	< 0.001/< 0.01
April	7,451	874	11.7	0.84(0.73-0.96)	0.73(0.63-0.83)	
May	5,025	442	8.8	0.62(0.53-0.72)	0.52(0.45-0.61)	
June	7,782	378	4.9	0.35(0.30-0.41)	0.42(0.35-0.49)	
July	16,273	719	4.4	0.32(0.28-0.37)	0.40(0.34-0.46)	

August	9,284	441	4.8	0.34(0.29-0.39)	0.37(0.32-0.44)	
September	7,633	373	4.9	0.34(0.29-0.41)	0.38(0.32-0.45)	
HOSPITALIZED PATIENTS						
		ICU admission				
Before March 31	979	462	47.6	1	1	< 0.001/< 0.01
April	1,581	631	40.4	0.80(0.71-0.91)	0.75(0.66-0.85)	
May	930	388	42.0	0.81(0.70-0.93)	0.85(0.73-0.98)	
June	1,203	447	37.3	0.75(0.65-0.86)	0.81(0.70-0.94)	
July	2,181	755	34.8	0.70(0.62-0.80)	0.74(0.64-0.84)	
August	1,314	472	36.1	0.72(0.62-0.83)	0.73(0.63-0.84)	
September	1,106	436	39.5	0.77(0.67-0.89)	0.82(0.70-0.95)	
October						
November						
		Mechanical Ventilation				
Before March 31	979	283	29.2	1	1	< 0.001/0.04
April	1,581	282	18.2	0.60(0.50-0.71)	0.56(0.47-0.66)	
May	930	120	13.1	0.39(0.31-0.49)	0.45(0.36-0.57)	
June	1,203	135	11.4	0.30(0.24-0.38)	0.35(0.27-0.44)	
July	2,181	255	11.9	0.31(0.26-0.38)	0.33(0.27-0.40)	
August	1,314	125	9.7	0.26(0.20-0.33)	0.26(0.21-0.33)	
September	1,106	114	10.5	0.29(0.23-0.36)	0.32(0.25-0.41)	
		Mortality				
Before March 31	979	236	24.1	1	1	
April	1,581	367	23.2	0.93(0.79-1.11)	0.65(0.55-0.78)	
May	930	134	14.4	0.56(0.45-0.70)	0.44(0.35-0.55)	
June	1,203	153	12.7	0.49(0.39-0.61)	0.45(0.35-0.57)	
July	2,181	261	12.0	0.45(0.37-0.55)	0.39(0.31-0.48)	< 0.001/< 0.01
August	1,314	170	12.9	0.49(0.39-0.61)	0.38(0.30-0.48)	
September	1,106	138	12.5	0.47(0.37-0.59)	0.38(0.30-0.49)	
ICU ADMITTED PATIENTS						
		Mechanical Ventilation				< 0.001/0.03
Before March 31	429	242	57.0	1	1	
April	560	240	43.7	0.81(0.67-0.98)	0.79(0.65-0.97)	
May	339	91	27.4	0.50(0.39-0.65)	0.56(0.42-0.73)	
June	406	100	25.2	0.37(0.28-0.48)	0.40(0.30-0.53)	

July	637	172	27.5	0.40(0.32-0.51)	0.40(0.31-0.50)	
August	421	91	22.0	0.34(0.26-0.45)	0.32(0.24-0.43)	
September	396	93	23.9	0.36(0.28-0.47)	0.38(0.29-0.51)	
October						
November						
		Mortality				< 0.001/0.01
Before March 31	429	168	39.2	1	1	
April	560	201	35.9	1.04(0.84-1.29)	0.71(0.56-0.89)	
May	339	77	22.7	0.65(0.49-0.88)	0.51(0.37-0.69)	
June	406	94	23.2	0.64(0.48-0.86)	0.54(0.40-0.73)	
July	637	135	21.2	0.53(0.41-0.69)	0.48(0.36-0.63)	
August	421	95	22.6	0.59(0.44-0.79)	0.44(0.32-0.60)	
September	396	80	20.2	0.54(0.40-0.74)	0.46(0.33-0.63)	
PATIENTS WHO WERE MECHANICALLY VENTILATED						
		Mortality				< 0.001/0.07
Before March 31	247	144	58.3	1	1	
April	245	138	56.3	1.04(0.80-1.36)	0.85(0.64-1.11)	
May	96	30	31.3	0.57(0.37-0.88)	0.48(0.30-0.76)	
June	108	43	39.8	0.80(0.53-1.21)	0.63(0.41-0.98)	
July	180	79	43.9	0.98(0.68-1.40)	0.86(0.59-1.27)	
August	90	42	46.7	0.99(0.63-1.53)	0.81(0.51-1.29)	
September	78	33	42.3	0.77(0.49-1.22)	0.63(0.39-1.02)	

* FOR **ALL PATIENTS**: Adjusted for age, sex, race (White, Black, other, or missing/unknown), ethnicity, BMI, geographic region, Charlson comorbidity index, diabetes, chronic kidney disease, hypertension, obstructive sleep apnea, obesity hypoventilation, fever, and dyspnea (stratified by VA facility)

* FOR **HOSPITALIZED, ICU ADMITTED AND VENTILATED PATIENTS :** Adjusted for age, sex, race, ethnicity, BMI, geographic region, Charlson comorbidity index, diabetes, chronic kidney disease, congestive heart failure, hypertension, obstructive sleep apnea, obesity hypoventilation, fever, dyspnea and the following laboratory tests: albumin, aspartate aminotransferase, creatinine, white blood cell count, neutrophil-to-lymphocyte ratio (stratified by VA facility).

**Non-parametric Wilcoxon-type test for trend over time across ordered groups

†Interrupted time series test for difference in 30-day outcome rate slope before and after July 1, 2020.

Figure 1

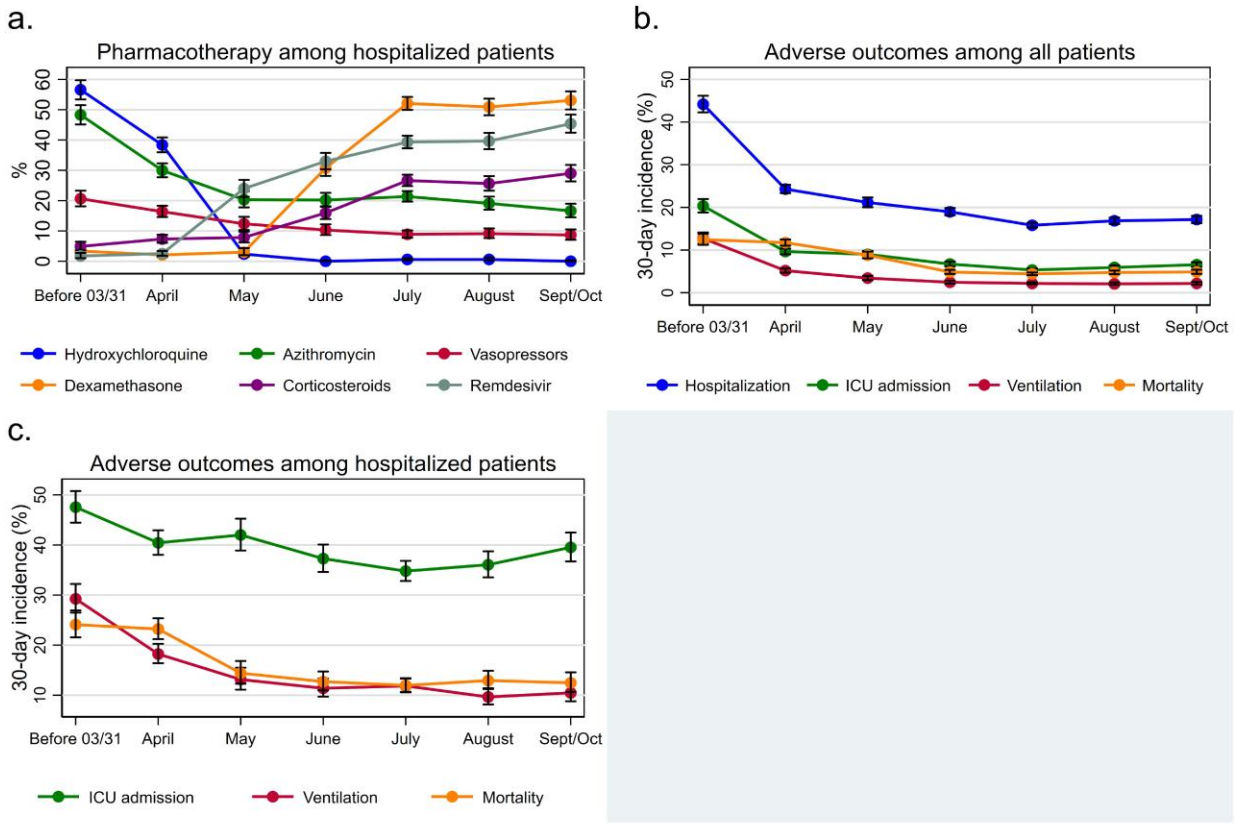
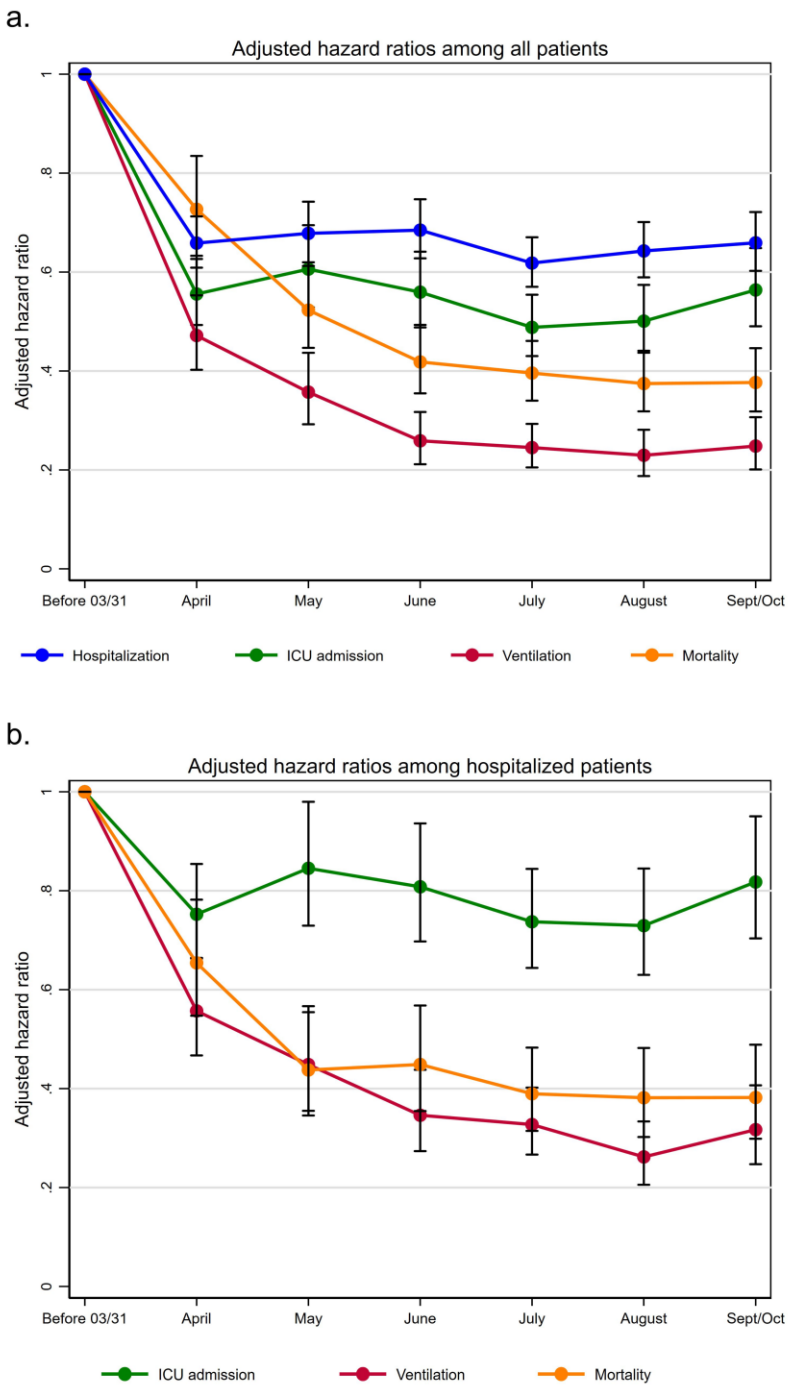


Figure 2


a.
Adjusted hazard ratios among all patients
Adjusted hazard ratio
0
.2
.4
.6
.8
1
Before 03/31
April
May
June
July
August
Sept/Oct
Hospitalization
ICU admission
Ventilation
Mortality
b.
Adjusted hazard ratios among hospitalized patients
Adjusted hazard ratio
0
.2
.4
.6
.8
1
Before 03/31
April
May
June
July
August
Sept/Oct
ICU admission
Ventilation
Mortality