







Sotrovimab Lowers the Risk of COVID-19 Related Hospitalization or Death in a Large Population Cohort in the United Arab Emirates

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Sotrovimab, an anti-severe acute respiratory syndrome-coronavirus 2 monoclonal antibody is being utilized to prevent progression of coronavirus disease 2019 (COVID-19). Therefore, to understand its benefits, we have conducted a retrospective analysis of all non-hospitalized patients with symptomatic COVID-19 who received a single infusion of sotrovimab and/or oral favipiravir at any Dubai COVID-19 related healthcare center between July 1, 2021, and October 31, 2021. The main outcome was to evaluate the risk of hospitalization for patients with COVID-19 or all-cause death within 28 days of treatment initiation. In this analysis, which included 10,882 patients (1,135 in the sotrovimab group, 2,653 in the sotrovimab/favipiravir group, and 7,094 in the favipiravir group), sotrovimab or sotrovimab/favipiravir reduced the risk of hospitalization (13 patients (1.5%) in the sotrovimab group and 71 patients (2.9%) in the sotrovimab/favipiravir group vs. 251 patients (4%) in the favipiravir group; hazard ratio (HR) for sotrovimab: 0.16, 95% confidence interval (CI): 0.09–0.28, $P < 0.001$; and for sotrovimab/favipiravir, HR: 0.42, 95% CI: 0.32–0.56, $P < 0.001$), or death by day 28 from the start of treatment (no death in the sotrovimab group and 2 deaths in the the sotrovimab/favipiravir group vs. 10 deaths in the favipiravir group; odds ratio: 0.18, 95% CI: 0.04 to 0.81, $P = 0.26$). Safety was assessed in all the 3,788 patients in the sotrovimab and sotrovimab/favipiravir groups, and the reported adverse events were by 34 patients (<1%). In conclusion, sotrovimab was found to reduce the risk of progression of COVID-19 when administrated early to non-hospitalized patients with symptomatic COVID-19. No safety concern was detected.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ Sotrovimab, an anti-severe acute respiratory syndrome-coronavirus 2 monoclonal antibody is being utilized to prevent progression of coronavirus disease 2019 (COVID-19) in high-risk patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ To understand the benefits of sotrovimab in a large population cohort of non-hospitalized patients with mild to moderate COVID-19.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✔ Sotrovimab was found to reduce the risk of progression of COVID-19 when administrated early to non-hospitalized patients with symptomatic COVID-19. No safety concern was detected.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✔ The results from this large population cohort study may strengthen the evidence-based rationale for administration of sotrovimab, especially to high-risk patients.

Over 2 years since the pandemic unfolded, morbidity and mortality from coronavirus disease 2019 (COVID-19) remain substantial, creating an urgent need for developing more effective

therapies against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), the virus causing COVID-19. Remdesivir first and more recently, two oral antivirals nirmatrelvir/ritonavir,

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and molnupiravir, as well as sotrovimab, an intravenous monoclonal antibody drug were approved under an Emergency Use Authorization (EUA), based on randomized controlled trial (RCT) data, for people with mild-to-moderate COVID-19 deemed at risk of progressing to serious illness.¹⁻⁴ Sotrovimab is a human monoclonal antibody that neutralizes SARS-CoV-2, and several other respiratory coronaviruses, including SARS-CoV-1.⁵ Recently, preclinical data confirmed potent *in vitro* and *in vivo* inhibitory activity of sotrovimab against SARS-CoV-2 resulting in effective viral clearance.⁶ Moreover, sotrovimab is an engineered Fc-fusion monoclonal antibody that contains two-amino acid Fc modification to increase its half-life in the respiratory mucosa.⁷ The interaction with Fc receptors can also mediate clearance of virus-infected cells through a variety of immune effector mechanisms.^{5,6} On the other hand, favipiravir is an anti-influenza drug that early in the pandemic was reported to have *in vitro* inhibitory activity against SARS-CoV-2 and it has been used as an antiviral agent to treat COVID-19.⁸ It is a nucleotide analogue prodrug that selectively inhibit viral RNA polymerase complex and result in SARS-COV-2 lethal mutagenesis.⁸ However, the efficacy of favipiravir therapy is still debatable in non-hospitalized patients with mild to moderate COVID-19⁹⁻¹¹ but was commonly used in multiple countries' COVID-19 treatment-protocols until recently.

Sotrovimab efficacy among high-risk patients with mild to moderate COVID-19 was based on recent published clinical trials that found a single intravenous dose of sotrovimab (500 mg), compared with placebo, significantly reduced the risk of all-cause hospitalization or death through day 29.^{1,12} Furthermore, sotrovimab was also associated with a reduction from baseline to day 8 in nasopharyngeal viral load and reduction from baseline to day 7 in the FLU-PRO Plus questionnaire total score of COVID-19 related symptom severity and duration.¹² Therefore, the lower number of these events prompted a "conditional" recommendation of its use by treatment guidelines panels.¹³

Moreover, there are, to our knowledge, no published real-world data on the effectiveness of sotrovimab treatment to prevent development of severe COVID-19 and its outcomes. We therefore sought to examine the association between sotrovimab treatment and the risk of hospitalization or death among a large population-based cohort of patients with COVID-19 in the city of Dubai, United Arab Emirates.

METHODS

Study design

This study was a retrospective analysis of administrative data from the SALAMA healthcare system. SALAMA is the Dubai Health Authority's (DHA) unified electronic medical record system which covers all the hospitals and clinics under the Government of Dubai. The study used patients' data of those who received sotrovimab infusion (a single dose of 500 mg), a combination of sotrovimab infusion and oral favipiravir (1,600 mg twice a day on day 1 and then 600 mg twice a day for 10 days), or oral favipiravir alone at any Dubai COVID-19 related healthcare center between June 22, 2021, and October 31, 2021. The retrieved data from the SALAMA system for each of the patient were as follows; patients demographics, such as age, gender, and nationality; date of COVID-19's positive reverse transcriptase-polymerase chain reaction (RT-PCR) and negative RT-PCR test results, type and date of medication received being either sotrovimab and/or favipiravir; date for other COVID-19 adjacent therapy, such as ascorbic acid and cholecalciferol; COVID-19 related-symptoms and oxygen saturation level SpO₂ at the time of receiving treatment; post-infusion status of sotrovimab; type and date of different doses of COVID-19 vaccine received being mRNA vaccine; diagnosis name, problem lists, and medical history at patient level; next visit date, location (name of clinic or hospital), and department name (family medicine clinic or emergency department); and survival status (alive/dead).

Patients and treatment selection

The studied patients were aged 18 years or older, tested positive for SARS-CoV-2 by RT-PCR test, and had mild to moderate COVID-19 related symptoms with SpO₂ ≥ 94% on room air that did not require hospital admission. Mild illness was defined as individuals with any of

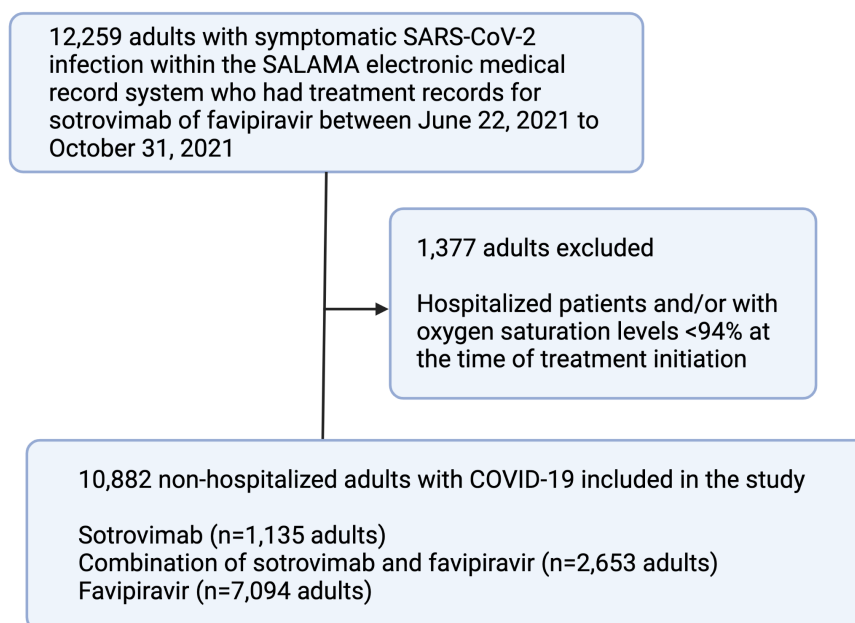


Figure 1 Flowchart of study population. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

the following signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, and muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging. Whereas moderate illness was defined as individuals who have evidence of lower respiratory disease by clinical assessment or imaging, and a saturation of oxygen (SpO₂) ≥94% on room air at sea level.¹⁴ Patients were excluded if they had received treatment while hospitalized, or if they had SpO₂ level <94% and required supplemental oxygen.

In this study, the selection for treatment with sotrovimab and/or favipiravir was based on the published national treatment protocol for management of adult patients with COVID-19 that included risk stratification and treatment recommendations of COVID-19.^{14,15} As such, a single infusion of sotrovimab or a 10-day course of oral favipiravir alone was recommended for management of nonhospitalized patients with mild to moderate COVID-19 who had at least 1 of the following risk factors of progression to severe or critical respiratory COVID-19: 65 years of age or older, obese

or overweight (body mass index ≥25), diabetes mellitus (DM), cardiovascular disease (including congenital heart disease) or hypertension, chronic lung diseases (such as chronic obstructive pulmonary disease (COPD), moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, or pulmonary hypertension), with an immunocompromising condition or receiving immunosuppressive treatments, chronic kidney disease (CKD), pregnancy, sickle cell disease, neurodevelopmental disorders (like cerebral palsy), other medical conditions, such as genetic or severe congenital conditions, or conditions that require technology dependency (including tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19). Of note, the above risk factors were apparent for each of the study population in the “diagnosis name, problem lists, and medical history at patient level” section retrieved from the SALAMA system.

Furthermore, the study population had either a single infusion of sotrovimab or a 10-day course of oral favipiravir alone. The combination of sotrovimab and favipiravir was initiated on the same day, as the

Table 1 Baseline characteristics of patients with COVID-19 receiving sotrovimab, a combination of sotrovimab and favipiravir, or favipiravir alone

Characteristics	Sotrovimab (n = 1,135)	Sotrovimab/favipiravir (n = 2,653)	Favipiravir (n = 7,094)	P value
Age, median (range) year	42 (34–52)	45 (36–57)	37 (30–44)	<0.001
Male sex, n (%)	582 (51)	1,404 (53)	3,506 (49)	0.007
White, n (%) ^a	804 (71)	1,783 (67)	3,741 (53)	<0.001
Vaccination status, n (%) ^b				
One vaccination	96 (8)	197 (7)	525 (7)	0.446
Two vaccinations	239 (21)	1,039 (39)	2,486 (35)	<0.001
Time from the last dose of vaccine to start of treatment, median (range), days	110 (86–139)	115 (72–163)	106 (69–149)	0.201
Risk factors for COVID-19 progression—n (%)				
Age ≥65 year	97 (15)	314 (12)	234 (3)	<0.001
DM	185 (16)	780 (29)	627 (9)	<0.001
Overweight (BMI ≥25 kg/m ²)	408 (36)	436 (16)	240 (3)	<0.001
CVDs	25 (2)	169 (6)	140 (2)	<0.001
HTN	224 (20)	840 (32)	778 (11)	<0.001
CKD	19 (1.7)	69 (2.6)	90 (1.3)	<0.001
Asthma	56 (5)	255 (10)	300 (4)	<0.001
COPD and other chronic lung diseases ^c	6 (0.5)	81 (3)	104 (1.5)	<0.001
Immunocompromised ^d	14 (1)	89 (3)	73 (1)	<0.001
Neurodevelopmental disorders ^e	11 (1)	25 (0.9)	42 (0.6)	0.107
Genetic disorders ^f	6 (0.5)	18 (0.7)	33 (0.5)	0.430
Sickle cell disease	3 (0.3)	5 (0.2)	7 (0.1)	0.272
COVID-19 related symptoms				
Fever	814 (72)	1,943 (73)	5,124 (72)	0.523
Cough	545 (48)	1,279 (48)	3,565 (50)	0.112
Sore throat	319 (28)	725 (27)	2,037 (29)	0.395
Malaise	560 (49%)	1,313 (49%)	3,504 (49%)	0.995
Shortness of breath	147 (13)	360 (14)	868 (12)	0.109
Oxygen saturation, SpO ₂ , median (range)	96 (95–97)	96 (95–97)	96 (95–97)	0.178
Time from positive test to start of treatment, median (range), days ^g	2 (1–3)	3 (3)	3 (3)	<0.001

BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension.

^aWhite ethnicity or White race. ^bReceiver of mRNA vaccines. ^cCOPD and other chronic lung diseases, such as interstitial lung disease, cystic fibrosis, and pulmonary HTN. ^dThe national guideline defines an immunocompromised condition as being on chemotherapy for cancer, being within 1 year out from receiving a hematopoietic stem cell or solid organ transplant, untreated HIV infection with CD4 T lymphocyte count <200, combined primary immunodeficiency disorder, and receipt of prednisone >20 mg/day for more than 14 days. ^eNeurodevelopmental disorders include cerebral palsy, autism, mental retardation, conduct disorders, and impairments in vision and hearing. ^fGenetic disorders such as G6PD (glucose-6-phosphate dehydrogenase) deficiency. ^gSevere acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection confirmed by polymerase chain reaction (PCR).

single infusion of sotrovimab was followed by the 10-day course of oral favipiravir.

Outcomes

The primary efficacy outcome measured was the risk of COVID-19 related hospitalization through day 28. In the emergency department visit, patients were evaluated for COVID-19 pneumonia as the primary diagnosis, and hospitalization lasting >24 hours. Additional secondary outcomes for patients with progression to severe or critical respiratory COVID-19 included the need for supplemental oxygen during hospital stay, length of stay, and all-cause death through day 28.

Statistical analysis

In the unadjusted univariate analysis, for continuous variables, means and SDs or medians and interquartile ranges were reported, as appropriate. For categorical variables, percentages were compared across the treatment groups using a χ^2 test (Chi-square test analyses).

In the adjusted analysis of the risk of COVID-19 related hospitalization through 28-day, a Cox proportional hazard model was developed adjusted for patients' demographic factors, including age and male sex, risk factors for COVID-19 progression, such as diabetes mellitus (DM), overweight, cardiovascular disease, hypertension, CKD, asthma, COPD, and other chronic lung diseases, immunocompromised; and vaccination status of patients. Time zero was considered to be the treatment initiation date in all survival analyses. Kaplan–Meier survival curves were constructed to show cumulative survival over the 28-day period of follow-up. Moreover, treatment was considered as a time-varying covariate to avoid “immortal time bias” or “survivor selection bias,” which occurs because patients who live longer are more likely to receive treatment earlier than those who die early.^{16–18}

In this study, because the time from diagnosis of COVID-19 (positive PCR test) to the start of treatment was different for individual patients, treatments were considered as a time-varying covariate in the model. All selected variables were tested for multicollinearity to avoid any strong correlation between the variables. The presence of collinearity was examined by the evaluation of variance inflation factors and magnitude of standard errors.

In the subgroup analysis of different patient risk factors of COVID-19 progression in relation to COVID-19 related hospitalization, a Cox proportional hazard model was developed adjusted for demographics, such as age and male sex; patient high-risk factors for COVID-19 progression, including DM, overweight, cardiovascular disease, hypertension, CKD, asthma, COPD and other chronic lung diseases, immunocompromised; and vaccination status. The *p* value for interaction was evaluated by including an interaction term (comorbidity \times treatment) in the Cox proportional hazard model.

Furthermore, the effect of sotrovimab and/or favipiravir treatment groups on the use of supplemental oxygen during the hospital stay was evaluated by an ordinal logistic regression model adjusted for demographics, such as age and male sex, patient high-risk factors of disease progression, such as DM, cardiovascular disease, CKD, COPD and other chronic lung diseases, immunocompromised, and vaccination status. The length of hospital stay between these treatment groups were assessed using a generalized linear mixed model, which included fixed effect of treatment and random effect of age, male sex, DM, cardiovascular disease, CKD, COPD and other chronic lung diseases, immunocompromised, and vaccination status of patients. Additionally, for evaluating the ratio of all-cause mortality through 28 days, a multivariate logistic regression model was developed adjusted for age, male sex, DM, overweight, cardiovascular disease, hypertension, CKD, asthma, COPD and other chronic lung diseases, immunocompromised, and vaccination status.

All tests were 2-tailed and a *P* value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS (version 26.0), R software (version 3.6.1) and PRISM (version 8). The ethical approval for this study was obtained from the Dubai Scientific Research Ethics Committee (DSREC), Dubai Health Authority at Rashid Hospital (DSREC-12/2020_02).

RESULTS

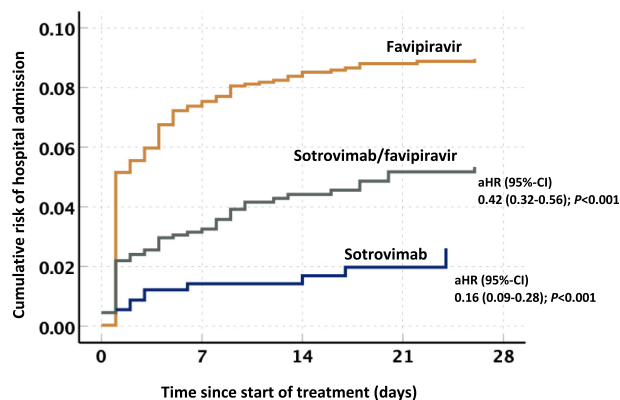
Patient characteristics

Out of the 10,882 non-hospitalized adults with COVID-19 within the SALAMA system and who met the study criteria were 1,135 patients received sotrovimab, 2,653 patients received a combination of sotrovimab and favipiravir (sotrovimab/favipiravir), and 7,094 patients received favipiravir during the study period (Figure 1). Overall, baseline characteristics of patients at the time of treatment initiation are presented in Table 1. As it shows, patients in the sotrovimab and sotrovimab/favipiravir groups were relatively older than patients in the favipiravir group (42 years and 45 years in the sotrovimab and sotrovimab/favipiravir groups, respectively vs. 37 years in the favipiravir group). Around half of the patients in all the treatment groups were men (51% in the sotrovimab, 53% in the sotrovimab/favipiravir, and 49% in the favipiravir groups) and patients with White ethnicity were more predominant in the sotrovimab and sotrovimab/favipiravir groups than in the favipiravir group (71% in sotrovimab and 67% in the sotrovimab/favipiravir vs. 53% in the favipiravir groups). According to the vaccination status of patients, approximately one-third of patients in the sotrovimab/favipiravir and favipiravir groups had the 2 doses of COVID-19 mRNA vaccine (39% in the sotrovimab/favipiravir group and 35% in the favipiravir group), whereas one-fifth (21%) of patients in the sotrovimab group had received the vaccines ($P < 0.001$). There was no significant difference in the length of the last COVID-19 vaccine to treatment initiation among the three groups (>100 days length of time, $P = 0.201$). Patients were also similar with respect to COVID-19 related symptoms and oxygen saturation levels at the time of treatment initiation (Table 1).

Furthermore, out of all the risk factors for COVID-19 progression included in the guidelines,¹⁵ the most commonly found in the three groups were an age of 65 years or older, DM, overweight, and hypertension, which were more predominant in the sotrovimab and sotrovimab/favipiravir groups than in the favipiravir group (Table 1). Accordingly, there were 15% of patients with older than 65 years of age in the sotrovimab and 12% in the sotrovimab/favipiravir groups vs. 3% in the favipiravir group ($P < 0.001$). DM was among 16% of patients in the sotrovimab and 29% of patients in the sotrovimab/favipiravir groups vs. 9% of patients in the favipiravir group ($P < 0.001$). Moreover, 36% of patients in the sotrovimab and 16% of patients in the sotrovimab/favipiravir groups were overweight compared with 3% of patients in favipiravir group ($P < 0.001$) and hypertension were among 20% in the sotrovimab and 32% in the sotrovimab/favipiravir groups vs. 11% in the favipiravir group ($P < 0.001$).

There were also relatively higher proportions of patients with asthma and other chronic lung diseases (like, COPD, interstitial lung disease, cystic fibrosis, and pulmonary hypertension) in the sotrovimab or sotrovimab/favipiravir group compared with the favipiravir group. As such, 5% of patients in the sotrovimab and 10% of patients in the sotrovimab/favipiravir groups had asthma compared with 4% in the favipiravir ($P < 0.001$), and 3% of patients in the sotrovimab/favipiravir compared with 1.5% in the favipiravir group ($P < 0.001$) had COPD or other chronic lung diseases. Additionally, 3% of patients in the sotrovimab/favipiravir group had an immunocompromising condition or were receiving immunosuppressive treatment, such as cancer chemotherapy at the time of treatment

(a) COVID-19 related hospitalization by 28 days



No. of patients hospitalized (>24 hrs)	Time since start of treatment (days)				
	0	7	14	21	28
Favipiravir (n=251)	0	229	15	5	2
Sotrovimab/favipiravir (n=71)	0	55	10	5	1
Sotrovimab (n=13)	0	9	1	1	2

(b) Sotrovimab/Favipiravir vs. Favipiravir

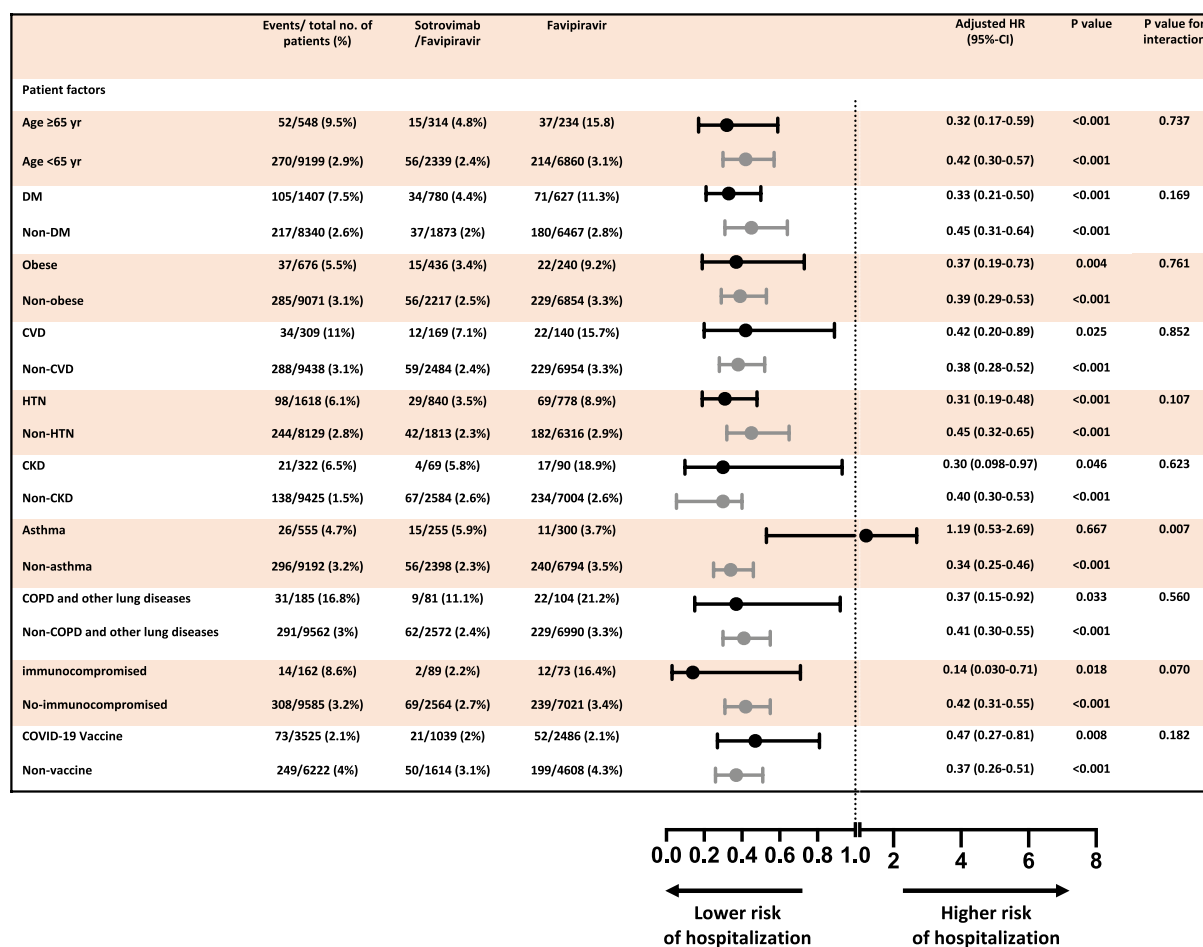


Figure 2 The effect of treatment groups on COVID-19 related hospitalization through 28 days of treatment initiation. The effect of treatment groups on hospital admission of total cohort (a). Subanalysis of sotrovimab and sotrovimab/favipiravir effect stratified by patient risk factors on hospital admission (b-d). CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension.

(c) Sotrovimab vs. Favipiravir

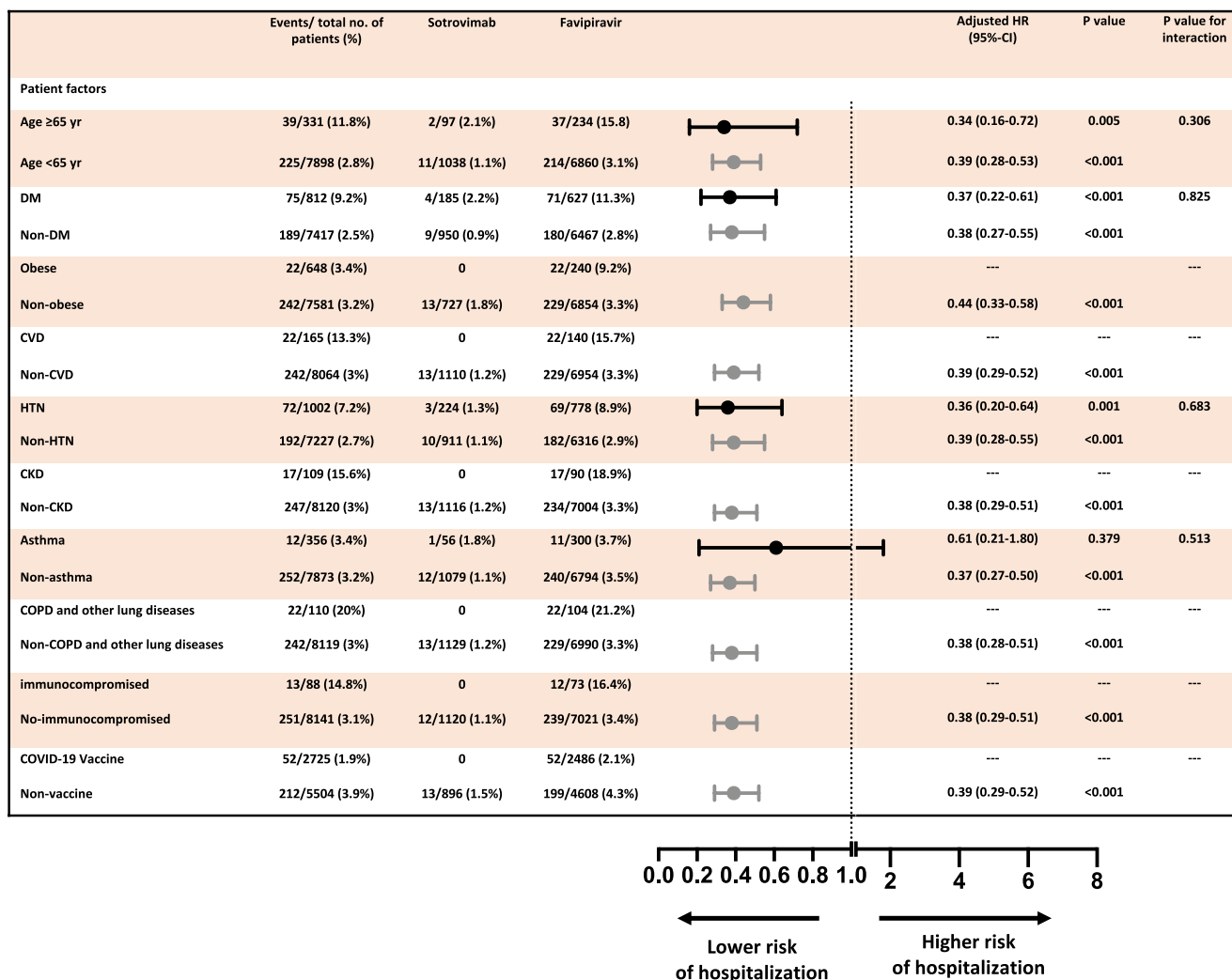


Figure 2 (Continued)

initiation as compared with 1% of patients in the favipiravir group ($P < 0.001$). The three groups were similar with respect to any of the neurodevelopmental disorders as well as other rare genetic diseases.

The primary outcome of COVID-19 related hospitalization

Among the 10,882 patients treated with sotrovimab, sotrovimab/favipiravir, or favipiravir, 331 cases (3%) of COVID-19 related hospitalizations lasting > 24 hours were observed during the 28 days of follow-up after treatment initiation; 13 (3.9%) in the sotrovimab group, 71 (21.2) in the sotrovimab/favipiravir group, and 251 (74.9%) in the favipiravir group. Furthermore, the results of adjusted Cox regression showed that, after adjusting for patient demographic factors including age and male sex; patient high-risk factors for COVID-19 progression, such as DM, overweight, cardiovascular diseases, hypertension, CKD, asthma, COPD and other chronic lung diseases, and immunocompromised; and the vaccination status; treatment with sotrovimab or sotrovimab/favipiravir was associated with lower risk of 28-day COVID-19 related hospitalization than treatment with

favipiravir (adjusted hazard ratio (HR) for sotrovimab: 0.16, 95% confidence interval (CI): 0.09–0.28, $P < 0.001$; and for sotrovimab/favipiravir, HR: 0.42, 95% CI: 0.32–0.56, $P < 0.001$; **Figure 2a, Table 2**). It is noteworthy that several patient high-risk factors, such as older than 65 years of age (HR: 1.74, $P = 0.002$), DM (HR: 1.87, $P < 0.001$), cardiovascular disease (HR: 1.55, $P = 0.024$), CKD (HR: 1.71, $P = 0.027$), COPD and other chronic lung diseases (HR: 2.27, $P < 0.001$), and immunocompromised (HR: 1.78, $P = 0.039$) were independently associated with a higher risk of hospitalization for COVID-19 whereas vaccination was associated with a lower risk (HR: 0.25, $P < 0.001$; **Table 2**).

Furthermore, results of subgroup analyses by patients' high-risk factors for disease progression was consistent with the main findings and showed that both sotrovimab and sotrovimab/favipiravir were consistently associated with a lower risk of hospitalization in all the subgroups (**Figures 2b, 1c**). There was no difference between sotrovimab and sotrovimab/favipiravir in this regard (**Figure 2d**).

(d) Sotrovimab vs. Sotrovimab/Favipiravir

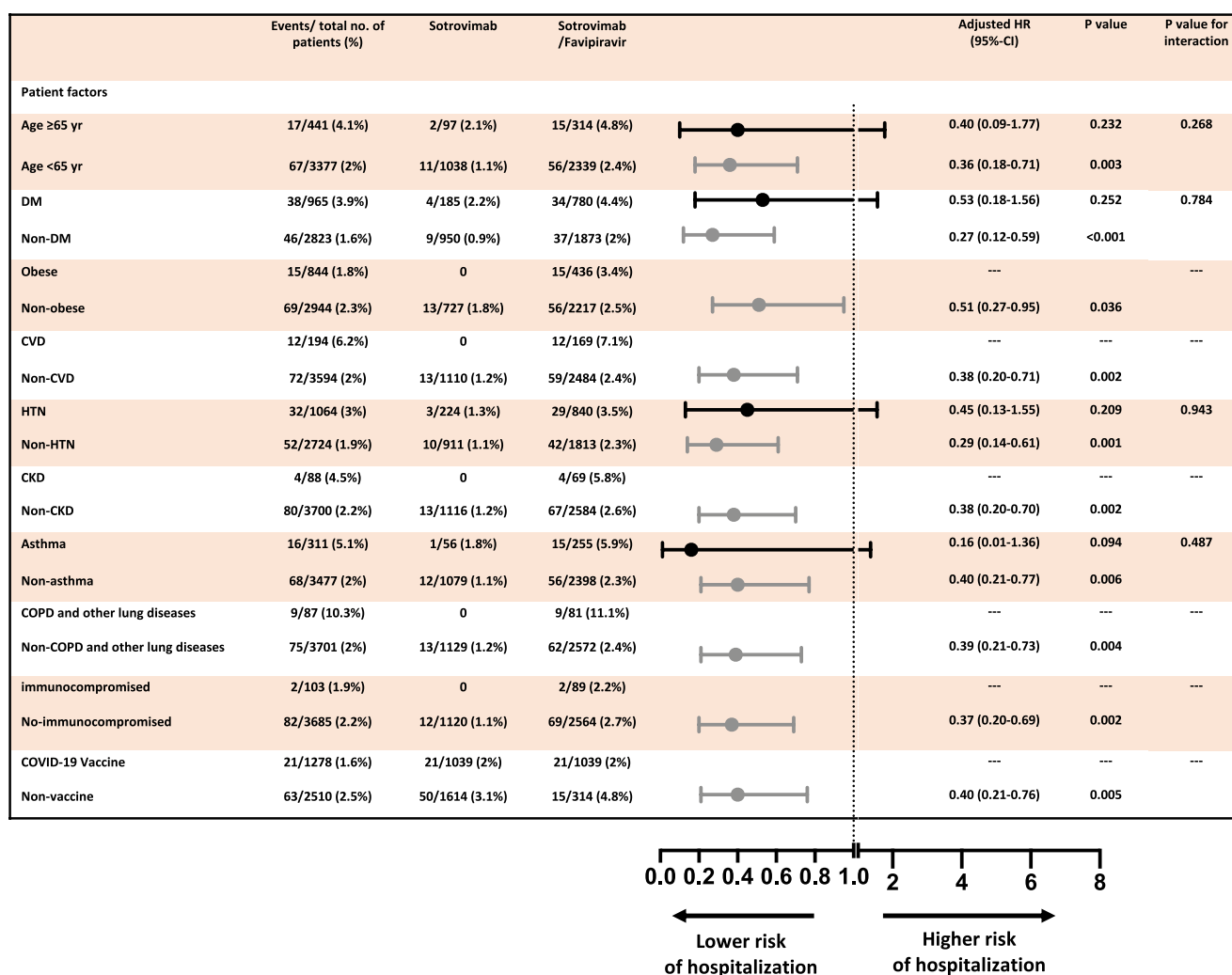


Figure 2 (Continued)

The secondary outcomes of use of oxygen supplement during admission, length of hospital stay, or death by 28 days

Out of 331 cases of COVID-19 related hospitalizations, 123 (36.7%) cases had disease progression in the hospital that warranted the use of supplemental oxygen; 3 (2.4%) in the sotrovimab group and 18 (14.6) in the sotrovimab/favipiravir group compared with 102 (82.9%) of patients in the favipiravir group ($P = 0.036$; **Figure 3a**). Moreover, results of adjusted ordinal regression showed that, after adjusting with age, male sex, DM, cardiovascular diseases, CKD, COPD and other chronic lung diseases, immunocompromised, and vaccination status; patients in the sotrovimab and sotrovimab/favipiravir groups were associated with lower need of supplemental oxygen during hospital stay (odds ratio (OR) for sotrovimab: 0.377; 95% CI: 0.369–0.386, $P < 0.001$; and OR for sotrovimab/favipiravir: 0.477; 95% CI: 0.459–0.498, $P < 0.001$).

In addition, patients receiving sotrovimab and sotrovimab/favipiravir had a shorter hospital stay (mean, 95% CI) of 6 (95%

CI: 4.9–7.05) days in the sotrovimab and 7.01 (95% CI: 5.8–8.2) days in the sotrovimab/favipiravir group compared to those receiving favipiravir (8.19 (95% CI: 7.6–8.78) days ($P = 0.039$; **Figure 3b**). Furthermore, by day 28, the number of deceased patients was significantly lower in the sotrovimab/favipiravir treated group (2 patients), compared with the favipiravir group (10 patients), adjusted OR: 0.18, 95% CI: 0.04–0.81, $P = 0.026$; **Figure 3c**). By day 28, no patient had died in the sotrovimab group.

Additionally, the safety of sotrovimab treatment was assessed for all patients who received this medication ($n = 3,788$). Adverse events were reported by 34 (< 1%) patients including 14 infusion-related reactions that led to discontinuation of sotrovimab (mild to moderate dyspnea), and 20 serious adverse events, including an acute hypersensitivity reaction during the intravenous infusion that led to hospital admission. No death was reported due to adverse events and all deaths reported were due to COVID-19 pneumonia.

Table 2 The risk of COVID-19 related hospitalization with sotrovimab or the combination of sotrovimab/favipiravir by day 28 (n = 335): Results of Cox Hazards model

Variables	No. of patients receiving treatment/no. of events per variable			Adjusted HR	P value
	Sotrovimab	Sotrovimab/ favipiravir	Favipiravir		
Age ≥ 65 year	2/54 (3.7%)	15/54 (27.8%)	37/54 (68.5%)	1.74 (1.23–2.46)	0.002
Male sex	6/169 (3.6%)	33/169 (19.5%)	130/169 (76.9%)	1.18 (0.95–1.47)	0.116
DM	4/109 (3.7%)	34/109 (31.2%)	71/109 (65.1%)	1.87 (1.42–2.48)	<0.001
Obesity (BMI ≥ 25 kg/m ²)	0	15/37 (40.5%)	22/37 (59.5%)	0.92 (0.64–1.33)	0.684
CVDs	0	12/34 (53.3%)	22/34 (64.7%)	1.55 (1.05–2.28)	0.024
HTN	3/101 (3%)	29/101 (28.7%)	69/101 (68.3%)	1.06 (0.79–1.43)	0.671
CKD	0	4/21 (19%)	17/21 (81%)	1.71 (1.06–2.76)	0.027
Asthma	1/27 (3.7%)	15/27 (55.6%)	11/27 (40.7%)	1.08 (0.73–1.62)	0.679
COPD and other chronic lung diseases ^a	0	9/31 (29%)	22/31 (71%)	2.27 (1.50–3.00)	<0.001
Immunocompromised ^b	0	2/15 (13.3%)	12/15 (80%)	1.78 (1.03–3.09)	0.039
White ^c	11/238 (4.6%)	58/238 (24.4%)	169/238 (71%)	0.90 (0.70–1.16)	0.437
COVID-19 vaccine ^d	0	21/73 (28.8%)	52/73 (71.2%)	0.25 (0.19–0.32)	<0.001
Sotrovimab	13/335 (3.9%)	–	–	0.16 (0.09–0.28)	<0.001
Sotrovimab/favipiravir	–	71/335 (21.2%)	–	0.42 (0.32–0.56)	<0.001
Favipiravir	–	–	251/335 (74.9%)	1	

BMI, Body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; DM, diabetes mellitus; HR, Hazard ratio; HTN, hypertension.

^aCOPD and other chronic lung diseases, such as interstitial lung disease, cystic fibrosis, and pulmonary HTN. ^bThe national guideline defines an immunocompromised condition as being on chemotherapy for cancer, being within 1 year out from receiving a hematopoietic stem cell or solid organ transplant, untreated HIV infection with CD4 T lymphocyte count <200, combined primary immunodeficiency disorder, and receipt of prednisone >20 mg/day for more than 14 days. ^cWhite ethnicity or White race. ^dReceiver of the two doses of mRNA vaccines.

DISCUSSION

In this large population-based cohort of patients with COVID-19, a lower proportion of patients treated with sotrovimab and sotrovimab/favipiravir compared with those receiving favipiravir had disease progression that led to hospital admission or death. Overall, no safety warning was identified for both sotrovimab and sotrovimab/favipiravir in our studied cohort. To the best of our knowledge, this is the first and largest cohort analysis conforming that addition of sotrovimab to COVID-19 treatment has the potential to prevent severe complications of COVID-19. Such studies are essential to ensure confidence of newly approved medications (with EUA) for the fight against COVID-19.

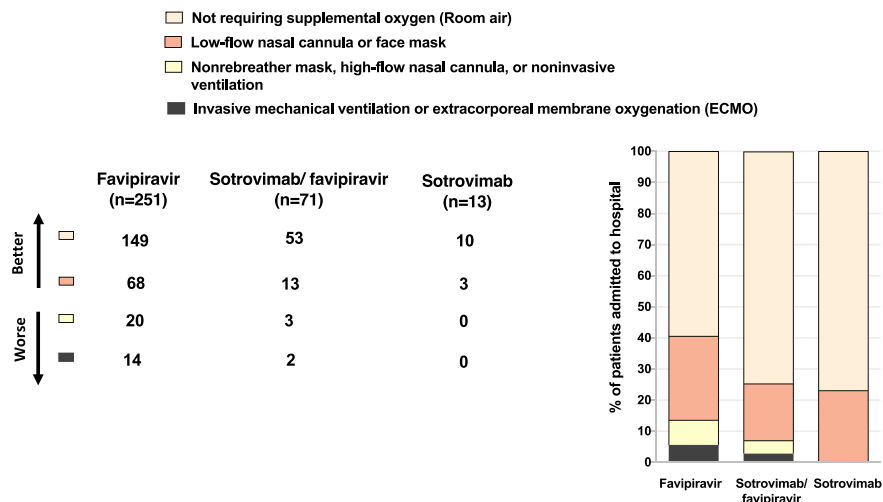
Our findings are concordant with those of the single RCT¹ showing that administration of sotrovimab reduces the risk of hospitalization in outpatients with COVID-19 compared with placebo. Here, we were able to highlight the effect of sotrovimab on progression of COVID-19 in a much larger population-based cohort of patients with mild–moderate COVID-19; and compared that to favipiravir treatment which is more reflective of real world COVID-19 management protocols. Importantly, treatment with sotrovimab or sotrovimab/favipiravir was more efficient than favipiravir alone in reducing hospitalization across all high-risk patients' groups, such as the elderly and patients with obesity, DM, or CKD. In contrary to the inconclusive RCT data that had only 2 mortality events,¹ we observed an association between sotrovimab or sotrovimab/favipiravir use and lower mortality at 28 days.

The addition of sotrovimab has also resulted in favorable outcomes for hospitalized patients measured by lower use of supplementary oxygen, as well as lower death rate compared with favipiravir treatment (Figure 3). Similar to previous studies,^{1,19} we also did not find low safety signals in both the sotrovimab and sotrovimab/favipiravir groups, defined as the composite of death and serious adverse events, demonstrating its therapeutic potential.

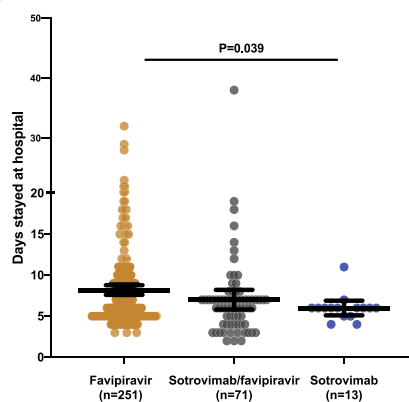
Furthermore, this study included patients over ~4 months of the pandemic, between June 22, 2021, and October 31, 2021, and although we do not have the results of viral sequencing of these patients; according to the United Arab Emirates national monitoring system, the most common variants during the study period were the following: Alpha/B.11.7, 11.3%; Beta/B.1.351, 39.2%; and Delta/B.1.617.2, 33.9%. Similar reports were reported for the efficient neutralizing ability of sotrovimab against Alpha, Beta, and Delta variants *in vitro*, in comparison with other proposed monoclonal anti-SARS-CoV-2 antibodies.²⁰ However, a recent study has shown that sotrovimab has lower neutralizing activity against the Omicron variants (BA.1) and (BA.1.1), *in vitro*, compared to Alpha, Beta, and Delta variants, and to have even less neutralizing activity against omicron (BA.2),²¹ that has become the predominant omicron sub-lineage. Therefore, sotrovimab is not currently available for treatment of COVID-19 in many places.

On the other hand, our study has few limitations. First, our study was not an RCT and therefore we cannot completely rule out the possible impact of bias due to unmeasured patient factors

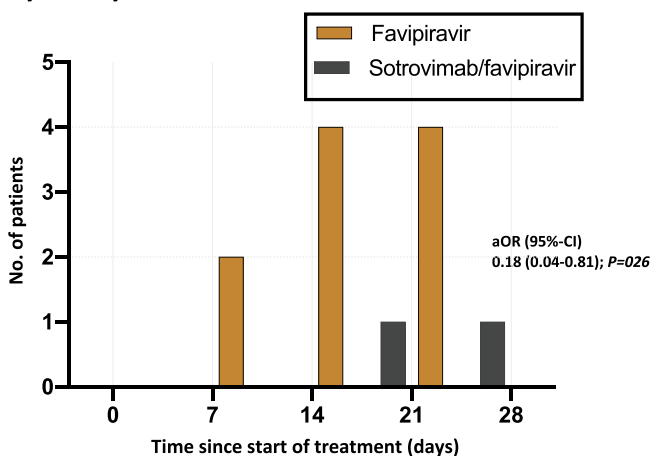
(a) Oxygen requirement at hospital



(b) Length of stay at hospital



(c) All-cause death by 28 days



No. of Death	0	7	14	21	28
Favipiravir (n=10)	0	2	4	4	0
Sotrovimab/favipiravir (n=2)	0	0	0	1	1

Figure 3 The effect of treatment groups on the need of supplementary oxygen and all-cause death within 28 days following treatment initiation. The need of supplementary oxygen during hospital stay (a), length of hospital stay (b), and all-cause death (c) within 28 days following treatment initiation. CI, confidence interval.

or other residual confounding. However, the adequate number of events in the study allowed us to adjust for many potential confounders in the Cox model. Second, we might have missed the COVID-19 related hospitalizations of those patients admitted to hospitals outside the coverage of Government of Dubai and the SALAMA system, although the chances are low as these hospitals are the only places providing free COVID-19 related treatment to these patients in the city of Dubai. Third, baseline levels of neutralizing antibody against the receptor binding domain of the SARS-CoV-2 spike and nucleocapsid proteins were not measured in our study population. However, we have adjusted for the status of COVID-19 vaccine in our analysis.

In conclusion, early addition of sotrovimab to COVID-19 therapy is safe and reduced the risk of hospitalization and death due to COVID-19 when compared with alternative antivirals, such as favipiravir, especially for high-risk patients.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

F.S.S.A., H.A.H.A., I.T., R.H., N.S.S.A., and B.S. wrote the manuscript. F.S.S.A., H.A.H.A., I.T., N.S.S.A., and R.H. designed the research. F.S.S.A., H.A.H.A., A.A.S.H., and N.S.S.A. performed the research. F.S.S.A. analyzed the data. Q.H. contributed new reagents/analytical tools.

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