Reduced Mortality with Ondansetron Use in SARS-CoV-2 Infected Inpatients

Vafa Bayat, MD, PhD¹, Russell Ryono, PharmD¹, Steven Phelps, PhD¹, Eugene Geis, PhD¹,
Farshid Sedghi, MS¹, Payam Etminani¹, Mark Holodniy, MD²,³

¹Bitscopic Inc., Palo Alto, California

²Public Health Surveillance and Research, Department of Veterans Affairs, Washington, DC

³Division of Infectious Disease & Geographic Medicine, Stanford University School of Medicine, Stanford, California

Corresponding author:
Vafa Bayat, MD, PhD (vafa@bitscopic.com, (650) 946-7272)
Program Head, Research and Development
Bitscopic, Inc, 715 Colorado Avenue, Suite B, Palo Alto, CA 94303, United States

Alternate corresponding author:
Russell Ryono, PharmD (russell@bitscopic.com, (408) 636-6674)
Director of Clinical Applications
Bitscopic, Inc, 715 Colorado Avenue, Suite B, Palo Alto, CA 94303, United States
Abstract

Background

The COVID-19 pandemic has led to a surge in clinical trials evaluating investigational and approved drugs. Retrospective analysis of drugs taken by COVID-19 inpatients provides key information on drugs associated with better or worse outcomes.

Methods

We conducted a retrospective cohort study of 10,741 patients testing positive for SARS-CoV-2 infection within three days of admission to compare risk of 30-day all-cause mortality in patients receiving ondansetron using multivariate Cox proportional-hazard models. All-cause mortality, length of hospital stay, adverse events such as ischemic cerebral infarction, and subsequent positive COVID-19 tests were measured.

Results

Administration of ≥8 mg ondansetron within 48 hours of admission was correlated with an adjusted hazard ratio for 30-day all-cause mortality of 0.55 (95% CI 0.42–0.70, p<0.001) and 0.52 (95% CI 0.31–0.87, p=0.012) for all and ICU-admitted patients, respectively. Decreased lengths of stay (9.2 vs. 11.6, p<0.001), frequencies of subsequent positive SARS-CoV-2 tests (53.6% vs. 75.0%, p=0.01), and long-term risks of ischemic cerebral ischemia (3.2% vs. 6.1%, p<0.001) were also noted.
Conclusions

If confirmed by prospective clinical trials, our results suggest ondansetron, a safe, widely available drug, could be used to decrease morbidity and mortality in at-risk populations.

Keywords: Coronavirus; Pneumonia, viral; Nausea; Vomiting
Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has produced significant morbidity and mortality worldwide [1]. Potential therapies are limited in number or are currently under investigation in clinical trials. This has motivated efforts by the biomedical community to perform in vitro and in silico testing of repurposed drugs with potential [2]. These methods are limited by their requirement of either supportive in vitro data from which a hypothesis can be developed and tested in a retrospective population or the need for extensive literature analysis.

Recently, an association between metformin and improved outcomes such as decreased mortality in COVID-19 patients has been recognized and is currently being investigated in multiple prospective trials listed in clinicaltrials.gov [3-6]. Nicotine is also being studied by several groups who have found counterintuitively that smokers and nicotine-product users have generally less severe COVID19 symptoms, with one of the principal hypotheses being that nicotine inhibits cytokine storm development [7-9]. Clinical trials utilizing nicotine patches for prevention and treatment of COVID-19 infection in hospitalized patients are currently ongoing [10, 11].

Ondansetron is a commonly used serotonin 5-HT3 receptor antagonist given to patients experiencing nausea and/or vomiting—experienced in 8–9% of SARS-CoV-2 infected patients, due mostly to the virus’s propensity to infect ACE2 Receptor-expressing cells of the gut [12]. Previous studies using ondansetron have shown that 5-HT3 receptor antagonism is associated with antiviral, anti-inflammatory and anticoagulant effects [13-15]. In a retrospective cohort study, ondansetron was found to be associated with reduced rates of venous thromboembolisms in hospitalized patients, almost to the same extent as aspirin [16].
Additionally, ondansetron is postulated to have a neuroprotective effect in relation to cerebral ischemic infarctions (strokes) [17, 18].

After ondansetron administration, viral shedding was decreased in rotavirus-infected patients and in mice, although the underlying mechanism remains unknown [19, 20]. Potential antiviral effects of ondansetron against SARS-CoV-2 have recently been described. Ondansetron was found to significantly inhibit the cytopathic effects of SARS-CoV-2 infection *in vitro* [21]. An *in silico* study predicted ondansetron could inhibit the SARS-CoV-2 E protein’s calcium ion trafficking [22]. The importance of calcium signaling in the viral life cycle has been well documented [23], and it has been proposed that decreasing intracellular calcium accumulation could play an important role in reducing COVID-19 severity [24].

The objective of this study was to examine the impact of ondansetron on COVID-19 infection 30-day all-cause mortality and other clinical outcomes.

**Methods**

**Sources of Data**

The U.S. Department of Veterans Affairs (VA) healthcare system serves over 9 million veterans at over 1,200 Veterans Health Administration sites of care throughout the United States and U.S. territories [25]. All VA facilities were included in this analysis. We collected data from 10,741 U.S. veteran inpatients who were admitted from March 1st through December 3rd, 2020 and had a positive SARS-CoV-2 qualitative polymerase chain-reaction (PCR) or antigen assay result within three days of their admission. Inpatient barcode medication administration (BCMA) records and SARS-CoV-2 test sample times permitted us to calculate the time interval between the first positive SARS-CoV-2 test and the
administration of specific drug doses. Only admitted patients who survived at least 2 days after their first positive SARS-CoV-2 test were included in this analysis, as they were deemed to have had the opportunity to have had at least 2 days of therapeutic interventions. SARS-CoV-2 test data, BCMA, inpatient and outpatient medication, laboratory data for the hospital stay of interest, intensive care unit (ICU) admission status, as well as comorbidity, demographic, and self-reported ethnicity data for the prior three years of outpatient and inpatient visits were included in our analysis. Relevant data sources from VA sites were maintained, integrated, and normalized using the Bitscopic Praedico® platform [26].

**Statistical analysis**

To test for correlations between patient outcomes and each of over 200 medications, we focused on the 84 medications given to at least 400 patients. Outcomes were assessed with adjusted and multivariate models. Factors associated with 30-day and 90-day mortality were investigated using Cox proportional-hazards models. The Charlson Comorbidity Index (CCI) score was determined using comorbidity-associated International Classification of Diseases, Tenth Revision (ICD-10) codes from the prior three years of health visits. No imputation was performed. For subsequent analysis, patients were divided into three ondansetron groups: patients receiving no ondansetron post-SARS-CoV-2 test (group 0), those receiving up to 8 mg in the first 48 hours post-SARS-CoV-2 test (group 1), and those receiving 8 mg or more in the same time period (group 2). The proportional-hazards assumption for the Cox models was investigated and confirmed graphically through Kaplan-Meier survival analysis. No censoring was required due to the broad availability of patient follow-up data post-admission. All results are presented with 95% confidence intervals. Statistical tests were 2-tailed, with p<0.05 considered significant.

For the analysis of subsequent development of venous thromboembolism, pulmonary thromboembolism, ischemic cerebral infarction and myocardial infarction, presented as 100-
day incidence, we included patients who survived at least 2 weeks post-admission and whose admission date was at least 60 days prior to the date of the analysis (24 January 2021). For this student T-test analysis we combined ondansetron groups 1 and 2. All analyses were conducted with R [27] and Excel (Microsoft) [28].

Results

Characteristics of SARS-CoV-2-Positive inpatients

A total of 10,741 hospitalized inpatients testing positive for SARS-CoV-2 and surviving for at least 48 hours in hospital were included. The median age was 71 years and 94.9% were male. Demographic and clinical characteristics are summarized in Table 1.

Medications and outcomes of hospitalized patients

We first examined the associated 30-day all-cause mortalities for the 84 drugs or drug classes for which at least 400 patients received them. The three drugs associated with the lowest 30-day all-cause mortalities were metformin, nicotine, and ondansetron (Supplementary Table 1). Given that ondansetron has not been studied in hospitalized COVID-19 patients and there are no clinical trials underway in COVID-19 patients, and unlike metformin and nicotine, that are both essentially continuation of care for comorbidities of diabetes and nicotine addiction, respectively, and thus may have known and unknown confounders, we decided to focus on ondansetron for the remainder of this study.

The median ondansetron dose in the first 48 hours of admission of patients in group 1 and group 2 was 4 mg (n=750) and 8 mg (n=451), respectively. Patients generally received the majority of the total doses they would receive during their hospitalization in the first 48 hours after admission (Supplementary Figure 1), with 75% of doses given intravenously and 25% as oral tablets.
Thirty-day all-cause mortality estimates are listed in Table 2 and shown in Figure 1. These measurements showed significant mortality reduction in ondansetron groups 1 and 2 versus no ondansetron (13.5% and 10.6% versus 17.5%; p-values 0.005 and <0.001, respectively). Mortality reduction was significant for both ICU and non-ICU patients (15.0% vs. 26.8% for ICU patients in ondansetron group 2 vs. group 0, p=0.026, and 9.7% vs. 14.9%, for non-ICU patients in ondansetron group 2 vs. group 0, p=0.008), as well as for those with hypertension (in ondansetron group 2 vs. group 0, 12.3% vs. 18.5%, p=0.007). The following cohorts also suggested improved survival with ondansetron, but the cohort sizes were insufficient to achieve statistical significance: females (4.8% vs. 10.1%, p=0.176), diabetes (15.2% vs. 18.2%, p=0.298), COPD/emphysema (13.3% vs. 19.8%, p=0.128), moderate to severe kidney disease (16.7% vs. 24.1%, p=0.213), and cancer history (13.8% vs. 20.3%, p=0.101).

Cox proportional hazard analysis was used to test for potential confounding variables such as other demographic and clinical variables like age group, gender, cancer history, diabetes, and CCI as well as treatment with remdesivir or dexamethasone (Table 3). We noted that Groups 1 and 2 had fewer comorbidities and were on average younger (Table 1). After controlling for CCI, the 30-day mortality hazard ratio for Group 2 was 0.65 (95% CI 0.49–0.87, p=0.003) and Group 1 was 0.79 (95% CI 0.65–0.97, p=0.023). After controlling for age group, the 30-day mortality hazard ratio for Group 2 was 0.84 (95% CI 0.63–1.12, p=0.23) and Group 1 was 0.95 (95% CI 0.77–1.16, p=0.59). In summary, co-morbidities as determined by the Charlson Comorbidity Index score are not a confounder but age is a likely confounder for 30-day mortality. We also examined 90-day all-cause mortality for age as a confounder and presented it in Supplementary Table 2 with results for all of the same variables reported in Table 2. Controlling for age group, the 90-day mortality hazard ratios for Group 2 was 0.78 (95% CI 0.61–1.01, p=0.06) and for Group 1 was 0.89 (95% CI 0.74–
1.06, p=0.20). None of the other variables were found to have a significant interaction term in the Cox analysis for 30- and 90-day mortality, and so we focused on results for the univariate models. We found that a total dose of ≥8 mg ondansetron given in the first 48 hours of hospital admission (Group 2) was associated with a decrease in all-cause 30-day mortality of 45% for all patients and 48% for ICU patients (Table 3) versus those given no ondansetron. Group 1 (>0 and <8 mg) was also associated with better outcomes, but to a lesser degree, indicating that the improved survival associated with ondansetron is likely dose-sensitive.

**Medical chart review of high ondansetron-administered patients**

To investigate whether nausea/vomiting was associated with reduced disease severity, which would introduce a possible confounding variable in our analysis, we examined mortality associated with the anti-emetic drug metoclopramide, a dopamine D2 and 5-HT-3 receptor antagonist used for the same indication. Cox analysis found that COVID-19 patients receiving metoclopramide had an elevated 30-day mortality hazard ratio of 1.74 (95% CI 1.45–2.08, p<0.001). The inclusion of ICU status and a CCI score greater than 7 as possible confounding variables in the analysis resulted in no evidence of interaction effects.

We further reviewed records of 100 random patients in ondansetron group 2 to determine indication for ondansetron use. We found 94% exhibiting nausea, 63% vomiting, 44% diarrhea, 25% mild respiratory symptoms (not requiring supplemental oxygen), and 56% moderate to severe respiratory symptoms (Supplementary Figure 2). In this random sample of patients, ondansetron was therefore taken by patients for its labeled use (nausea/vomiting).
Duration of hospitalization, subsequent PCR positivity, and venous thromboembolism risk

Excluding patients who died or the small number not yet discharged (n=33), patients in ondansetron groups 1 and 2 had shorter hospital stays compared to group 0 (means: group 0: 11.60 days, group 1: 10.01 days (p=0.0034), group 2: 9.22 days (p<0.001)) (Table 1).

Patients in ondansetron Group 2 were also less likely to have a subsequent positive SARS-CoV-2 test over the subsequent four weeks after their initial positive test (group 2: 15/28; 53.6% vs. group 0: 393/524; 75.0%) (p=0.012) (Table 4).

Rates of ischemic cerebral ischemia and myocardial infarction events for groups 1 and 2 combined were significantly decreased among those who received ondansetron (3.2% vs. 6.1%, p<0.001 and 0.0% vs. 0.3%, p=0.045, respectively) while venous thromboembolism and pulmonary embolism for groups 1 and 2 combined did not differ significantly from group 0 (3.5% vs. 3.7%, p=0.79; and 4.9% vs. 5.0%, p=0.84, respectively) (Supplementary Table 3).

Remdesivir and dexamethasone analysis

We next determined whether improved survival with ondansetron use was related to remdesivir and dexamethasone usage in our Cox proportional hazards model. Remdesivir and dexamethasone did not significantly affect survival in the presence of ondansetron (Table 3). Regardless of whether patients received either of these two medications for COVID-19 treatment, administration of ondansetron resulted in higher survival.
Discussion

In this large retrospective study of patients hospitalized for SARS-CoV-2 infection, we found that a total dose of ≥8 mg ondansetron given in the first 48 hours of hospital admission (Group 2) was associated with decreases in all-cause 30-day mortality of 39% for all patients and 46% for ICU patients (Table 3). Group 1 (>0 and <8 mg) was also associated with better outcomes, but to a lesser degree, indicating that the improved survival associated with ondansetron was likely dose-sensitive. Next we tested the hypothesis that these patients were somehow different, perhaps in respect to nausea and vomiting. In a meta-study of 55 studies comprising 10,014 COVID-19 patients, 8.3% of patients exhibited nausea and 6.5% vomiting. Neither were found to be statistically significantly associated with more severe illness [29]. These numbers are compatible with our study where 1,435/13,612 (10.5%) were given ondansetron in the first 48 hours of hospital admission. Patients who took ondansetron in the first 48 hours were more likely to be admitted to the ICU than those who were not (26.0% vs. 20.9%), another indication that they are not patients with milder illness.

Consistent with this, another meta-analysis of COVID-19 patients revealed that symptoms such as nausea and vomiting, associated with gastrointestinal tract infection, were more likely to be associated with multiorgan involvement, develop acute respiratory distress syndrome, and be admitted to the ICU [30]. This discounts the hypothesis that nausea or vomiting are symptoms associated with milder disease.

Limitations

A limitation of our analysis was this was not a randomized clinical trial in which patients receiving these drugs were carefully matched for COVID-19 disease severity, age, and comorbidities. We noted the ondansetron groups were younger and had fewer comorbidities for unknown reasons, and there was an interaction with age but not...
comorbidities. The retrospective design of this study also limited our ability to fully address variability in ondansetron dosing regimens. Although we observed that ≥ 8 mg administered within the first 48 hours of hospitalization was associated with improved survival, the exact optimal dosing regimen and duration remain unestablished. In contrast with other existing intravenously administered treatment options, however, the availability of ondansetron as an oral dosage form offers significant advantages in being more readily accessible to patients with milder disease making it a potential candidate for adjunctive use in SARS-CoV-2 infections upon (or prior to) hospitalization. Lastly, although the numbers in this study were large, the identification of a significant impact of ondansetron use in subgroups such as those patients with a diabetes diagnosis was limited by subgroup size.

Conclusions

In one of the largest cohorts of hospitalized COVID-19 patients to date, we retrospectively identified that administration of the anti-emetic drug ondansetron was associated with an adjusted 45% reduction in 30-day all-cause mortality in hospitalized patients and a 48% reduction in ICU patients. Our data also suggests that a reduction in ischemic cerebral infarctions and myocardial infarctions may play a significant role in this, through possible anti-inflammatory or antiviral effects of ondansetron [21, 22]. Ondansetron’s widespread availability, affordability, and limited side effect profile make it an excellent candidate for future prospective clinical trials. Further analysis of the other drugs that we identified preliminarily as being associated with positive outcomes may also be warranted.
Author contributions

VB, RR, SP, EG, FS, PE and MH contributed to study conception, design, data analysis, and the writing of the manuscript. All authors have read, edited, and approved the final manuscript.
Funding

This work was supported by Bitscopic’s R&D budget and intramural funding from the Department of Veterans Affairs.

Patient Consent Statement

This project was approved by the Stanford University Institutional Review Board under the protocol entitled “Public Health Surveillance in the Department of Veterans Affairs”. As the project was considered minimal risk, consent to participate was not required. Bitscopic is operating under a 10-year Research and Development agreement with the VA signed in 2019.

Potential Conflicts of interests

All of the authors, with the exception of Dr. Mark Holodniy, are all employees of Bitscopic, Inc. Otherwise they declare no competing interests.

Acknowledgements

We thank Renle Chu and Michael Luo, who assisted with literature review, and Chong Lee, Hemal Parekh, and Joel Mewton for assistance with data extraction and troubleshooting. We thank Drs. Prashant Loyalka and Paul Khavari for critical reading of the manuscript. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.
References

1.Organization WH. COVID-19 weekly epidemiological update. 19 January 2021 ed, 2021.
2.Vijayvargiya P, Esquer Garrigos Z, Castillo Almeida NE, Gurram PR, Stevens RW, Razonable RR. Treatment Considerations for COVID-19: A Critical Review of the Evidence (or Lack Thereof). Mayo Clin Proc 2020; 95(7): 1454-66.
3.Scheen AJ. Metformin and COVID-19: From cellular mechanisms to reduced mortality. Diabetes Metab 2020; 46(6): 423-6.
4.Malhotra A, Hepokoski M, McCowen KC, J YJS. ACE2, Metformin, and COVID-19. iScience 2020; 23(9): 101425.
5.Luo P, Qiu L, Liu Y, et al. Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. Am J Trop Med Hyg 2020; 103(1): 69-72.
6.ClinicalTrials.gov. Metformin Glycinate, Treatment of Patients With COVID-19 and Severe Acute Respiratory Syndrome Secondary to SARS-CoV-2 (DMMETCOV19-2). 12 November 2020 ed. Bethesda (MD): National Library of Medicine (US), 2021.
7.Kloc M, Ghobrial RM, Kubiak JZ. How nicotine can inhibit cytokine storm in the lungs and prevent or lessen the severity of COVID-19 infection? Immunol Lett 2020; 224: 28-9.
8.Polosa R, Caci G. COVID-19: counter-intuitive data on smoking prevalence and therapeutic implications for nicotine. Intern Emerg Med 2020; 15(5): 853-6.
9.Farsalinos K, Barbouni A, Niaura R. Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? Intern Emerg Med 2020; 15(5): 845-52.
10.ClinicalTrials.gov. Efficacy of Nicotine in Preventing COVID-19 Infection (NICOID-PREV). 12 October 2020 ed. Bethesda (MD): National Library of Medicine (US), 2021.
11.ClinicalTrials.gov. Evaluation of the Efficacy of Nicotine Patches in SARS-CoV2 (COVID-19) Infection in Hospitalized Patients (NICOID). 29 October 2020 ed. Bethesda (MD): National Library of Medicine (US), 2021.
12.Andrews PLR, Cai W, Rudd JA, Sanger GJ. COVID-19, nausea, and vomiting. J Gastroenterol Hepatol 2020.
13.Motavallian A, Minaiyan M, Rabbani M, Mahzouni P, Andalib S. Anti-inflammatory effects of alosetron mediated through 5-HT3 receptors on experimental colitis. Res Pharm Sci 2019; 14(3): 228-36.
14.Mainou BA, Ashbrook AW, Smith EC, Dorset DC, Denison MR, Dermody TS. Serotonin Receptor Agonist 5-Nonyloxytryptamine Alters the Kinetics of Reovirus Cell Entry. J Virol 2015; 89(17): 8701-12.
15.Fakhouri G, Rahimian R, Ghia JE, Khan WI, Dehpour AR. Impact of 5-HT(3) receptor antagonists on peripheral and central diseases. Drug Discov Today 2012; 17(13-14): 741-7.
16.Datta A, Matlock MK, Dang NL, et al. "Black Box" to "Conversational" Machine Learning: Ondansetron Reduces Risk of Hospital-Acquired Venous Thromboembolism. IEEE J Biomed Health Inform 2020; PP.
17.Murozono M, Miyashita R, Takeda A, Ynagita K, Sato E, Ogiiwara Y. Co-administration of Cyclosporin A and Ondansetron decreases transient local cerebral ischemic injury in the mouse. Neuro Endocrinol Lett 2017; 38(3): 163-8.
18.Sharma A, Patnaik R, Sharma HS. Neuroprotective effects of 5-HT3 receptor antagonist ondansetron on morphine withdrawal induced brain edema formation, blood-brain barrier dysfunction, neuronal injuries, glial activation and heat shock protein upregulation in the brain. Int Rev Neurobiol 2019; 146: 209-28.
19.Bialowas S, Hagbom M, Nordgren J, et al. Rotavirus and Serotonin Cross-Talk in Diarrhoea. PLoS One 2016; 11(7): e0159660.
20. Hagbom M, Novak D, Ekstrom M, et al. Ondansetron treatment reduces rotavirus symptoms-A randomized double-blinded placebo-controlled trial. PLoS One 2017; 12(10): e0186824.
21. Touret F, Gilles M, Barral K, et al. In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. Sci Rep 2020; 10(1): 13093.
22. Dey D, Borkotoky S, Banerjee M. In silico identification of Tretinoin as a SARS-CoV-2 envelope (E) protein ion channel inhibitor. Comput Biol Med 2020; 127: 104063.
23. Clark KB, Eisenstein EM. Targeting host store-operated Ca(2+) release to attenuate viral infections. Curr Top Med Chem 2013; 13(16): 1916-32.
24. Jayaseelan VP, Paramasivam A. Repurposing calcium channel blockers as antiviral drugs. J Cell Commun Signal 2020; 14(4): 467-8.
25. Health R. Resources and Capabilities of the Department of Veterans Affairs to Provide Timely and Accessible Care to Veterans. 2015.
26. Holodniy M, Winston C, Lucero-Obusan C, et al. Evaluation of Praedico™, A Next Generation Big Data Biosurveillance Application. Online J Public Health Inform 2015; 7(1): e133.
27. Chambers J. Software for Data Analysis: Programming with R: Springer, 2008.
28. Divisi D, Di Leonardo G, Zaccagna G, Crisci R. Basic statistics with Microsoft Excel: a review. J Thorac Dis 2017; 9(6): 1734-40.
29. Barek MA, Aziz MA, Islam MS. Impact of age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: A meta-analysis with 55 studies and 10014 cases. Heliyon 2020; 6(12): e05684.
30. Gul F, Lo KB, Peterson J, McCullough PA, Goyal A, Rangaswami J. Meta-analysis of outcomes of patients with COVID-19 infection with versus without gastrointestinal symptoms. Proc (Bayl Univ Med Cent) 2020; 33(3): 366-9.
Table 1. Demographic and Clinical Characteristics of 10,741 COVID-19 Positive Inpatients

| Table 1. Demographic and Clinical Characteristics of 10,741 COVID-19 Positive Inpatients |
|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
|                                    | Ondansetron group 0 (no ondansetron) (n=9,540) | Ondansetron group 1 (<8 mg in first 24 hours) (n=750) | Ondansetron group 2 (≥8 mg in first 24 hours) (n=451) | All patients (n=10,741) |
| Male sex – no. (%)                  | 9,125 (95.6)                                  | 675 (90.0)                                      | 388 (86.0)                                      | 10,188 (94.9) |
| Median age (interquartile range) – year | 72 (IQR 63-78)                                | 66 (IQR 55-73)                                 | 63 (IQR 49-72)                                 | 71 (IQR 62-77) |
| Age group 1 (≤49) – no. (%)         | 708 (7.4)                                     | 127 (16.9)                                     | 117 (25.9)                                     | 952 (8.9) |
| Age group 2 (50-59) – no. (%)       | 963 (10.1)                                    | 121 (16.1)                                     | 78 (17.3)                                      | 1,162 (10.8) |
| Age group 3 (60-69) – no. (%)       | 2,193 (23.0)                                  | 204 (27.2)                                     | 102 (22.6)                                     | 2,499 (23.3) |
| Age group 4 (≥70) – no. (%)         | 5,676 (59.5)                                  | 298 (39.7)                                     | 154 (34.1)                                     | 6,128 (57.1) |
| White, non-Hispanic (%)             | 4,694 (49.2)                                  | 385 (51.3)                                     | 231 (51.2)                                     | 5,310 (49.4) |
| Black or African-American (%)       | 3,179 (33.3)                                  | 222 (29.6)                                     | 132 (29.3)                                     | 3,533 (32.9) |
| Hispanic or Latino (%)              | 773 (8.1)                                    | 71 (9.5)                                       | 40 (8.9)                                       | 884 (8.2) |
| Other race (%)                      | 167 (1.6)                                    | 21 (2.8)                                       | 15 (2.7)                                       | 203 (1.8) |
| Unknown race (%)                    | 664 (7.0)                                    | 41 (5.5)                                       | 30 (6.7)                                       | 735 (6.8) |
| Previously healthy – no. (%)        | 1,223 (12.8)                                  | 126 (16.8)                                     | 94 (20.8)                                      | 1,443 (13.4) |
| At least one underlying condition, including obesity – no. (%) | 8,317 (87.2)                                  | 624 (83.2)                                     | 357 (78.8)                                     | 9,298 (86.6) |
| Respiratory – no. (%)               | 3,325 (34.9)                                  | 237 (31.6)                                     | 105 (23.2)                                     | 3,667 (34.1) |
| Hypertension – no. (%)              | 7,476 (78.4)                                  | 557 (74.3)                                     | 308 (68.0)                                     | 8,341 (77.7) |
| Diabetes – no. (%)                  | 4,882 (48.8)                                  | 341 (45.5)                                     | 211 (43.0)                                     | 5,210 (48.5) |
| Obesity – no. (%)                   | 3,300 (34.6)                                  | 304 (40.5)                                     | 163 (36.1)                                     | 3,167 (29.5) |
| Average length of stay excluding patients who died at discharge (days ± SD) | 11.60 ± 12.90                                | 10.01 ± 11.10                                 | 9.22 ± 9.28                                    | 11.38 ± 12.65 |
| Median length of stay excluding patients who died at discharge (days ± SD) (p-value relative to group 0) | 6.86 ± 13.66 | 6.01 ± 11.76 (p = 0.0034**) | 6.50 ± 9.55 (p < 0.001)** | 6.81 ± 13.39 |

Numbers of patients and percentages from each of the above demographics and clinical comorbidities for each of the ondansetron groups are shown. In addition, the average and median lengths of stay are shown. P-values are given asterisks (*) as follows. * represents <0.05. ** represents <0.01. *** represents <0.001.
Table 2. 30-Day All-Cause Mortality for Ondansetron Groups for Specific Subgroups

| Group | Group 0 (n=9,540) | Group 1 (n=750) | Group 2 (n=451) | P-value comparing groups 0 and 1 | P-value comparing groups 0 and 2 | P-value comparing groups 0 and 1/2 |
|-------|-------------------|----------------|----------------|-------------------------------|-------------------------------|---------------------------------|
| Overall (%) | 17.5 | 13.5 | 10.6 | 0.005** | <0.001*** | <0.001*** |
| Non-ICU (%) | 14.9 | 10.7 | 9.7 | 0.006** | 0.008** | <0.001** |
| ICU (%) | 26.8 | 24.7 | 15.0 | 0.628 | 0.026* | 0.070 |
| Obesity (%) | 12.3 | 13.3 | 8.6 | 0.863 | 0.524 | 0.232 |
| Ventilation (%) | 39.4 | 26.2 | 20.8 | 0.126 | 0.107 | <0.001*** |
| Intubation (%) | 58.8 | 62.0 | 52.2 | 0.765 | 0.676 | 0.984 |
| Hypertension (%) | 18.5 | 14.9 | 12.3 | 0.038* | 0.007** | <0.001*** |
| Diabetes (%) | 18.2 | 16.7 | 15.2 | 0.529 | 0.298 | 0.222 |
| Moderate or severe kidney disease (%) | 24.1 | 20.4 | 16.7 | 0.362 | 0.213 | 0.114 |
| COPD/emphysema (%) | 19.8 | 18.1 | 13.3 | 0.588 | 0.128 | 0.161 |
| Cancer history (%) | 20.3 | 18.3 | 13.8 | 0.500 | 0.101 | 0.117 |
| Female (%) | 10.1 | 6.7 | 4.8 | 0.47 | 0.260 | 0.124 |
| African-American or Black (%) | 15.1 | 10.8 | 11.4 | 0.103 | 0.296 | 0.041* |
| Hispanic or Latino (%) | 15.9 | 16.9 | 10.0 | 0.961 | 0.435 | 0.686 |
| Age group 1: <=49 (%) | 2.4 | 3.1 | 1.7 | 0.851 | 0.897 | 0.960 |
| Age group 2: 50-59 (%) | 5.0 | 5.8 | 6.4 | 0.874 | 0.777 | 0.544 |
| Age group 3: 60-69 (%) | 12.4 | 13.2 | 9.8 | 0.816 | 0.530 | 0.877 |
| Age group 4: >=70 (%) | 23.6 | 21.1 | 20.1 | 0.374 | 0.372 | 0.182 |

Groups were defined as follows: ICU=patients who were in the ICU at any time during their COVID-19 admission; Non-ICU=patients who were never in ICU during their COVID-19 admission; Hypertension=patients with an ICD10 code of hypertension in the prior 3 years; Obesity=patients with either a BMI ≥ 30 in the past year or an ICD10 code of obesity in the prior 3 years; Diabetes=patients with an ICD10 code of Diabetes in the prior 3 years; Hispanic=patients who self-identified in 2019-2020 as Hispanic or Latino; African-American=patients who self-identified in 2020 as Black or African-American. P-values are given asterisks (*) as follows. * represents <0.05. ** represents <0.01. *** represents <0.001.
Table 3. Results of COX Proportional-Hazards Models Examining the Relation of Ondansetron-Taking in the First 48 Hours of Hospital Admission to 30-Day Mortality in Hospitalized Patients.

| Characteristic                                      | Total Population (n=10,741) | ICU (n=2,369) | Non-ICU (n=8,372) |
|-----------------------------------------------------|-----------------------------|---------------|-------------------|
|                                                     | Hazard Ratio (95% CI)       | p-value       | Hazard Ratio (95% CI) | p-value       | Hazard Ratio (95% CI) | p-value |
| All COVID-19 inpatients                            | 1.83 (1.68-2.00)            | <0.001***     | 1.83 (1.68-2.00)    | <0.001***     | 1.83 (1.68-2.00)    | <0.001*** |
| Ondansetron therapy:                               |                             |               |                   |               |                   |         |
| <8 mg within 48 hours (group 1)                    | 0.75 (0.61-0.91)            | 0.004**       | 0.9 (0.64-1.25)    | 0.527         | 0.7 (0.54-0.9)     | 0.005**  |
| >=8 mg within 48 hours (group 2)                   | 0.58 (0.44-0.77)            | <0.001***     | 0.53 (0.3-0.94)    | 0.029*        | 0.63 (0.45-0.88)   | 0.006**  |
| Remdesivir therapy                                 | 1.12 (1.02-1.23)            | 0.015*        | 1.06 (0.91-1.25)   | 0.441         | 1.08 (0.96-1.22)   | 0.18     |
| Dexamethasone therapy                              | 1.45 (1.33-1.59)            | <0.001***     | 1.28 (1.1-1.5)     | 0.002**       | 1.47 (1.31-1.65)   | <0.001*** |
| Risk factors:                                       |                             |               |                   |               |                   |         |
| Charlson Comorbidity Index >=7                     | 1.88 (1.72-2.07)            | <0.001***     | 1.74 (1.49-2.04)   | <0.001***     | 1.96 (1.74-2.19)   | <0.001*** |
| Obesity                                             | 0.72 (0.65-0.79)            | <0.001***     | 0.8 (0.68-0.95)    | 0.01*         | 0.65 (0.57-0.74)   | <0.001*** |
| Hypertension                                        | 1.4 (1.24-1.58)             | <0.001***     | 1.13 (0.92-1.38)   | 0.236         | 1.52 (1.31-1.77)   | <0.001*** |
| Diabetes                                            | 1.14 (1.04-1.25)            | 0.004**       | 1.16 (0.99-1.36)   | 0.058         | 1.11 (0.99-1.25)   | 0.062    |
| Cancer                                              | 1.4 (1.24-1.57)             | <0.001***     | 1.28 (1.05-1.57)   | 0.016*        | 1.45 (1.25-1.67)   | <0.001*** |
| Age:                                                |                             |               |                   |               |                   |         |
| 50-59 yr                                            | 2.16 (1.34-3.49)            | 0.002**       | 2.3 (1.04-5.09)    | 0.041*        | 1.99 (1.09-3.64)   | 0.026*   |
| 60-69 yr                                            | 5.37 (3.52-8.21)            | <0.001***     | 5.67 (2.78-11.59)  | <0.001***     | 4.94 (2.92-8.37)   | <0.001*** |
| 70+ yr                                              | 10.85 (7.19-16.38)          | <0.001***     | 9.06 (4.5-18.23)   | <0.001***     | 11.58 (6.95-19.29) | <0.001*** |
| Female                                              | 0.49 (0.37-0.65)            | <0.001***     | 0.72 (0.48-1.09)   | 0.125         | 0.4 (0.27-0.58)    | <0.001*** |
| Race:                                               |                             |               |                   |               |                   |         |
| African-American or Black                           | 0.79 (0.71-0.88)            | <0.001***     | 0.89 (0.75-1.07)   | 0.225         | 0.73 (0.64-0.84)   | <0.001*** |
| American Indian or Alaska Native                    | 1.46 (0.96-2.2)             | 0.075         | 2.03 (1.04-3.93)   | 0.037*        | 1.26 (0.74-2.14)   | 0.393    |
| Asian                                               | 1.09 (0.66-1.82)            | 0.728         | 0.75 (0.24-2.34)   | 0.619         | 1.26 (0.71-2.22)   | 0.435    |
| Hispanic or Latino                                  | 0.85 (0.71-1.02)            | 0.081         | 1.39 (1.06-1.83)   | 0.018*        | 0.67 (0.53-0.85)   | <0.001*** |
| Native Hawaiian or Pacific Islander                 | 1.05 (0.68-1.61)            | 0.838         | 0.83 (0.31-2.23)   | 0.715         | 1.16 (0.72-1.88)   | 0.536    |
| Unknown                                             | 1.11 (0.93-1.32)            | 0.259         | 1.23 (0.9-1.68)    | 0.201         | 1.08 (0.88-1.34)   | 0.453    |
| Ondansetron controlling for Age:                   |                             |               |                   |               |                   |         |
| Ondansetron group 1                                 | 0.95 (0.77-1.16)            | 0.595         | 1.11 (0.8-1.56)    | 0.523         | 0.9 (0.7-1.16)     | 0.413    |
| Ondansetron group 2                                 | 0.84 (0.63-1.12)            | 0.228         | 0.69 (0.39-1.23)   | 0.206         | 0.94 (0.67-1.31)   | 0.698    |
| Age 50-59 yr                                        | 2.14 (1.32-3.46)            | 0.002**       | 2.29 (1.03-5.08)   | 0.041*        | 1.98 (1.08-3.62)   | 0.027*   |
| Age 60-69 yr                                        | 5.29 (3.46-8.08)            | <0.001***     | 5.64 (2.76-11.53)  | <0.001***     | 4.89 (2.88-8.29)   | <0.001*** |
| Age 70+ yr                                          | 10.63 (7.03-16.07)          | <0.001***     | 8.99 (4.46-18.11)  | <0.001***     | 11.41 (6.84-19.03) | <0.001*** |
| Ondansetron controlling for CCI:                    |                             |               |                   |               |                   |         |
| Ondansetron group 1                                 | 0.79 (0.65-0.97)            | 0.023*        | 0.91 (0.65-1.27)   | 0.592         | 0.75 (0.58-0.97)   | 0.026*   |
Patients receiving ≥8 mg ondansetron in the first 48 hours (group 2) had better mortality outcomes than those receiving none across all patients, whether ICU or non-ICU. Patients receiving 0–8 mg ondansetron (group 1) also had better outcomes, although the small sample size (n=150) prevented statistical significance from being attained for ICU patients. The reference group for the hazard ratio for each risk factor is the group of all patients in the study without that risk factor. Results for ondansetron, remdesivir and dexamethasone therapies are from univariate analysis; adding the Charlson Comorbidity Index or other therapies as covariates does not significantly alter the results. P-values are given asterisks (*) as follows. * represents <0.05. ** represents <0.01. *** represents <0.001.
Table 4. Results of Subsequent SARS-CoV-2 PCR or Antigen Tests Within 28 Days After Admission Date

|                      | 7–14 day SARS-CoV-2 positive test patients (%) | 14–21 day SARS-CoV-2 positive test patients (%) | 21–28 day SARS-CoV-2 positive test patients (%) | 7–28 day SARS-CoV-2 positive test patients (%) |
|----------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Group 0 (no ondansetron) | 250/307 (81.4)                                  | 123/167 (73.7)                                  | 54/92 (58.8)                                     | 427/566 (75.4)                                   |
| Group 1 (0–8 mg ondansetron/first 48 hours) | 18/21 (86)                                      | 9/14 (64)                                       | 3/4 (75)                                         | 30/39 (76)                                       |
| Group 2 (≥8 mg ondansetron/first 48 hours)   | 11/15 (73)                                      | 4/8 (50)                                        | 0/5 (0)                                          | 15/28 (54)                                       |

Patients who received ondansetron in the first 48 hours post-admission were less likely to have positive SARS-CoV-2 test results in the subsequent four weeks.
Figure 1. Kaplan-Meier curve showing survival rates of hospitalized patients who received or didn’t receive ondansetron in the 30 days post-admission for their first positive COVID-19 admission.

Patients in groups 1 and 2 ondansetron (0–8 mg/first 48 hours admission (green) and ≥8 mg/first 48 hours admission (blue), respectively) had improved survival compared to group 0 (no ondansetron (red)) on Kaplan-Meier analysis at 30 days.
Group 2 Ondansetron, 89.4 ± 2.9% (N = 451, 48 deaths)
Group 1 Ondansetron, 86.5 ± 2.5% (N = 750, 101 deaths)
Group 0 Ondansetron, 82.5 ± 0.8% (N = 9,540, 1,673 deaths)

Group 0 Ondansetron: 0 mg/first 48h
Group 1 Ondansetron: 0-8 mg/first 48h
Group 2 Ondansetron: ≥8 mg/first 48h

Group 2 Ondansetron, 85.0 ± 8.2% (N = 80, 12 deaths)
Group 1 Ondansetron, 75.3 ± 7.2% (N = 150, 37 deaths)
Group 0 Ondansetron, 73.2 ± 1.9% (N = 2,139, 574 deaths)

Group 2 Ondansetron, 90.3 ± 3.1% (N = 371, 36 deaths)
Group 1 Ondansetron, 89.3 ± 2.5% (N = 600, 64 deaths)
Group 0 Ondansetron, 85.2 ± 3.1% (N = 7,401, 1,099 deaths)