Impact of SARS-CoV-2 Viral Load on Risk of Intubation and Mortality Among Hospitalized Patients with Coronavirus Disease 2019

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Summary: We evaluated 678 hospitalized patients with coronavirus disease 2019 and found that 35.0% of patients with a high SARS-CoV-2 viral load on admission died, compared to 17.6% and 6.2% of patients with medium and low viral loads, respectively.

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ABSTRACT

Background: Patients hospitalized with coronavirus disease 2019 (COVID-19) frequently require mechanical ventilation and have high mortality rates, but the impact of viral burden on these outcomes is unknown.

Methods: We conducted a retrospective cohort study of patients hospitalized with COVID-19 from March 30 to April 30, 2020 at two hospitals in New York City. SARS-CoV-2 viral load was assessed using cycle threshold (Ct) values from a reverse transcription-polymerase chain reaction assay applied to nasopharyngeal swab samples. We compared patient characteristics and outcomes among patients with high, medium, and low admission viral loads and assessed whether viral load was independently associated with risk of intubation and in-hospital mortality.

Results: We evaluated 678 patients with COVID-19. Higher viral load was associated with increased age, comorbidities, smoking status, and recent chemotherapy. In-hospital mortality was 35.0% with a high viral load (Ct<25; n=220), 17.6% with a medium viral load (Ct 25-30; n=216), and 6.2% with a low viral load (Ct>30; n=242; *P*<0.001). The risk of intubation was also higher in patients with a high viral load (29.1%), compared to those with a medium (20.8%) or low viral load (14.9%; *P*<0.001). High viral load was independently associated with mortality

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(adjusted odds ratio [aOR] 6.05; 95% confidence interval [CI]: 2.92-12.52; *P*<0.001) and intubation (aOR 2.73; 95% CI: 1.68-4.44; *P*<0.001) in multivariate models.

Conclusions: Admission SARS-CoV-2 viral load among hospitalized patients with COVID-19 independently correlates with the risk of intubation and in-hospital mortality. Providing this information to clinicians could potentially be used to guide patient care.

Key Words: SARS-CoV-2; Coronavirus Disease 2019; Viral load; Hospitalized Patients; Outcomes

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel pathogen that has rapidly caused a devastating pandemic of coronavirus disease 2019 (COVID-19). As of June 10, 2020, SARS-CoV-2 had infected more than 7 million people and killed more than 400,000 people throughout the world [1]. Although the majority of patients who develop COVID-19 have mild presentations [2], 18-33% of patients who are hospitalized require mechanical ventilation and up to 20% of hospitalized patients die [3-7]. Investigations of risk factors for intubation and mortality with COVID-19 in hospitalized patients have largely focused on patient characteristics, such as older age, obesity, and comorbidities, as well as presenting symptoms and laboratory parameters [5, 7-9]. In contrast, the impact of SARS-CoV-2 viral load on clinical outcomes in hospitalized patients has not been thoroughly investigated. In two studies of hospitalized patients in China, those with severe presentations of COVID-19 had higher viral loads than those with mild presentations, but the impact of SARS-CoV-2 viral load on the risk of intubation or death was not evaluated [10, 11].

The current standard-of-care test to diagnose COVID-19 is to collect a nasopharyngeal (NP) swab and use a reverse transcription-polymerase chain reaction (RT-PCR) assay to detect SARS-CoV-2 RNA [12]. These RT-PCR assays only report to clinicians whether SARS-CoV-2 is detected or not detected. However, these assays also contain quantitative information on cycle threshold (Ct) values that are inversely correlated with viral load and are not reported clinically. We hypothesized that assessing SARS-CoV-2 viral load by analyzing Ct values from an initial NP swab sample could be a clinically valuable tool to identify patients at highest risk of intubation and death and provide insights into the pathogenesis of COVID-19. We therefore conducted this retrospective analysis of SARS-CoV-2 viral loads on admission, clinical presentations, and outcomes at two affiliated New York City hospitals using a high-throughput RT-PCR assay.

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METHODS

Study Population and Setting:

This retrospective observational study consisted of all patients who were hospitalized at NewYork-Presbyterian Hospital/Weill Cornell Medical Center and affiliated Lower Manhattan Hospital and had a NP swab sample collected and analyzed for SARS-CoV-2 by the cobas 6800 RT-PCR system (Roche Molecular Systems, Inc., Branchburg, NJ) between March 30, 2020 and April 30, 2020. The predominant NP swab collection and transport kits used were the BD Universal Viral Transport System (Becton, Dickinson and Company, Franklin Lakes, NJ) and the Universal Transport Medium (Hardy Diagnostics, Santa Maria, CA). Patients who did not have an NP swab sample collected and analyzed within one day of hospital admission or whose sample was analyzed on a different diagnostic platform or at a different institution were excluded. The policy during the study period was to only perform SARS-CoV-2 tests in patients who were thought to require hospital admission; however, some patients who were tested were subsequently discharged from the emergency department (ED) without hospital admission.

Viral Load Assessment:

The cobas SARS-CoV-2 RT-PCR test received Emergency Use Authorization approval by the United States Food and Drug Administration and was performed according to the manufacturer's instructions [13]. This assay amplifies two different targets within the SARS-CoV-2 genome: ORF1ab, a SARS-CoV-2-specific target and the E gene, a pan-Sarbecovirus target that is present in SARS-CoV-2 and SARS-CoV, but not in seasonal coronaviruses or

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Middle East respiratory syndrome-CoV. For routine clinical care, results are classified as detected if either the ORF1ab or E gene is detected, or not detected if neither target is detected. However, the instrument also generates a Ct value for each target that correlates inversely with quantitative viral load and is not released to clinicians. The Ct value represents the number of replication cycles required for sufficient gene amplification to produce a fluorescent signal that crosses a predefined threshold.

For this study, we reviewed Ct values for both gene targets for all initial SARS-CoV-2 tests that were performed on NP swab samples that were collected from study subjects for routine clinical care within one day of hospital admission. We separated the Ct values for the SARS-CoV-2-specific target (ORF1ab) into terciles based upon the quantitative values. We then designated high viral load samples as the lowest Ct tercile, medium viral load samples as the middle tercile, and low viral load samples as the highest tercile. Specimens that were designated positive for SARS-CoV-2, but for which only the E gene was detected, were designated low viral load samples.

Data Collection:

Data were retrospectively abstracted manually from the electronic medical record using a quality-controlled protocol and entered into a REDCap database [14]. All data collectors were trained and a random re-sampling of data previously showed high interrater reliability (mean Cohen's kappa of 0.92) [5]. Data included demographics, comorbidities, social characteristics, selected outpatient medications on admission, presenting symptoms on arrival to the hospital, oxygen supplementation required within three hours of presentation, laboratory parameters, chest radiograph findings, concurrent bloodstream infections, in-hospital complications, and in-hospital mortality. Clinical data after hospital discharge were not consistently available, and thus

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only outcomes that occurred during the hospital admission were analyzed. The study was approved by the Institutional Review Board (#20-03021681) at Weill Cornell Medicine with a waiver of informed consent.

Statistical Analysis:

We compared baseline characteristics and outcomes of hospitalized patients with COVID-19 who had high, medium, and low initial viral loads using the non-parametric nptrend command in STATA (StataCorp, College Station, TX) that tests for trend across ordered groups. Continuous variables were represented with medians and interquartile ranges (IQR) and categorical variables were represented as proportions. A two-sided *P* value of ≤0.05 was used to designate statistical significance. The risk of in-hospital intubation and death was also compared across eight different numerical Ct value ranges. We also constructed Cox proportional hazard models to compare the cumulative risks of intubation and death during the inpatient admission among patients with high, medium, and low viral loads. We then identified baseline factors that were associated with in-hospital mortality and intubation using univariate logistic regression models. All variables that were statistically significantly associated with each outcome were then entered into separate multivariate logistic regression models. Adjusted odds ratios of mortality and intubation were calculated for each of these variables with 95% confidence intervals (CI). Analyses were conducted using STATA, version 15.0.

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RESULTS

Cycle threshold values and establishment of viral load categories:

A total of 678 NP swab samples were available for analysis from unique hospitalized patients who met the study inclusion criteria (Figure 1). Ct values for the ORF1ab locus ranged from 14.3 to 36.4 (Supplemental Figure) and 10 samples were considered positive for SARS-CoV-2 based on detection of the E gene even though ORF1ab was not detected. The median Ct value was 27.9. The lowest third of Ct values were <25.2, the middle third were between 25.2 and 30.3, and the highest third were >30.3. For simplicity, we designated high viral load samples to have Ct values <25 (n=220), medium viral load samples to have Ct values 25-30 (n=216), and low viral load samples to have Ct values >30 or for which only the E gene was detected (n=242). Of the 49 patients who had a positive SARS-CoV-2 test but were discharged from the ED and not admitted, the median Ct value was 29.1.

Patient characteristics and presentations stratified by viral load:

The median age of patients with high, medium, and low viral loads was 72, 69, and 63 years, respectively (P<0.001; Table 1). In addition to older age, patients with higher viral loads were more likely to have coronary artery disease, congestive heart failure, cerebrovascular disease, hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and active cancer. They were also more likely to be a former or current smoker or have received recent chemotherapy. Patients with high viral loads had a median of 7 days from symptom onset until hospital admission, compared to 8 and 10 days for patients with medium and low viral loads, respectively (P<0.001). Patients with higher viral loads were also more likely to

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require oxygen by a non-rebreather, high-flow nasal cannula, or mechanical ventilation within three hours of presentation to the ED, but were less likely to present with fever, nausea, or vomiting. Lymphopenia, anemia, and thrombocytopenia were more common among patients with higher viral loads; whereas, alanine aminotransferase elevations were less common. There were no differences in chest x-ray findings among patients with high, medium, or low viral loads. There were also no differences in viral loads among different racial or ethnic categories or between patients who did and did not use angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), or hydroxychloroquine.

Outcomes stratified by viral load:

The last day of study follow-up was June 8, 2020. By that day, 19.2% of patients had died during their admission, 75.8% had been discharged alive, 1.6% had been transferred to another hospital, and 3.4% were still hospitalized. The risk of intubation and death increased with higher viral loads. In-hospital mortality was 35.0% in patients with a high viral load, compared to 17.6% in patients with a medium viral load, and 6.2% in patients with a low viral load (P<0.001; Table 1). The risk of intubation was 29.1% in patients with a high viral load, compared to 20.8% and 14.9% in patients with a medium or low viral load, respectively (P<0.001; Table 1). These associations were also observed in time-based analyses (Figure 2), where compared to a low viral load, a high viral load was associated with a hazard ratio (HR) of 5.06 (95% CI: 2.86-8.96; P<0.001) for in-hospital mortality and a HR of 2.15 (95% CI: 1.31-3.53; P=0.003) for intubation; whereas, a medium viral load was associated with mortality (HR 2.52; 95% CI: 1.36-4.67; P=0.003) but not with risk of intubation (HR 1.53; 95% CI: 0.91-2.60; P=0.11). When viral load was assessed by continuous Ct values instead of being grouped into

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high, medium, and low viral load categories, the risk of death increased with decreasing Ct values and the risk of intubation was greater with Ct values <27 compared to >27 (Figure 3).

In a multivariate model that adjusted for age, race, coronary artery disease, congestive heart failure, cerebrovascular disease, hypertension, COPD, days of symptoms prior to admission, symptoms upon presentation, initial chest x-ray findings, and level of oxygen support within three hours of arrival to the ED (Table 2), having a high viral load was independently associated with increased risk of in-hospital mortality (adjusted odds ratio [aOR] 6.05; 95% CI: 2.92-12.52; *P*<0.001) compared to having a low viral load. The risk of in-hospital mortality was also higher in patients with a medium viral load compared to a low viral load, but this association was not statistically significant (aOR 2.06; 95% CI: 0.98-4.34; *P*=0.058). Compared to those with a low viral load, having a high viral load was also independently associated with increased risk of intubation (aOR 2.73; 95% CI: 1.68-4.44; *P*<0.001); whereas, the risk of intubation associated with a medium viral load did not reach statistical significance (aOR 1.59; 95% CI: 0.96-2.63; *P*=0.07). Patients with higher viral loads were also more likely to develop myocardial infarction, congestive heart failure, and acute kidney injury requiring hemodialysis (Table 1).

DISCUSSION

This study demonstrated that patients who were admitted to the hospital with high SARS-CoV-2 viral loads, as assessed by Ct values of NP swab samples, were more likely to be intubated or die during their hospitalization. This association persisted even when adjusting for age, comorbidities, presenting symptoms, chest radiography findings, and degree of presenting hypoxia.

While prior studies indicated that viral load correlates with severity of COVID-19 presentation [10, 11], our study of a larger cohort of hospitalized patients adds to this knowledge

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base by identifying that admission viral load has important prognostic implications. Reporting SARS-CoV-2 viral load based on Ct values from admission NP swab samples could therefore help identify patients who are at highest risk of adverse outcomes and who therefore may benefit from more intensive monitoring. Identifying high viral load patients could also be helpful for allocating scare therapeutic interventions such as antiviral agents (e.g., remdesivir) [15]. Our findings also suggest that stratification or adjustment for baseline viral load would benefit the design of clinical trials of antiviral agents for COVID-19. It is also possible that viral load could be used along with other factors, such as age, comorbidities, and severity of symptoms and hypoxia to decide upon the need for hospital admission. However, additional studies that evaluate viral loads and clinical outcomes among all patients who present to the ED are warranted prior to pursuing this strategy clinically.

Older age and the presence of comorbidities such as hypertension, coronary artery disease, congestive heart failure, COPD, and cancer are known to be associated with worse outcomes in COVID-19 [2, 7, 16, 17]. Such patients may have decreased cardiopulmonary reserve and thus are less likely to tolerate the physiologic insults caused by COVID-19. Our findings suggest these patients also have higher SARS-CoV-2 viral loads when they present to the hospital, which may contribute to the worse outcomes observed in these patients. Reasons for higher viral loads specifically in these populations are not well understood and warrant further investigation.

Given that SARS-CoV-2 uses the angiotensin-converting enzyme 2 receptor (ACE2) for entry into host cells [18], there have been concerns that use of ACEIs and ARBs may upregulate ACE2 expression and lead to increased viral proliferation into host cells [19]. Although patients with hypertension and congestive heart failure were more likely to have higher viral loads, use of ACEIs and ARBs was not associated with higher viral load. Our findings are consistent with those of observational studies that have not demonstrated worse outcomes in

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patients who use ACEIs or ARBs [20-22] and support the recommendations of professional societies of not discontinuing these medications in the setting of COVID-19 [23].

Another notable finding from this study is that there were no differences in admission SARS-CoV-2 viral loads or outcomes among different racial or ethnic groups. In the U.S., Hispanic and black communities have been disproportionately affected by COVID-19, with a greater proportion of deaths among these patients than what would be expected based on their population proportions [24-26]. Our finding that admission viral loads were not different among race and ethnicity groups suggests that these disparities are not to related to viral load, but instead may be related to comorbid illnesses and non-biological factors such as social determinants of health. This further underscores the importance of studies that examine the impact of social determinants of health on outcomes during the COVID-19 pandemic.

We also found that patients with higher viral loads were more likely to develop myocardial infarction, congestive heart failure, and acute kidney injury. It is unclear whether these associations were from chance, were related to increased hypoxia in heart and kidney tissue, or were related to increased viral infection of these organs. A recent autopsy study demonstrated that SARS-CoV-2 frequently directly infects both the heart and kidney [27] and kidney injury and myocardial injury are commonly reported complications of severe COVID-19 [28, 29]. Additional studies are warranted to assess the relationship between viral loads in NP swab samples, disease burden in the heart and kidney, and clinical outcomes.

Our study has limitations. We only evaluated the viral load of a single NP swab sample per patient at the time of hospital admission, and thus could not assess viral load dynamics over time or the infectious burden at the time of infection onset. However, we found that this single sample on admission had important prognostic implications among hospitalized patients. In order to maintain consistency, we only analyzed Ct values from a single diagnostic platform,

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and thus our findings may not apply to all COVID-19 diagnostic assays. However, other studies have demonstrated that the Panther Fusion SARS-CoV-2 Test (Hologic, Inc.) and the Xpert Xpress SARS-CoV-2 (Cepheid, Inc.), two commonly used RT-PCR assays, yield nearly identical Ct values as the cobas 6800 assay used in this study [30, 31]. Thus, we suspect that our findings may also be applicable to other diagnostic platforms. We encourage others to evaluate the relationship between clinical outcomes and Ct values using other diagnostic platforms and other patient populations. Another potential role for reporting SARS-CoV-2 viral loads through Ct values is to guide the use of isolation precautions, given that viral load correlates with infectivity [32-34]. Our study did not assess this potential use of Ct values, but we believe this is an important area for future investigation. Another limitation is that our study was retrospective and relied on data that were documented in the electronic medical record, and thus could have misclassified patient characteristics or outcomes. However, our data abstraction process utilized a standardized protocol and our queries identified high interrater reliability for data collection. Lastly, we focused on in-hospital mortality, and did not capture deaths that occurred after discharge from the hospital.

In conclusion, we found that admission SARS-CoV-2 viral loads, as determined by Ct values that are generated with standard-of-care diagnostic assays, are independently associated with intubation and death among hospitalized patients with COVID-19. These findings highlight the critical role of viral load in SARS-CoV-2 pathogenesis and suggest that Ct values should be reported to assist clinicians in identifying patients at high risk for adverse COVID-19-related outcomes.

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NOTES

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FIGURE LEGENDS

Figure 1. Study flow diagram.

Figure 2. Probability of in-hospital survival (2A) and freedom from intubation (2B) during the COVID-19 hospitalization among patients with high, medium, and low viral loads. A medium viral load was associated with a hazard ratio (HR) of in-hospital mortality of 2.52 (95% CI: 1.36-4.67; *P*=0.003) and a HR of intubation of 1.53 (95% CI: 0.91-2.60; *P*=0.11) compared to a low viral load. A high viral load was associated with a HR of in-hospital mortality of 5.06 (95% CI: 2.86-8.96; *P*<0.001) and a HR of intubation of 2.15 (95% CI: 1.31-3.53; *P*=0.003) compared to a low viral load.

Figure 3. Cycle threshold values from nasopharyngeal swab samples on admission and risk of intubation and death during the hospitalization.

Supplemental Figure. Histogram of cycle threshold values for the SARS-2-CoV-2-specific locus (ORF1ab).

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Table 1. Baseline Characteristics of Hospitalized Patients with COVID-19 Stratified by Admission Viral Load

Variables	High viral load (Ct<25) n=220	Medium viral load (Ct 25-30) n=216	Low viral load (Ct>30) n=242	*P*[1]
Age, years	**72 (60-81)**	**69 (58-79)**	**63 (50-73)**	**<0.001**
Female gender	81 (36.8)	84 (38.9)	99 (40.9)	0.37
Race[2] (n=585)				
White	89 (45.1)	79 (43.4)	91 (44.2)	0.54
Black	25 (12.7)	27 (14.8)	30 (14.6)	0.74
Asian	42 (21.3)	32 (17.6)	36 (17.5)	0.23
Hispanic ethnicity[2] (n=628)	48 (23.9)	54 (27.1)	60 (26.3)	0.58
Comorbidities				
Obesity: BMI >30[2] (n=663)	60 (27.6)	70 (33.5)	79 (33.3)	0.20
Coronary artery disease	**44 (20.0)**	**45 (21.8)**	**31 (12.8)**	**0.039**

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Congestive heart failure	**28 (12.7)**	**15 (6.9)**	**13 (5.4)**	**0.004**
Cerebrovascular disease	**27 (12.3)**	**15 (6.9)**	**13 (5.4)**	**0.007**
Diabetes	82 (37.3)	71 (32.9)	77 (31.8)	0.22
Hypertension	**136 (61.8)**	**144 (66.7)**	**121 (50.0)**	**0.008**
Chronic pulmonary disease	49 (22.3)	40 (18.5)	38 (15.7)	0.07
COPD	**21 (9.6)**	**11 (5.1)**	**9 (3.7)**	**0.009**
Asthma	20 (9.1)	22 (10.1)	20 (8.3)	0.75
Chronic kidney disease	**32 (14.6)**	**22 (10.2)**	**20 (8.3)**	**0.032**
ESRD	**22 (10.0)**	**13 (6.0)**	**12 (5.0)**	**0.035**
HIV infection	4 (1.8)	3 (1.4)	5 (2.1)	0.83
Active cancer	**22 (10.0)**	**14 (6.5)**	**6 (2.5)**	**0.001**
Solid tumor	**13 (5.9)**	**8 (3.7)**	**5 (2.1)**	**0.032**
Hematologic malignancy	**9 (4.1)**	**6 (2.8)**	**2 (0.8)**	**0.025**
Transplant recipient	15 (6.8)	8 (3.7)	9 (3.7)	0.12
Rheumatologic disease	12 (5.5)	13 (6.0)	12 (5.0)	0.81
Social characteristics				
Former or current smoker	**78 (35.5)**	**54 (25.0)**	**62 (25.6)**	**0.022**
Known sick contacts	41 (18.6)	41 (19.0)	34 (14.1)	0.18
Healthcare worker	7 (3.2)	10 (4.6)	9 (3.7)	0.80
Home medications				
ACE inhibitor/ARB	68 (30.9)	74 (34.3)	68 (28.1)	0.49
Hydroxychloroquine	5 (2.3)	1 (0.5)	9 (3.7)	0.27
Immunosuppressive medications	27 (12.3)	21 (9.7)	19 (7.9)	0.11
Oral steroids	13 (5.9)	11 (5.1)	9 (3.7)	0.19

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Calcineurin inhibitor	11 (5.0)	7 (3.2)	9 (3.7)	0.49
Mycophenolate	12 (5.5)	7 (3.2)	9 (3.7)	0.36
Chemotherapy within the previous six months	**9 (4.1)**	**3 (1.4)**	**1 (0.4)**	**0.004**
Clinical presentation				
Days of symptoms prior to admission[2] (n=611)	**7 (3-9)**	**8 (5-13)**	**10 (6-14)**	**<0.001**
Symptoms				
Fever	**138 (62.7)**	**152 (70.4)**	**173 (71.5)**	**0.046**
Cough	160 (72.7)	148 (68.5)	166 (68.6)	0.34
Dyspnea	156 (70.9)	136 (63.0)	169 (69.8)	0.85
Sore throat	18 (8.2)	17 (7.9)	11 (4.6)	0.12
Headache	16 (7.3)	15 (6.9)	25 (10.3)	0.23
Myalgias	38 (17.3)	41 (19.0)	54 (22.3)	0.17
Nausea or vomiting	**30 (13.6)**	**31 (14.3)**	**51 (21.1)**	**0.03**
Diarrhea	49 (22.3)	50 (23.2)	68 (28.1)	0.14
Altered mental status	38 (17.3)	41 (19.0)	29 (12.0)	0.11
Anosmia	7 (3.2)	12 (5.6)	14 (5.8)	0.20
Aguesia	12 (5.5)	20 (9.3)	20 (8.3)	0.27
Highest oxygen requirement within three hours of arrival to the ED				
No supplemental oxygen required	78 (35.5)	84 (38.9)	92 (38.0)	0.58
Oxygen by nasal cannula	**81 (36.8)**	**86 (39.8)**	**113 (46.7)**	**0.03**

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Oxygen by non-rebreather mask, high-flow nasal cannula, or non-invasive mechanical ventilation	**50 (22.7)**	**38 (17.6)**	**33 (13.6)**	**0.011**
Mechanical ventilation	**11 (5.0)**	**8 (3.7)**	**4 (1.7)**	**0.046**
Laboratory values				
Leukocytosis: WBC >11x10^9 cells/L^2 (n=602)	41 (22.2)	39 (19.8)	40 (18.6)	0.46
Lymphopenia: ALC <1x10^9 cells/L^2 (n=594)	**135 (71.8)**	**140 (72.5)**	**127 (59.6)**	**0.008**
Anemia: hemoglobin <12 g/dL^2 (n=602)	**52 (27.4)**	**45 (22.8)**	**41 (19.1)**	**0.048**
Thrombocytopenia: platelet count <150x10^9/L^2 (n=602)	**46 (24.2)**	**45 (22.8)**	**26 (12.1)**	**0.002**
AST elevation[2,3] (n=580)	118 (64.5)	144 (75.4)	142 (68.9)	0.38
ALT elevation[2,4] (n=589)	**46 (24.7)**	**44 (22.8)**	**79 (37.6)**	**0.004**
Troponin I >0.5 ng/mL^2 (n=229)	17 (14.5)	9 (8.4)	5 (6.8)	0.07
Inflammatory makers				
Procalcitonin^2 (n=504)	0.26 (0.12-0.64)	0.22 (0.1-0.56)	0.2 (0.11-0.45)	0.12
C-reactive protein^2 (n=373)	12.9 (7.8-20.4)	11.1 (6.3-19.0)	11.4 (6.7-20.2)	0.57
Ferritin^2 (n=521)	849 (409-1417)	842 (409-1542)	821 (340-1361)	0.42

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D-dimer[2] (n=405)	535 (309-990)	472 (300-980)	547 (354-1716)	0.17
Chest x-ray findings				
Clear	22 (10.0)	13 (6.0)	17 (7.0)	0.24
Unilateral infiltrates	27 (12.3)	23 (10.7)	25 (10.3)	0.51
Bilateral infiltrates	166 (75.5)	169 (78.2)	194 (80.2)	0.22
Concurrent bloodstream infection	8 (3.6)	5 (2.3)	3 (1.2)	0.09
Outcomes				
Intubation	**64 (29.1)**	**45 (20.8)**	**36 (14.9)**	**<0.001**
Days until intubation	2 (0-3)	2 (0-4)	2 (0-5)	0.66
In-hospital mortality	**77 (35.0)**	**36 (17.6)**	**14 (6.2)**	**<0.001**
Days until death	7 (4-14)	8 (3-15)	10 (3-32)	0.32
Other complications				
Myocardial infarction	**16 (7.3)**	**10 (4.6)**	**5 (2.1)**	**0.007**
Congestive heart failure	**14 (6.4)**	**6 (2.8)**	**6 (2.5)**	**0.032**
Arrhythmia	29 (13.2)	18 (8.3)	20 (8.3)	0.08
Acute kidney injury requiring hemodialysis	**33 (15.0)**	**18 (8.3)**	**7 (2.9)**	**<0.001**

Variables are expressed as No. (%) or median (interquartile ranges).

Abbreviations: ACE, angiotensin-converting enzyme; ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; Ct, cycle threshold; ED, emergency department; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; WBC, white blood cell count.

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[1]*P* values were calculated using the non-parametric nptrend command in STATA, version 15.0, that tests for trend across ordered groups.

[2]This variable was not assessed in all participants. The denominator is listed next to the variable.

[3]AST elevation indicates a value >34 units/L.

[4]ALT elevation indicates a value >55 units/L.

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Table 2: Multivariate logistic regression models of factors associated with intubation and in-hospital mortality.[1]

	Intubation		Mortality	
Variable	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age, per year increase			**1.10 (1.07-1.13)**	**<0.001**
White race			1.00 (0.58-1.72)	0.99
Obesity	1.41 (0.93-2.12)	0.10		
Coronary artery disease			1.48 (0.79-2.78)	0.22
Congestive heart failure			2.10 (0.89-4.93)	0.09
Cerebrovascular disease			1.24 (0.54-2.86)	0.61
Hypertension			0.74 (0.41-1.33)	0.31
COPD			0.65 (0.23-1.82)	0.42
Use of oral steroids as an outpatient	1.86 (0.84-4.12)	0.13		
Days of symptoms prior to admission, per day increase			0.97 (0.92-1.02)	0.23
Symptoms on admission				
Fever	1.37 (0.87-2.17)	0.18	1.38 (0.77-2.46)	0.28
Cough			0.64 (0.36-1.13)	0.12
Dyspnea	**1.99 (1.20-3.30)**	**0.008**		

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Headache			0.56 (0.16-1.97)	0.37
Myalgias			1.24 (0.60-2.58)	0.56
Nausea or vomiting			0.50 (0.21-1.19)	0.12
Altered mental status			1.29 (0.65-2.55)	0.46
Aguesia			0.88 (0.26-3.00)	0.84
Highest level of supplemental oxygen within 3 hours of arrival to the ED[2]				
None			Reference	
Oxygen by nasal cannula			**3.79 (1.86-7.73)**	**<0.001**
Oxygen by non-rebreather mask, high-flow nasal cannula, or non-invasive mechanical ventilation			**5.58 (2.50-12.46)**	**<0.001**
Mechanical ventilation			**23.34 (6.29-86.51)**	**<0.001**
Chest x-ray findings				
No infiltrates	Reference		Reference	
Unilateral infiltrates	1.72 (0.30-9.84)	0.54	**4.36 (1.09-17.45)**	**0.037**
Bilateral infiltrates	**9.94 (2.37-41.74)**	**0.002**	**4.98 (1.47-16.94)**	**0.01**
Viral load by nasal pharyngeal swab				
Low viral load (Ct>30)	Reference		Reference	

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Medium viral load (Ct 25-30)	1.59 (0.96-2.63)	0.07	2.06 (0.98-4.34)	0.058
High viral load (Ct<25)	**2.73 (1.68-4.44)**	**<0.001**	**6.05 (2.92-12.52)**	**<0.001**

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, cycle threshold; ED, emergency department; OR, odds ratio.

[1]Only variables that had a significant association with intubation or mortality in a univariate logistic regression model were included in the corresponding multivariate model.

[2]This variable was analyzed as a risk factor for mortality, but was not analyzed as a factor associated with intubation because one of the oxygen supplementation categories was mechanical ventilation.

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Figure 1

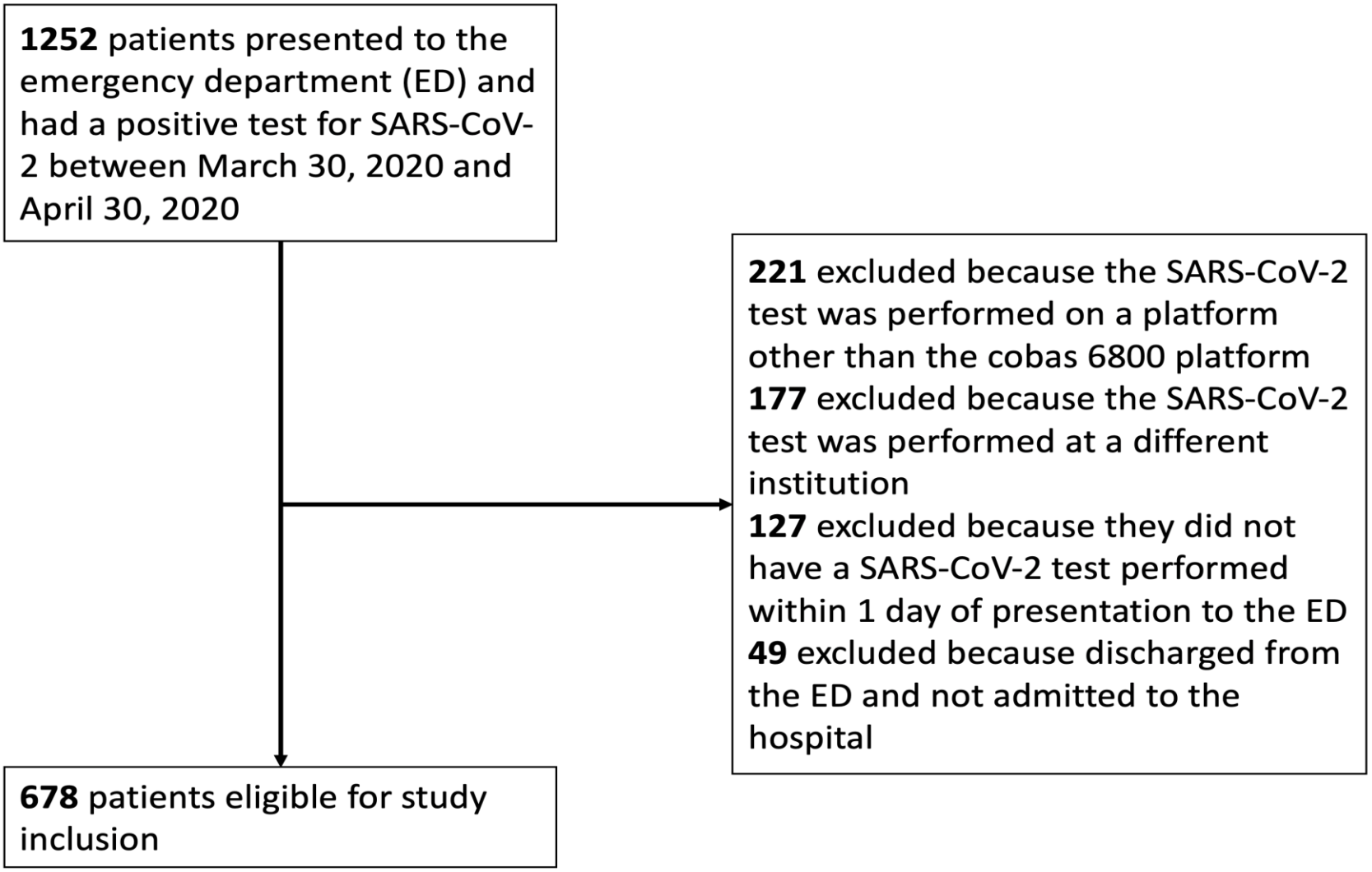

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Figure 2a

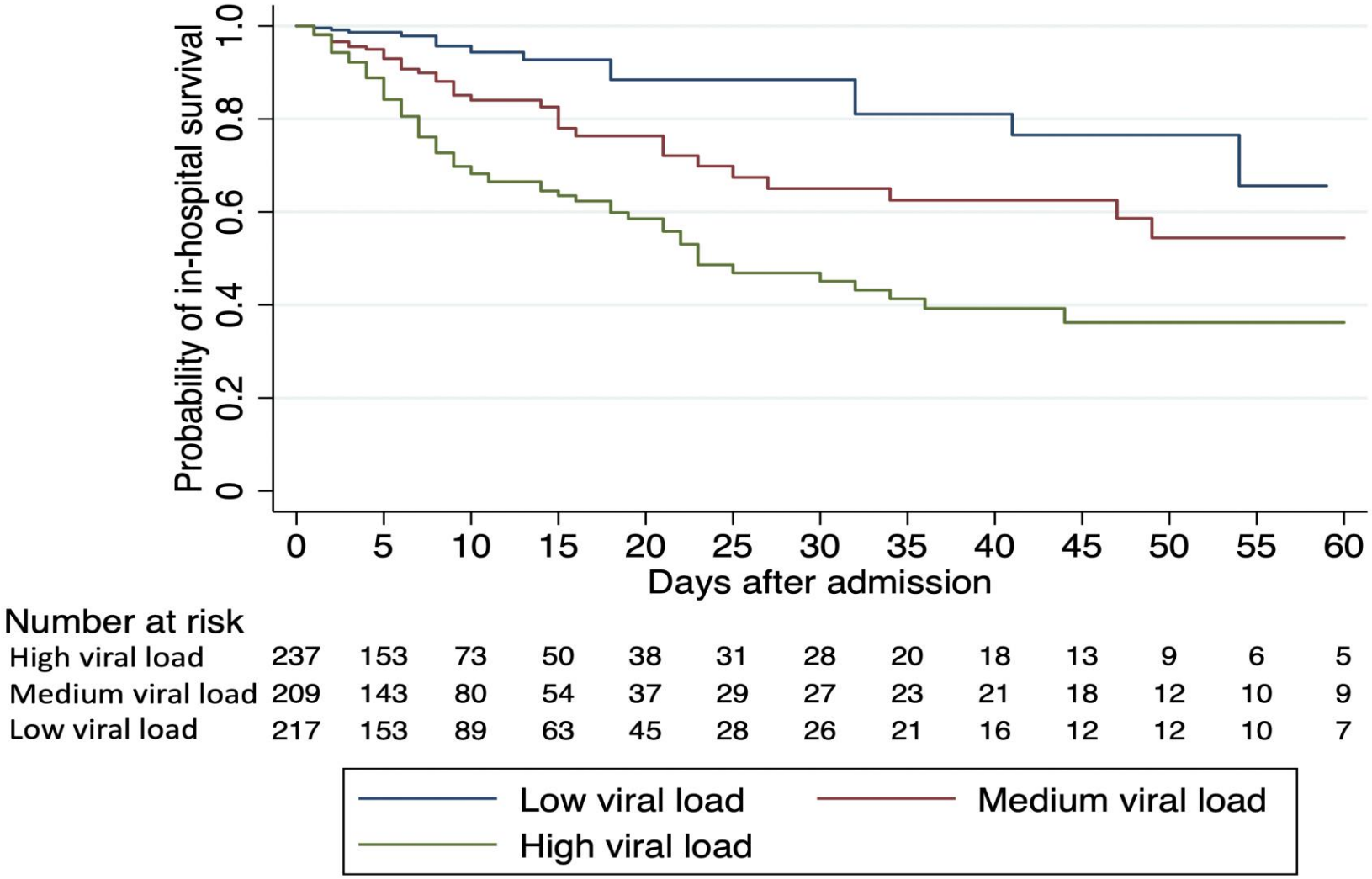

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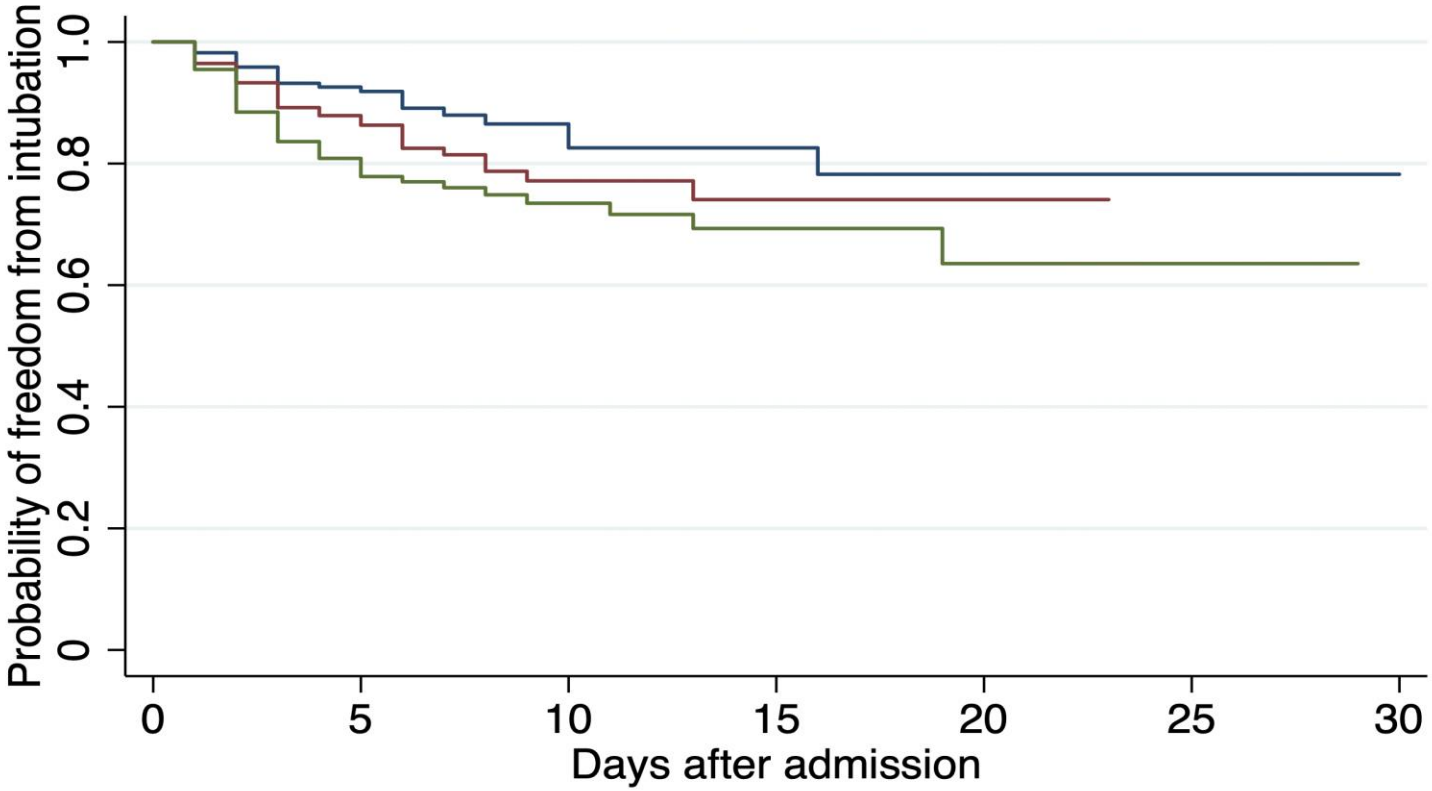
Figure 2b



Number at risk

High viral load	226	128	44	23	14	9	5
Medium viral load	198	112	42	18	6	3	3
Low viral load	199	108	47	24	11	3	2

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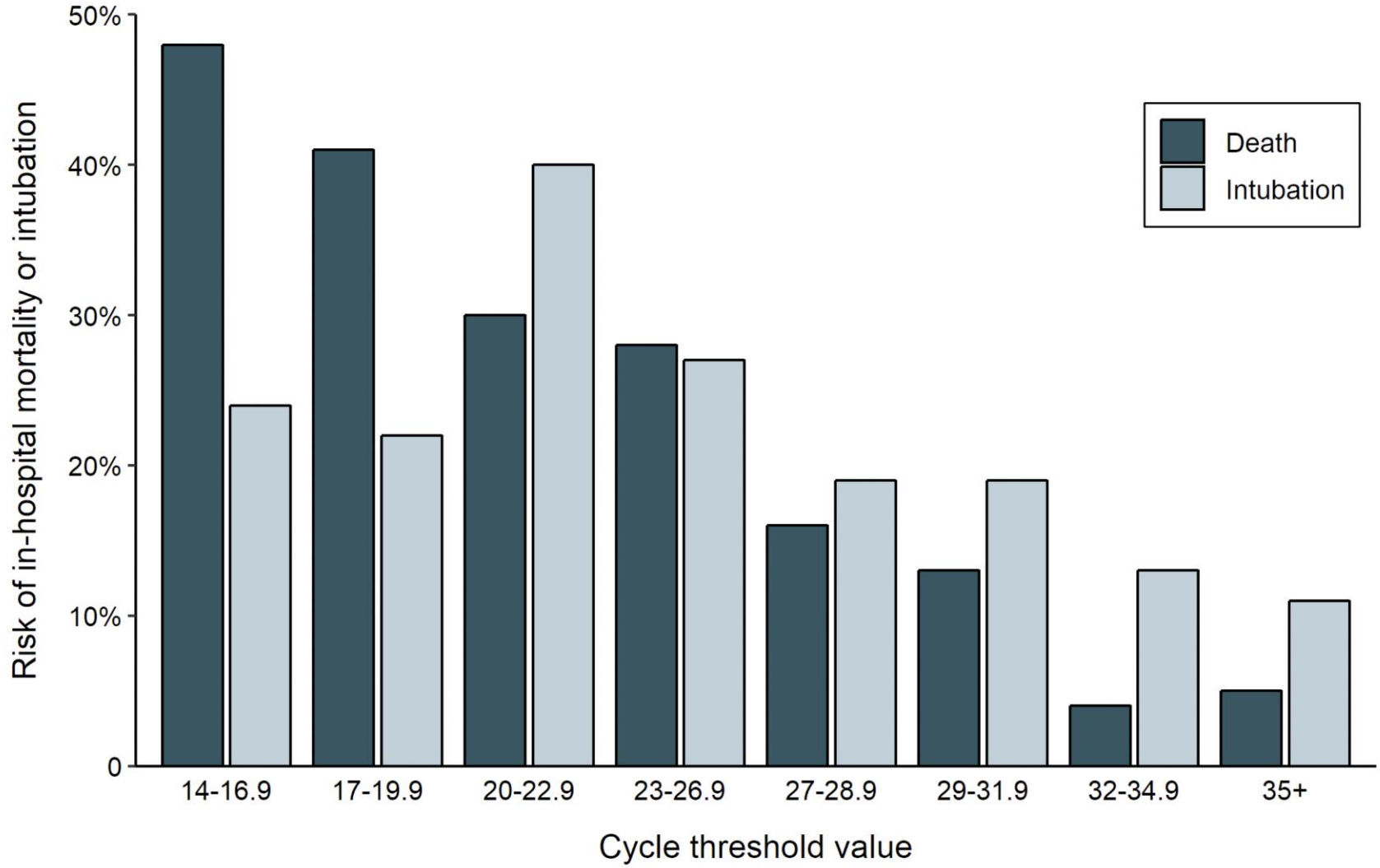
Figure 3



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