

# Sex-Related Differences in Clinical Presentation and Risk Factors for Mortality in Patients Hospitalized With Coronavirus Disease 2019 in New York City

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We evaluated sex-related differences in symptoms and risk factors for mortality in 4798 patients hospitalized with coronavirus disease 2019 in New York City. When adjusted for age and comorbidities, being male was an independent predictor of death with mortality significantly higher than females, even with low severe acute respiratory syndrome coronavirus 2 viral load at admission.

**Keywords.** COVID-19; sex; mortality; risk factors; viral load.

Over a year into the coronavirus disease 2019 (COVID-19) global pandemic [1, 2], we still lack a reliable algorithm to predict disease severity. Age [3], obesity, hypertension, diabetes [4], and high viral load at admission [5] are associated with increased mortality. Similar to other coronavirus outbreaks [6, 7], male sex is a risk factor for death from COVID-19 [8–10], with mortality 1.7 times higher in males than females [11]. The etiology of sex-related differences in COVID-19 mortality remains poorly understood, and the way these differences affect presentation and clinical course merits further investigation. We conducted a retrospective cohort study of COVID-19 patients between 3 March and 15 May 2020 in New York City to

understand how sex affects clinical symptoms and risk factors for mortality.

## MATERIALS AND METHODS

We included 4798 symptomatic adult patients ( $\geq 18$  years old) who presented to the emergency department and had a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse-transcription polymerase chain reaction (RT-PCR) test result at 1 of 3 New York–Presbyterian Hospitals (NYPH). Clinical data (eg, demographics, medical history, in-hospital mortality) were manually abstracted from electronic health records using a quality-controlled protocol described previously [12].

### SARS-CoV-2 Testing and Viral Load Measurement

SARS-CoV-2 infection was diagnosed through RT-PCR on nasopharyngeal swab specimens. Cycle threshold (Ct) values were used as surrogates for viral load in specimens tested using the cobas (Roche Molecular Systems) [13] or Xpert Xpress (Cepheid) [14] assays at admission. Viral load was classified as low, medium, or high based on previously published cutoffs [5, 15].

### Analysis

The primary outcome was in-hospital mortality. We summarized continuous variables as mean and standard deviation (SD), and summarized categorical variables as percentages. Group comparisons were assessed using a 2-sample *t* test for normally distributed continuous variables (eg, body mass index [BMI]) and  $\chi^2$  test for categorical variables (eg, race). Nonnormally distributed continuous variables (eg, D-dimer) were log-transformed before analysis. To determine the association between sex and mortality (binary outcome), we performed a multivariable logistic regression analysis adjusting for age, race/ethnicity, and comorbidities that were significantly different ( $P < .05$ ) (eg, diabetes, hypertension) between sexes in univariate analysis. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated. The probability of survival over time by viral load strata was calculated using standard Kaplan-Meier survival methods and compared using the log-rank test. All analyses were performed using R version 4.0.2 software.

### Patient Consent Statement

This study did not necessitate patient consent and was approved by the Weill Cornell Medicine Institutional Review Board.

## RESULTS

### Study Population

Of 4798 patients, 4225 (88%) were hospitalized and 2818 (58.5%) were male. Mean cohort age was 63 years (SD,

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17.5 years). Approximately one-third were white, 18% Asian, and 12% black, with the remainder declining to answer. One-third reported Hispanic ethnicity (Table 1).

The mean age of females was higher than males (65 vs 62 years,  $P < .001$ ). More females were obese (BMI  $\geq 30$  kg/m<sup>2</sup>) (36.9% vs 30.1%,  $P < .001$ ) or morbidly obese (BMI  $\geq 35$  kg/m<sup>2</sup>) (16.9% vs 9.9%,  $P < .001$ ) and had hypertension (56% vs 51.5%,  $P = .006$ ) or COPD (19.7% vs 13.7%,  $P < .001$ ). Males were significantly more likely to have coronary artery disease (CAD) (15.6% vs 12.2%,  $P = .003$ ) and renal disease (10.4% vs 7.3%,  $P = .001$ ). A higher percentage of males had no known comorbidities compared to females (35.4% vs 30.5%,  $P = .001$ ). Males and females had similar admission rates (88.5% vs 87.4%,  $P = .238$ ).

### Clinical Presentation

Females were more likely to present with gastrointestinal symptoms (diarrhea, nausea, vomiting) (35.9% vs 30.7%,  $P < .001$ ) and hypotension (6.5% vs 3.5%,  $P < .001$ ). Males were more likely to present with fever (66.1% vs 59.9%,  $P < .001$ ) and lower respiratory symptoms (eg, cough, dyspnea) (82.7% vs 78.8%,  $P = .001$ ). They more often required supplemental oxygen (54.8% vs 48.7%,  $P < .001$ ) and had radiologically documented pneumonia (81.7% vs 78.5%,  $P < .001$ ). These differences remained significant in multivariable analysis.

### Laboratory Values

Males had significantly more lymphopenia (absolute lymphocyte count  $< 1 \times 10^9$  cells/L) (58.1% vs 48.7%,  $P < .001$ ) and increased C-reactive protein (13.22 vs 10.75 mg/dL,  $P < .001$ ), ferritin (2.96 vs 2.70 ng/mL,  $P < .001$ ), and D-dimer (2.54 vs 2.42 ng/mL,  $P = .011$ ) at admission. Of the 2454 (58%) patients with viral load data at admission, there was no difference in number of patients with a low, medium, or high SARS-CoV-2 viral load by sex (Table 1).

### Hospital Course and Outcomes

Significantly more males required renal replacement therapy initiation (11.5% vs 6.7%,  $P < .001$ ). Males experienced longer hospitalization (mean, 11.5 vs 9.7 days,  $P = .001$ ) and were more likely to be treated with COVID-19 medications (eg, remdesivir, tocilizumab, or hydroxychloroquine). Males had higher mortality than females (25.2% vs 22.1%,  $P = .029$ ). After adjusting for age, race/ethnicity, and individual comorbidities (eg, obesity, CAD), being male was still a risk factor for mortality (aOR, 1.51 [95% CI, 1.27–1.80];  $P < .001$ ), as was history of stroke (aOR, 1.49 [95% CI, 1.11–1.98];  $P = .007$ ), CAD (aOR, 1.27 [95% CI, 1.02–1.58];  $P = .03$ ), diabetes (aOR, 1.27 [95% CI, 1.05–1.53];  $P = .01$ ), and obesity (aOR, 1.24 [95% CI, 1.02–1.5];  $P = .03$ ) (Supplementary Table 1).

Regardless of sex, people with high viral loads had higher mortality than people with medium or low viral loads (females:

high 34.3% vs medium 19.8% vs low 9.7%,  $P < .001$ ; males: high 35.0% vs medium 23.1% vs low 14.4%,  $P < .001$ ). However, among those with low viral loads, males had higher mortality than females (14.4% vs 9.7%,  $P = .036$ ), which remained significant after adjusting for age and comorbidities. Compared to medium or high viral loads, the effect of low viral loads on mortality was also significantly different in female vs males (interaction,  $P = .041$ ), including when adjusted for age and comorbidities. When comparing in-hospital survival over time, males with low and medium viral loads had comparable survival rates, whereas females with low viral loads had higher survival rates compared to females with medium viral loads (Figure 1).

## DISCUSSION

We found significant differences between how males and females presented with COVID-19 at 3 diverse New York City hospitals. Males presented more frequently with respiratory symptoms, fever, elevated inflammatory markers, and abnormal chest imaging. Females were more likely to present with gastrointestinal symptoms and hypotension. Though females were more likely to be obese, being male was associated with increased mortality, even when adjusted for age and comorbidities. Male mortality was also higher than female mortality when SARS-CoV-2 viral load was low at admission.

Our finding that being male was an independent predictor of COVID-19 mortality accords with previous studies [8–11]. Similar to other studies [4, 10, 16, 17], we found that history of stroke, CAD, diabetes, and obesity were all independent predictors of death. However, females presenting to the emergency department in our study had a similar number of known comorbidities as males and were equally likely to be admitted. Females were also more likely to be obese, yet still had lower rates of death. Studies in mice suggest that obesity-induced inflammation is worse in males compared with weight-matched females [18]. Furthermore, estrogen decreases insulin resistance and production of proinflammatory cytokines from adipose tissue [19]. This could explain why obese females have less severe outcomes with COVID-19.

The association between viral load distribution and mortality was also significantly different between males and females in our study. Mortality for males with low viral load was higher than for females, even when adjusted for age and comorbidities. Furthermore, unlike females, males with low or medium viral load had similar survival. Interestingly, males in our study presented with more inflammation (eg, elevated C-reactive protein), similar to reports from China and Italy [20, 21]. We hypothesize that sex differences in survival by viral load could be related to differences in the host immune response to SARS-CoV-2. Studies have shown sex differences in expression of the ACE2 receptor required for viral entry [22]. An immunologic study of patients with mild COVID-19 also found that

**Table 1. Patient Characteristics, Presentations, Laboratory Values, and Outcomes of Cohort, by Sex**

| Characteristic  | Overall <sup>a</sup> (N = 4798) | Female (n = 1980 [41.3%]) | Male (n = 2818 [58.7%]) |
|---|---------------------------------|---------------------------|-------------------------|
| <b>Demographics<sup>b</sup></b>                                 |                                 |                           |                         |
| Age <sup>c,d</sup> , y, mean (SD)                               | 63.12 (17.5)                    | 64.67 (18.52)             | 62.02 (16.64)           |
| <b>Race<sup>c,d</sup></b>                                       |                                 |                           |                         |
| White   | 1204 (29.4)                     | 516 (30.3)                | 688 (28.7)              |
| Asian   | 748 (18.3)                      | 294 (17.3)                | 454 (18.9)              |
| Black   | 505 (12.3)                      | 260 (15.3)                | 245 (10.2)              |
| Other/declined to answer  | 1641 (40.0)                     | 631 (37.1)                | 1010 (42.1)             |
| <b>Ethnicity<sup>c</sup></b>                                    |                                 |                           |                         |
| Hispanic, Latino, or Spanish origin                             | 1363 (33.3)                     | 548 (32.2)                | 815 (34.0)              |
| Not Hispanic, Latino, or Spanish origin                         | 1976 (48.2)                     | 1106 (46.1)               | 1106 (46.1)             |
| Other/declined to answer  | 759 (18.5)                      | 283 (16.6)                | 476 (19.9)              |
| <b>Hospital characteristics</b>                                 |                                 |                           |                         |
| <b>ED location<sup>b</sup></b>                                  |                                 |                           |                         |
| NYP Weill Cornell   | 1380 (33.7)                     | 572 (33.6)                | 808 (33.7)              |
| NYP Lower Manhattan   | 475 (11.6)                      | 203 (11.9)                | 272 (11.3)              |
| NYP Queens  | 2213 (54.0)                     | 915 (53.8)                | 1298 (54.2)             |
| Admitted to hospital  | 4225 (88.1)                     | 1730 (87.4)               | 2495 (88.5)             |
| <b>Comorbidities<sup>b</sup></b>                                |                                 |                           |                         |
| Cancer <sup>d</sup>   | 178 (4.3)                       | 83 (4.9)                  | 95 (4.0)                |
| Cirrhosis   | 41 (1.0)                        | 13 (0.8)                  | 28 (1.2)                |
| CAD <sup>c,d</sup>  | 581 (14.2)                      | 208 (12.2)                | 373 (15.6)              |
| COPD <sup>c,d</sup>   | 664 (16.2)                      | 335 (19.7)                | 329 (13.7)              |
| CVA <sup>d</sup>  | 264 (6.4)                       | 119 (7.0)                 | 145 (6.1)               |
| Diabetes mellitus <sup>d</sup>                                  | 1269 (31.0)                     | 521 (30.6)                | 748 (31.2)              |
| Hypertension <sup>c,d</sup>                                     | 2187 (53.4)                     | 952 (56.0)                | 1235 (51.5)             |
| Renal disease <sup>c,d</sup>                                    | 375 (9.2)                       | 125 (7.3)                 | 250 (10.4)              |
| <b>Obesity<sup>c,d,e</sup> (n = 3764)</b>                       |                                 |                           |                         |
| Class 1 obesity <sup>e</sup> (BMI 30.0–34.9 kg/m <sup>2</sup> ) | 756 (20.1)                      | 315 (20.0)                | 441 (20.2)              |
| Class 2/3 obesity <sup>c,e</sup> (BMI ≥35.0 kg/m <sup>2</sup> ) | 483 (12.8)                      | 266 (16.9)                | 217 (9.9)               |
| BMI <sup>c,e</sup> , kg/m <sup>2</sup> , mean (SD)              | 28.2 (6.67)                     | 28.72 (7.49)              | 27.88 (5.99)            |
| <b>No. of comorbidities<sup>c</sup></b>                         |                                 |                           |                         |
| 0   | 1367 (33.4)                     | 518 (30.5)                | 849 (35.4)              |
| 1   | 1057 (25.8)                     | 492 (28.9)                | 565 (23.6)              |
| ≥2  | 1674 (40.8)                     | 691 (40.6)                | 983 (41.0)              |
| <b>Home medications<sup>b</sup></b>                             |                                 |                           |                         |
| Noninvasive home oxygen <sup>e</sup> (n = 3828)                 | 105 (2.7)                       | 44 (2.8)                  | 61 (2.7)                |
| Oral steroids <sup>c</sup>                                      | 152 (3.7)                       | 79 (4.6)                  | 73 (3.0)                |
| <b>Presenting symptoms</b>                                      |                                 |                           |                         |
| Fever <sup>c</sup> , self-reported                              | 3049 (63.5)                     | 1186 (59.9)               | 1863 (66.1)             |
| Myalgia   | 979 (20.4)                      | 396 (20.0)                | 583 (20.7)              |
| Rhinorrhea  | 163 (3.4)                       | 71 (3.6)                  | 92 (3.3)                |
| Sore throat   | 302 (6.3)                       | 115 (5.8)                 | 187 (6.6)               |
| Pulmonary <sup>c</sup> (cough, dyspnea)                         | 3890 (81.1)                     | 1560 (78.8)               | 2330 (82.7)             |
| Gastrointestinal <sup>c</sup> (nausea, vomiting, diarrhea)      | 1576 (32.8)                     | 710 (35.9)                | 866 (30.7)              |
| <b>Neurological (anosmia, focal deficit)</b>                    |                                 |                           |                         |
| Anosmia or ageusia  | 184 (3.8)                       | 87 (4.4)                  | 97 (3.5)                |
| <b>Vitals</b>   |                                 |                           |                         |
| Fever (temperature >38°C)                                       | 799 (16.7)                      | 275 (13.9)                | 524 (18.6)              |
| Systolic BP <sup>c</sup> , mm Hg, mean (SD)                     | 128 (18.9)                      | 127.19 (20.18)            | 128.42 (17.97)          |
| Hypotension (systolic BP <90 mm Hg)                             | 227 (4.7)                       | 128 (6.5)                 | 99 (3.5)                |
| Tachycardia   | 1436 (29.9)                     | 554 (28.0)                | 882 (31.3)              |
| <b>Laboratory tests and other assessments<sup>e</sup></b>       |                                 |                           |                         |
| Lymphopenia <sup>c,f</sup> (n = 3568)                           | 1938 (54.3)                     | 700 (48.7)                | 1238 (58.1)             |
| Ferritin <sup>c,g</sup> , ng/mL, mean (SD) (n = 2351)           | 2.85 (0.468)                    | 2.70 (0.47)               | 2.96 (0.43)             |
| CRP <sup>c</sup> , mg/dL, mean (SD) (n = 2483)                  | 12.2 (9.05)                     | 10.75 (8.65)              | 13.22 (9.19)            |
| CPK <sup>c,g</sup> , U/L, mean (SD) (n = 1820)                  | 2.20 (0.481)                    | 2.07 (0.44)               | 2.27 (0.49)             |
| D-dimer <sup>c,g</sup> , ng/mL, mean (SD) (n = 1914)            | 2.49 (1.01)                     | 2.42 (1.02)               | 2.54 (1.00)             |

**Table 1. Continued**

| Characteristic  | Overall <sup>a</sup> (N = 4798) | Female (n = 1980 [41.3%]) | Male (n = 2818 [58.7%]) |
|---|---------------------------------|---------------------------|-------------------------|
| Viral load <sup>e</sup> (n = 2454)                              |                                 |                           |                         |
| Low   | 928 (37.8)                      | 391 (38.3)                | 537 (37.4)              |
| Medium  | 678 (27.6)                      | 281 (27.5)                | 397 (27.7)              |
| High  | 848 (34.6)                      | 348 (34.1)                | 500 (34.9)              |
| Abnormal CXR <sup>c,e</sup> (n = 4551)                          | 3921 (86.2)                     | 1555 (83.7)               | 2366 (87.9)             |
| Hospital course and outcomes <sup>h</sup>                       |                                 |                           |                         |
| Hospitalization length <sup>c,e</sup> , d, mean (SD) (n = 2499) | 10.7 (13.1)                     | 9.67 (11.90)              | 11.46 (13.81)           |
| New renal replacement <sup>c</sup>                              | 403 (9.5)                       | 116 (6.7)                 | 287 (11.5)              |
| In-hospital mortality <sup>c,i</sup>                            | 897 (23.9)                      | 341 (22.1)                | 556 (25.2)              |
| Medications and treatments                                      |                                 |                           |                         |
| Hydroxychloroquine <sup>e</sup>                                 | 2806 (66.4)                     | 1093 (63.2)               | 1713 (68.7)             |
| Remdesivir <sup>e</sup>   | 193 (4.6)                       | 65 (3.8)                  | 128 (5.1)               |
| Steroids  | 728 (17.2)                      | 283 (16.4)                | 445 (17.8)              |
| Tocilizumab <sup>e</sup>  | 179 (4.2)                       | 52 (3.0)                  | 127 (5.1)               |
| Tamiflu   | 78 (1.8)                        | 25 (1.4)                  | 53 (2.1)                |
| Supplemental oxygen <sup>e</sup>                                | 2507 (59.3)                     | 964 (55.7)                | 1543 (61.8)             |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPK, creatine phosphokinase; CRP, C-reactive protein; CVA, cardiovascular accident; CXR, chest radiograph; ED, emergency department; NYP, New York Presbyterian; SD, standard deviation.

<sup>a</sup>Unless noted each ED presentation counted as a separate instance.

<sup>b</sup>Each individual counted once, regardless of multiple ED visits, so as to not skew entry characteristics for patients with multiple ED presentations.

<sup>c</sup>Significant difference between males and females,  $P < .05$ .

<sup>d</sup>Included in multivariable analysis.

<sup>e</sup>Variable not assessed in all participants. The denominator is listed next to the variable. There were no sex differences with missing data.

<sup>f</sup>Lymphopenia defined as absolute lymphocyte count  $< 1 \times 10^9$  cells/L.

<sup>g</sup>Log-converted values.

<sup>h</sup>Unless noted, each hospital admission was counted as a separate event. For these variables, denominators for percentages are based only on admission numbers.

<sup>i</sup>Each admitted individual counted once for this variable, regardless of multiple admissions.

at presentation, males had increased activation of monocytes and decreased T-cell activation, which was associated with poor clinical outcomes. In contrast, females experienced increased T-cell activation and impaired monocyte activation [23]. The differences in activated immune pathways after initial infection [23, 24] may explain the observed differences in symptoms and laboratory values. Additional mechanistic research correlating symptoms with immune response would be useful for clinical management.

Our analysis has strengths and limitations. We had a diverse population spanning several months of the initial New York City COVID-19 surge, which allowed us to analyze how symptomology and comorbidities correlated with mortality. Early data such as ours, however, may not be as applicable to the current clinical context. It does provide specifics on the course of the infection before standards of care were established. Because of the changing algorithms for patient care, laboratory measurements, including viral load, were missing for some patients, especially early in the pandemic. However, there were no significant sociodemographic differences between people with and without viral load data. Therefore, our analysis provides novel insight into how viral load is differentially associated with mortality by sex. This information could assist clinicians in assessing patients, especially in resource-constrained settings.

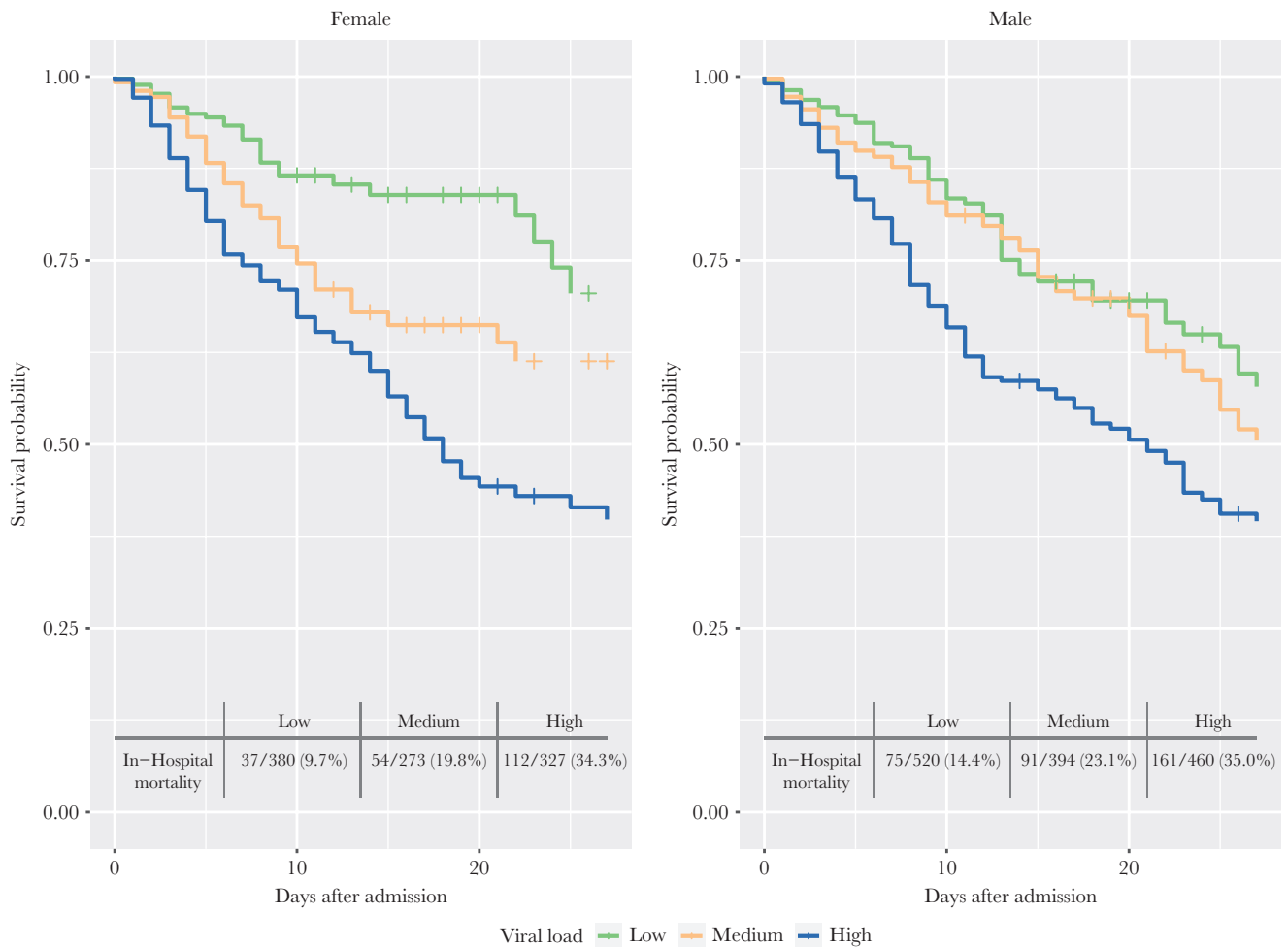
Our data provide strong rationale for future research on sex-dependent responses to COVID-19 treatments and vaccines.

## CONCLUSIONS

We identified significant sex differences in clinical presentation, in-hospital mortality, and risk factors for COVID-19 mortality. Females experienced less mortality than males despite having similar high-risk comorbidities and more obesity. Viral load distribution in females correlated with survival, while males had decreased survival over time even with low viral loads. Our data provide additional support that males clinically respond differently than females to SARS-CoV-2. Future studies should evaluate if the use of viral load values to predict mortality should be sex-adjusted. A dedicated effort to investigate sex differences is essential to ensure that treatment and vaccination algorithms benefit all populations equally.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.



**Figure 1.** Time to in-hospital death by severe acute respiratory coronavirus 2 viral load strata at admission in females and males. Kaplan-Meier curves (top): In females (left), viral load was inversely related to survival rate over time during hospitalization; females with a low viral load (green) had a significantly higher chance of survival compared to a medium (orange) or high (blue) viral load. In males (right), there was no significant difference in survival between males with a low or medium viral load. Males with a low or medium viral load had significantly higher survival compared to those with high viral load. Patients with a high viral load had the lowest chance of survival, regardless of sex. Table (bottom): Mortality was inversely related with viral load both in females and males. Among people with low viral loads, mortality was significantly higher in males vs females. Males and females had similar mortality in the medium and high groups.

## Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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