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Sex differences and disparities in cardiovascular outcomes of COVID-19

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Aims

Previous analyses on sex differences in case fatality rates at population-level data had limited adjustment for key patient clinical characteristics thought to be associated with coronavirus disease 2019 (COVID-19) outcomes. We aimed to estimate the risk of specific organ dysfunctions and mortality in women and men.

Methods and results

This retrospective cross-sectional study included 17 hospitals within 5 European countries participating in the International Survey of Acute Coronavirus Syndromes COVID-19 (NCT05188612). Participants were individuals hospitalized with positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from March 2020 to February 2022. Risk-adjusted ratios (RRs) of in-hospital mortality, acute respiratory failure (ARF), acute heart failure (AHF), and acute kidney injury (AKI) were calculated for women vs. men. Estimates were evaluated by inverse probability weighting and logistic regression models. The overall care cohort included 4499 patients with COVID-19-associated hospitalizations. Of these, 1524 (33.9%) were admitted to intensive care unit (ICU), and 1117 (24.8%) died during hospitalization. Compared with men, women were less likely to be admitted to ICU [RR: 0.80; 95% confidence interval (CI): 0.71–0.91]. In general wards (GWs) and ICU cohorts, the adjusted women-to-men RRs for in-hospital mortality were of 1.13 (95% CI: 0.90–1.42) and 0.86 (95% CI: 0.70–1.05; $p_{interaction} = 0.04$). Development of AHF, AKI, and ARF was associated with increased mortality risk (odds ratios: 2.27, 95% CI: 1.73–2.98; 3.85, 95% CI: 3.21–4.63; and 3.95, 95% CI: 3.04–5.14, respectively). The adjusted RRs for AKI and ARF were comparable among women and men regardless of intensity of care. In

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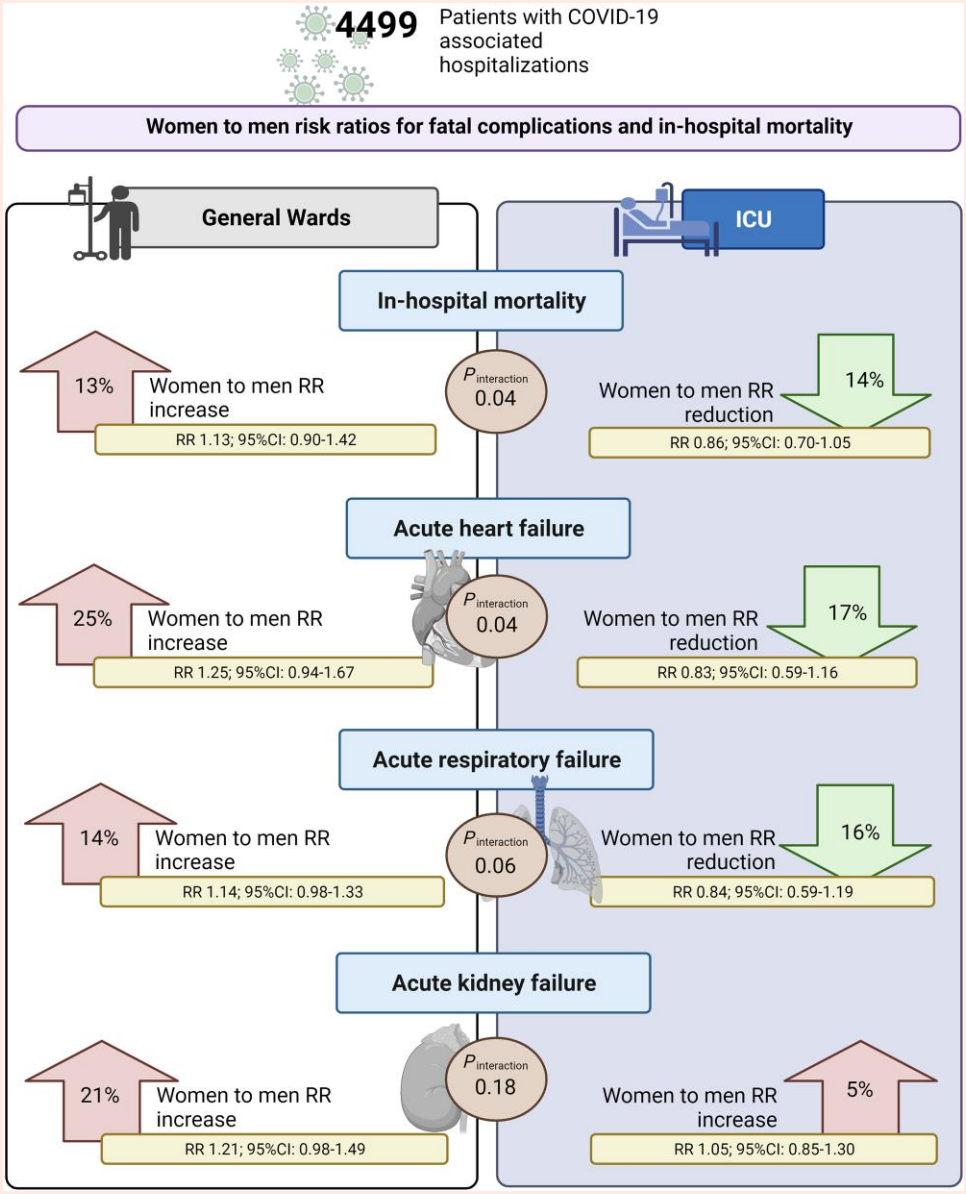
contrast, female sex was associated with higher odds for AHF in GW, but not in ICU (RRs: 1.25; 95% CI: 0.94–1.67 vs. 0.83; 95% CI: 0.59–1.16, $p_{interaction} = 0.04$).

Conclusions Women in GW were at increased risk of AHF and in-hospital mortality for COVID-19 compared with men. For patients receiving ICU care, fatal complications including AHF and mortality appeared to be independent of sex. Equitable access to COVID-19 ICU care is needed to minimize the unfavourable outcome of women presenting with COVID-19-related complications.

Graphical Abstract



Keywords COVID-19 • Women • Sex • Mortality • Acute respiratory failure • Acute heart failure • Acute kidney injury

1. Introduction

Global health data indicate higher coronavirus disease 2019 (COVID-19) case fatality rates among men than women in most European high-income countries. However, this was not the outcome seen in low- and middle-income countries. Case fatality rates in Estonia, India, Pakistan, Vietnam, and Slovenia are higher among women than men.[1,2] Controversial estimates on case fatality rates might reflect incomplete

COVID-19 data across countries, lack of case identification by sex, or higher risks for women or men in certain countries due to demographic factors or countries' specific comorbidity profiles. For all these reasons, whether women and men with COVID-19 had different rates of death or different risk factors for death is still matter of uncertainty.

Acute complications of COVID-19 can involve pulmonary and extrapulmonary organs. Nevertheless, few studies have investigated the extrapulmonary organ involvement in the acute phase of COVID-19, which may include cardiovascular and renal disorders.[3,4] Such complications have been tentatively explained by a relatively higher contribution of pre-existing comorbidities, such as cardiovascular disease (CVD), diabetes mellitus, or chronic kidney disease (CKD).[5] It is, however, widely recognized that the number of comorbidities increases with age and women have a longer life expectancy than men.[6] Thus, it is still unclear whether and how comorbidities may independently influence worse outcomes among men.

With these facts in mind, we conducted a multicentre international cohort study mainly in the early stages of the pandemic when hospitalized patients were vaccine-naïve and the population most readily tested for COVID-19, thus most accessible for research on sex-specific outcomes. We investigated the sex-related differences in risks of fatal complications and in-hospital mortality. We also investigated the difference in risks according to countries' income level. European middle-income countries differ from high-income countries not just in terms of available resources but also in having substantially younger age distributions and greater cardiovascular risk factor burden. These differences may be relevant to assess sex-related harms, and feasibility of therapeutic strategies tailored on sex.

2. Methods

We analysed information from the International Survey of Acute Coronavirus Syndromes (ISACS)-COVID 19 (NCT05188612) from March 2020 to February 2022. This study complies with the Declaration of Helsinki. The local research ethics committee from each hospital approved the study. Because patient information was collected anonymously, institutional review boards waived the need for individual-informed consent.

2.1 Participants

Details of the study design, sampling, and recruitment are described in the Supplementary material online, *Methods*. Briefly, we considered for inclusion individuals who were hospitalized with COVID-19 diagnosis in 17 centres of 5 European countries: Croatia, Italy, Macedonia, Romania, and Serbia. We excluded patients vaccinated against COVID-19. We also excluded people with previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The diagnosis of acute COVID-19 was defined by polymerase chain reaction testing evidence of SARS-CoV-2 RNA on nasopharyngeal swabs within 14 days prior to or during hospitalization. Field work was carried out by staff from each of the country's health services under a common protocol developed by the University of Bologna, which also coordinated the recruitment of patients. All data were transferred to the Department of Electrical and Computer Engineering, University of California, Los Angeles, where final statistical analyses were done.

2.2 Data collection and definition

The following variables were extracted from the electronic health records: demographic characteristics (age and sex), cardiovascular risk factors (tobacco smoking, systemic arterial hypertension, hypercholesterolaemia, diabetes, and obesity), pre-existing CVD [myocardial infarction, chronic coronary syndrome, heart failure, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), atrial fibrillation, pulmonary embolism, and haemorrhagic or ischaemic stroke], pre-existing pulmonary disease (asthma and chronic obstructive pulmonary disease), CKD, active cancer, major cognitive disorders, and immunosuppressive conditions, such as rheumatoid arthritis, lupus, or psoriasis (*Table 1*). We also noted the type of medications given prior and during hospitalization (*Table 2*). Definition of the patient-level data on conventional risk factors and pre-existing comorbidities are reported in the Supplementary material online, *Methods*. Diagnosis of COVID-19-related pneumonia was confirmed by chest X-ray and/or chest computed tomography (CT) performed in Emergency Rooms. Myocardial injury was defined as any elevation in cardiac troponins over the nominal reference values at the time of clinical presentation or during hospitalization. As the average median age of the patients enrolled in this study was 67 years, the elderly population was defined as people aged 67 and over. All participants underwent routine venous blood sampling on hospital admission. Reference values are reported in Supplementary material online, *Methods*. ISACS-COVID-19 includes countries in two income strata based on World Bank classification in 2020: two high-income countries (Croatia and Italy) and three middle-income countries (Macedonia, Romania, and Serbia; see Supplementary material online, *Methods*).

2.3 Outcome measures

The primary outcome was all-cause in-hospital mortality. Secondary key outcomes were acute respiratory failure (ARF), acute heart failure (AHF), and acute kidney injury (AKI; see Supplementary material online, *Methods*). Hypoxemia (PaO_2/FiO_2 ratio $\leq$300 mmHg) and/or the need of mechanical ventilation were grouped together for defining the occurrence of ARF. This definition was in line with some previous observations reporting that many patients with hypoxemia had not chance of mechanical ventilation.[7,8] Acute kidney injury was defined as an increase in serum creatinine by $\geq$0.3 mg/dL within 48 h according to the Kidney Disease: Improving Global Outcomes definition.[9] The diagnosis of AHF was initially based on clinical evaluation and was confirmed by chest radiography or CT. Other secondary outcomes included myocardial infarction and a composite venous thromboembolic endpoint consisting of acute deep venous thrombosis and pulmonary embolism. All endpoints were site reported.

2.4 Statistical analysis

We compared the baseline characteristics, treatment, and clinical outcomes between women and men. Baseline characteristics were reported as percentages for categorical variables and means with standard deviation (SD) for continuous variables (*Tables 1* and *2*, Supplementary material online, *Table S1*). We had complete data on sex and outcomes. Some patients had missing data on other variables. We used Multiple Imputation with Chained Equation (MICE) as the imputation method to treat missing data (Methods in the Supplement).[10] Estimates of the odds ratios (ORs) or relative risk ratios (RRs) and associated 95% confidence intervals (CIs) were obtained using logistic regression or inverse probability weighting models, respectively. Inverse probability weights were calculated using the propensity score to create a sample in which the distribution of measured baseline covariates was independent from sex (see Supplementary material online, *Methods*).[11] Because of the instability that can be induced by extreme weights, stabilized weights were used that also preserve the original sample size. We created a threshold for weights to avoid the impacts of the outliers. We used 0.01 as threshold of the propensity weighting. Standardized differences (SDs) after weighting were calculated to ensure balanced treatment groups with respect to baseline characteristics. Groups were considered balanced when the SD was <10% (see Supplementary material online, *Methods*).[12] Comparisons of outcomes between groups were made by two-sided *P*-value of <0.05. To account for differences in patient-level characteristics and illness severity among sexes, we prespecified the following covariates for inclusion in the models: demographics, cardiovascular risk factors, and clinical and biochemical features on hospital presentation (*Table 3*). Sensitivity analyses were conducted to estimate the effect of medications among women and men. To minimize concern about comparison of outcomes in subgroups, estimates were compared by test of interaction on the log scale.[13] A $P < 0.05$ was taken to indicate that the difference between the effects in women and men was unlikely to have occurred simply by chance (see Supplementary

Table 1 Baseline characteristics stratified by sex in patients hospitalized with COVID-19

Characteristics	Women ($n = 1851$)	Men ($n = 2648$)	Standardized difference
Mean age (SD), years	68.1 (15.6)	63.6 (15.2)	0.29
Cardiovascular risk factors, *n* (%)			
Diabetes mellitus	490 (26.5)	710 (26.8)	−0.01
Hypertension	1253 (67.7)	1673 (63.2)	0.10
Hypercholesterolaemia	486 (26.3)	741 (28.0)	−0.04
Current smokers	140 (7.6)	367 (13.9)	−0.20
Former smokers	179 (9.7)	515 (19.4)	−0.28
Obesity	422 (22.8)	562 (21.2)	0.04
History of comorbidities (*n*, %)			
Cardiovascular disease (n, %)	682 (36.8)	949 (35.8)	0.02
Prior myocardial infarction	139 (7.5)	313 (11.8)	−0.15
Prior angina pectoris	174 (9.4)	291 (11.1)	−0.05
Prior PCI	101 (5.5)	293 (11.1)	−0.20
Prior CABG	36 (1.9)	114 (4.3)	−0.14
Prior HF	321 (17.3)	347 (13.1)	0.12
Prior atrial fibrillation	254 (13.7)	350 (13.2)	0.01
Prior pulmonary embolism	40 (2.2)	54 (2.0)	0.009
Prior thrombosis	67 (3.6)	102 (3.9)	−0.01
Prior stroke	165 (8.9)	209 (7.9)	0.04
Asthma	92 (5.0)	52 (2.0)	0.16
COPD	151 (8.2)	238 (9.0)	−0.03
CKD	228 (12.3)	320 (12.1)	0.01
Major cognitive disorder	301 (16.3)	205 (7.7)	0.26
Active cancer	280 (15.1)	284 (10.7)	0.13
Immunosuppressive condition	61 (3.3)	99 (3.7)	−0.02
Laboratory findings on admission			
Mean blood leucocyte count, 10^9/L (SD)	8.5 (5.8)	9.1 (6.4)	−0.09
Mean blood platelet count, 10^9/L (SD)	239.1 (104.6)	228.2 (111.7)	0.10
Mean serum creatinine level, mg/dL (SD)	1.1 (1.0)	1.3 (1.1)	−0.14
Mean serum C-reactive protein, mg/dL (SD)	9.9 (9.5)	11.4 (9.9)	−0.15
Mean serum AST, U/L (SD)	96.7 (338.2)	105.6 (335.7)	−0.03
Mean serum ALT, U/L (SD)	80.1 (222.4)	99.4 (224.2)	−0.09
Mean serum LDH, U/L (SD)	532.2 (502.2)	613.7 (769.2)	−0.13
Clinical findings (*n*, %)			
X-ray/CT with signs of interstitial pneumonia on admission	1174 (63.4)	1839 (69.4)	−0.13
Myocardial injury during hospitalization	1567 (84.7)	2031 (76.7)	0.20
Country income level (*n*, %)			
Middle-income countries	1274 (68.8)	1881 (71.0)	−0.05
Outcomes			***P*-value**
Primary outcome: death (*n*, %)	455 (24.6)	662 (25.0)	0.75
Risk ratio (95% CI)	0.98 (0.85–1.12)		0.75
Secondary outcome: ICU (*n*, %)	574(31.0)	950 (35.9)	<0.001
Risk ratio (95% CI)	0.80 (0.71–0.91)		<0.001
Secondary outcome: AHF (*n*, %)	157 (8.5)	204 (7.7)	0.35
Risk ratio (95% CI)	1.11 (0.89–1.38)		0.34
Secondary outcome: ARF (*n*, %)	1288 (69.6)	1931 (72.9)	0.02
Risk ratio (95% CI)	0.85 (0.75–0.97)		0.01
Secondary outcome: AKI (*n*, %)	380 (20.5)	565 (21.3)	0.51
Risk ratio (95% CI)	0.95 (0.82–1.10)		0.51
Secondary outcome: myocardial infarction (*n*, %)	1 (0.1%)	5 (0.002%)	0.17
Risk ratio (95% CI)	0.28 (0.03–2.39)		0.24
Secondary outcome: venous thromboembolism (*n*, %)	5 (0.003%)	2 (0.001%)	0.15
Risk ratio (95% CI)	3.50 (0.68–18.05)		0.13

AHF, acute heart failure; ALT, alanine aminotransferase; AKI, acute kidney injury; ARF, acute respiratory failure; AST, aspartate aminotransferase; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ICU, intensive care unit; LDH, lactate dehydrogenase.

material online, *Methods*). All statistical analyses were performed using R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The study cohort comprised 4499 COVID-19 patients hospitalized within the hospitals participating to the ISACS-COVID-19 registry. Of these, 1524 (33.9%) were admitted to the intensive care unit (ICU), and 1117 (24.8%) died during hospitalization. There were 1851 (41.1%) women. More than half of the participants lived in a middle-income country (68.8% women and 71.0% men). The demographic and health characteristics of the COVID-19 population including prior comorbidities, clinical and laboratory findings on admission, and therapeutic management of women and men before weighting are presented in *Tables 1* and *2*.

Table 2 Medications administered prior and during hospitalization stratified by sex in patients hospitalized with COVID-19

Characteristics	Women ($n = 1851$)	Men ($n = 2648$)	Standardized difference
Therapy before hospital admission			
Direct oral anticoagulant	162 (8.8)	201 (7.6)	0.0424
Subcutaneous heparin	129 (7.0)	155 (5.9)	0.0456
VKA antagonists	101 (5.5)	194 (7.3)	−0.0765
ACE inhibitors	690 (37.3)	1019 (38.5)	−0.0248
Angiotensin receptor blockers	246 (13.3)	297 (11.2)	0.0633
Antiplatelet therapy	510 (27.6)	803 (30.3)	−0.0612
Beta 2 antagonists	93 (5.0)	112 (4.2)	0.0378
Beta-blockers	758 (41.0)	935 (35.3)	0.1163
Calcium channel blockers	330 (17.8)	479 (18.1)	−0.0068
Digoxin	45 (2.4)	58 (2.2)	0.0160
Diuretics	556 (30.0)	711 (26.9)	0.0707
Antidiabetic treatment	436 (23.6)	591 (22.3)	0.0294
Statins	456 (24.6)	663 (25.0)	−0.0093
Immunosuppressive treatment	64 (3.5)	83 (3.1)	0.0181
Proton-pump inhibitor	543 (29.3)	632 (23.9)	0.1240
Corticosteroids	187 (10.1)	218 (8.2)	0.0648
Psychotropic treatment	226 (12.2)	195 (7.4)	0.1636
Therapy during hospital stay			
Antiviral treatment	365 (19.7)	547 (20.7)	−0.0234
Hydroxychloroquine	297 (16.0)	424 (16.0)	0.0009
IL-1 inhibitors	50 (2.7)	92 (3.5)	−0.0447
IL-6 inhibitors	156 (8.4)	263 (9.9)	−0.0521
JAK inhibitors	28 (1.5)	65 (2.5)	−0.0676
Systemic glucocorticoids	1179 (63.7)	1836 (69.3)	−0.1197
Oral anticoagulant treatment	190 (10.3)	282 (10.6)	−0.0126
Heparins	1561 (84.3)	2277 (86.0)	−0.0466
Antiplatelet treatment	460 (24.9)	767 (29.0)	−0.0929
Antibiotic treatment	1520 (82.1)	2248 (84.9)	−0.0749
Diuretics	770 (41.6)	1135 (42.9)	−0.0256
Morphine	212 (11.5)	300 (11.3)	0.0039

Data are presented as numbers (%) or means (standard deviation), unless otherwise specified.
Abbreviations: ACE, angiotensin converting enzyme; VKA, vitamin K antagonist, IL, interleukin

3.1 Demographics and prior comorbidities in the overall population

Women were older. The mean age among women was 68.1 (15.6) compared with 63.6 (15.2) among men (*Table 1*). Women had a significantly (standardized difference > 10) higher occurrence of various chronic illnesses, such as hypertension (67.7% vs. 63.2%), asthma (5.0% vs. 2.0%), major cognitive disorder (16.3% vs. 7.7%), and cancer diagnoses (15.1% vs. 10.7%). Men were more likely to be current (13.9% vs. 7.6%) or former (19.4% vs. 9.7%) smokers.

3.2 Clinical and laboratory findings in the overall population

At presentation (*Table 1*), men were more likely to present with radiologic findings consistent with the diagnosis of COVID-19-related pneumonia (69.4% vs. 63.4%). C-reactive protein and lactate dehydrogenase (LDH) serum levels were higher in men than women (11.4 (SD 9.9) vs. 9.9 (SD 9.5) mg/dL and 613.7 (SD 769.2) vs. 532.2 (SD 502.2) U/L, respectively). In contrast, myocardial injury was more common in women than men (84.7% vs. 76.7%).

3.3 Treatment in the overall population

The most common treatments administered during hospitalization were: antibiotics, steroids, heparins hydroxychloroquine, antiviral agents, and diuretics (*Table 2*). Overall, men were more likely to receive steroids (69.3% vs. 63.7%). There were few significant sex differences in the use of medications before hospital admission. Women were more likely than men to receive beta-blockers (41.0% vs. 35.3%) and psychotropic medications (12.2% vs. 7.4%).

3.4 Unadjusted outcomes in the overall population

The rate of in-hospital mortality was 24.6% in women and 25.0% in men (RR: 0.98; 95% CI: 0.85–1.12; *Table 1*, *Figures 1* and *2*). The most common acute organ injuries observed in our cohort were ARF (69.6% in women and 72.9% in men; RR: 0.85; 95% CI: 0.75–0.97), AKI (20.5% in women and 21.3% in men; RR: 0.95; 95% CI: 0.82–1.10), and AHF (8.5% in women and 7.7% in men; RR: 1.11; 95% CI: 0.89–1.38). Other acute organ injuries were less frequent in this study, with only few patients experiencing myocardial infarction (0.1% in women and 0.002% in men) or the composite endpoint of venous thromboembolic events (0.003% in women and 0.001% in men). Patients with myocardial infarction and thromboembolic events were, therefore, excluded from further analyses.

3.5 Unadjusted outcomes and intensity of care

We further examined the risks and burdens of acute organ injuries in mutually exclusive groups by the care setting of the acute infection (that is, whether people were hospitalized in GW or admitted to ICU during the acute phase of COVID-19). There were 574 women and 950 men who received ICU-level care during admission (RR: 0.80; 95% CI: 0.71–0.91; *Table 1*). There were no significant differences in mortality between women and men among patients in ICU (52.1% vs. 51.8%, RR: 1.01; 95% CI: 0.82–1.25) and those in GW (12.2% vs. 10.0%; RR: 1.25; 95% CI: 0.99–1.58; $p_{interaction} = 0.09$; *Figure 1*, Supplementary material online, *Tables S1* and *S2*). Burdens of individual acute organ injuries are provided in *Figure 2* and Supplementary material online, *Table S1* and are discussed below. In GW, the odds to develop AHF were remarkably higher in women than in men (7.7% vs. 5.6%, RR: 1.40; 95% CI: 1.05–1.88) while no significant sex difference was seen in ICU patients (10.3% vs. 11.5%, RR: 0.88; 95% CI: 0.63–1.24; $p_{interaction} = 0.02$; Supplementary material online, *Table S3*). In contrast, the incidence of ARF and AKI was comparable among women and men regardless of the intensity of care ($p_{interaction} = 0.23$ and 0.35

Table 3 Inverse probability weighting: outcomes stratified by sex in patients hospitalized with COVID-19

Characteristics	Women ($n = 1851$)		Men ($n = 2648$)	Standardized difference
Mean age (SD), years	65.41 (6.0)		65.3 (15.0)	0.005
Cardiovascular risk factors (%)				
Diabetes mellitus	27.2		26.7	0.01
Hypertension	65.9		64.9	0.02
Hypercholesterolaemia	27.4		27.2	0.004
Current smokers	11.5		11.3	0.01
Former smokers	14.8		15.4	−0.02
Obesity	22.0		21.7	0.007
History of comorbidities (%)				
Cardiovascular disease	35.8		35.5	0.006
Asthma	3.1		3.1	0.003
COPD	9.6		8.8	0.03
CKD	12.8		12.4	0.01
Major cognitive disorder	10.8		10.9	−0.003
Active cancer	13.8		13.2	0.02
Immunosuppressive condition	3.5		3.6	−0.01
Laboratory findings on admission				
Mean blood leucocyte count, 10^9/L (SD)	9.1 (8.0)		8.9 (6.8)	0.02
Mean blood platelet count, 10^9/L (SD)	232.0 (112.6)		234.8 (128.4)	−0.02
Mean serum creatinine level, mg/dL (SD)	1.4 (1.5)		1.2 (1.2)	0.07
Mean serum C-reactive protein, mg/dL (SD)	10.8 (10.2)		10.8 (9.5)	0.005
Mean serum AST, U/L (SD)	115.7 (355.1)		104.7 (342.6)	0.03
Mean serum ALT, U/L (SD)	111.6 (389.8)		103.2 (298.3)	0.04
Mean serum LDH, U/L (SD)	617.9 (782.9)		586.3 (719.2)	0.04
Clinical findings on admission (%)				
X-Ray/CT with signs of interstitial pneumonia	66.8		66.8	0.001
Myocardial injury during hospitalization	81.0		80.0	0.03
Country income level (%)				
Middle-income countries	70.9		70.3	0.01
Outcomes				***P*-value**
Primary outcome: death (%)	25.1		24.7	0.77
Risk ratio (95% CI)		1.02 (0.89–1.17)		0.77
Secondary outcome: AHF (%)	8.6		8.0	0.49
Risk ratio (95% CI)		1.08 (0.87–1.34)		0.49
Secondary outcome: ARF (%)	71.8		71.1	0.60
Risk ratio (95% CI)		1.04 (0.91–1.18)		0.60
Secondary outcome: AKI (%)	22.5		21.3	0.35
Risk ratio (95% CI)		1.07 (0.93–1.24)		0.35

Data are % or means (standard deviation), unless otherwise specified.
AHF, acute heart failure; ALT, alanine aminotransferase; AKI, acute kidney injury; ARF, acute respiratory failure; AST, aspartate aminotransferase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ICU, intensive care unit; LDH, lactate dehydrogenase.

for ARF and AKI, respectively; see Supplementary material online, *Table S3*).

3.6 Balancing clinical covariates and outcomes in the overall population

Assessment of covariate balance after application of inverse probability weighting suggested that covariates were well balanced (*Table 3*). The rate of in-hospital mortality (*Figure 1*) was similar between women and men (25.1% vs. 24.7%; RR: 1.02; 95% CI: 0.89–1.17). The risk of mortality did not change when controlling for different countries' income levels, medication use, history of CVD, and younger (≤67 years) or older age (see Supplementary material online, *Tables S4–S8* and *Figure S1*). As well, the burdens of each of the acute organ injuries under scrutiny did not differ between women and men (*Figure 2* and *Table 3*).

3.7 Balancing clinical covariates and intensity of care

There was a good balance in the covariate distributions between women and men (*Table 4*). The risk of in-hospital mortality of women compared with men decreased in a graded fashion according to the intensity of care setting. In the GW, there was a 13% increase in risk of death for women compared with men (RR: 1.13; 95% CI: 0.90–1.42), whereas in the ICU, there was a 14% reduction in risk for women compared with men (RR: 0.86; 95% CI: 0.70–1.05; *Figure 1*). The RRs from the ICU and GW

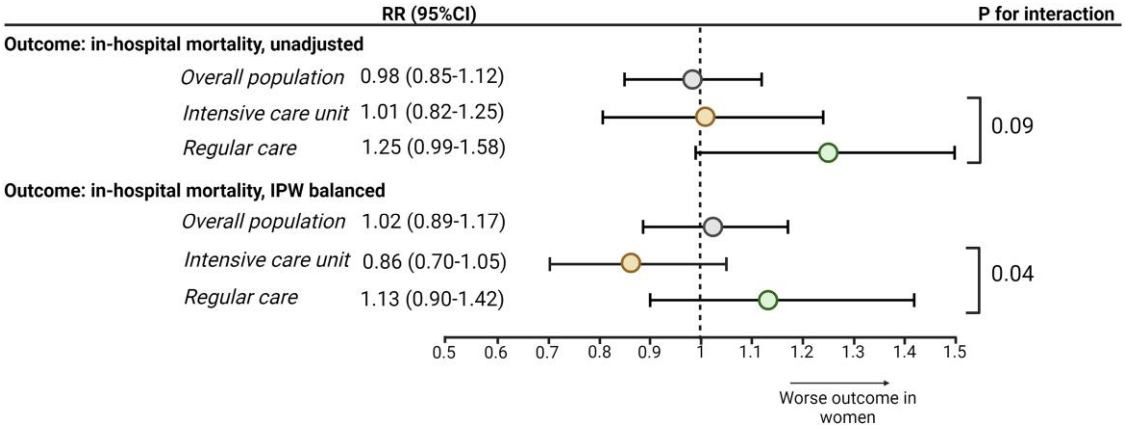


Figure 1 Women to men risk ratios for in-hospital mortality. CI, confidence interval; IPW, inverse probability weighting; RR, risk ratio. Image created with Biorender.

subgroups significantly differed from each other ($p_{interaction} = 0.04$) supporting a different impact of the acute infection on the outcomes of women and men according to the care setting (see Supplementary material online, *Table S9*). The burden of AHF analysed by care setting was consistent with the observed rates of mortality (*Table 4*). Female sex was associated with higher odds for AHF in patients admitted to GW, but not in those admitted to ICU [7.5% vs. 6.1% (RR: 1.25; 95% CI: 0.94–1.67) and 10.0% vs. 11.8% (RR: 0.83; 95% CI: 0.59–1.16); $p_{interaction} = 0.04$; see Supplementary material online, *Table S10A–C*). In contrast, the adjusted risks for ARF and AKI were comparable among women and men, regardless of the intensity of care.

3.8 Multivariable modelling

Multivariable modelling confirmed the associations between major complications and death. Development of AHF, AKI, and ARF was associated with an increased risk of mortality (OR: 2.27, 95% CI: 1.73–2.98; 3.85, 95% CI: 3.21–4.63; and 3.95, 95% CI: 3.04–5.14, respectively; *Figure 3*) To better understand the difference in the rates of AHF and outcomes among women and men, we compared the baseline comorbidities that were found to be predictors of mortality in separate sex-specific analyses. Then, we used the interaction test to estimate whether differences in odd ratios were actually significant between women and men (*Figure 4*). The results identified only one significant sex interaction, namely, a diagnosis of active cancer ($p_{interaction} = 0.01$). We tested the robustness of results using a sex-stratified inverse probability of treatment weighting model. Diagnosis of active cancer was associated with increased mortality in women (OR: 2.02; 95% CI: 1.42–2.88), but not in men (OR: 1.14; 95% CI: 0.82–1.57), and the risk of AHF differed significantly between women and men (RR: 1.77; 95% CI: 1.03–3.06; see Supplementary material online, *Table S11*).

4. Discussion

To our knowledge, this is the first study to report sex differences in risks of mortality and main complications associated with fatal outcomes from COVID-19 across the care settings of the acute infection. This study showed four main findings. First, there was a substantially increased risk of COVID-19 in-hospital mortality in women compared with men among patients managed in GW, but no sex difference in risk of death for patients admitted to ICU. Second, the most frequent complications associated with fatal outcomes were ARF, AKI, and AHF. Third, AHF was more commonly seen in women compared with men in patients receiving care in GW, but not in those admitted to ICU. Fourth, the rates of ARF and AKI were comparable among women and men either in GW or in ICU. In summary, the blanket assumption that men are more susceptible than women to present with severe complications from COVID-19 can hide how there are groups of women that are more vulnerable to poor outcomes than men. Inequality in hospital care might result in outcome disparities for women.

Previous studies have shown a higher risk of case fatality rates associated with male sex.[14–17] Case fatality rates represent the number of confirmed deaths divided by the number of confirmed cases. As so if women are more likely to get tested for COVID-19 through routine surveillance, it is plausible that a greater number of mild and asymptomatic cases will be detected among women than among men. Higher testing among women may artificially lower the case fatality rate in women compared with men. In line with these thoughts, studies analysing sex differences in COVID-19 deaths in patients admitted to hospital suggests that the picture is much more complicated. Trends vary widely by state in the United States of America.[18] A large study in Italy found a similar in-hospital mortality pattern among men and women.[19] In Massachusetts, the relative increase in mortality registered during the height of the first COVID-19 surge was identical for women and men.[20] Our study agreed with these findings, showing that once the patient is admitted to hospital the overall in-hospital mortality is similar between women and men even after adjustment for baseline comorbidities and medications given before and during hospitalization (RR: 1.02; 95% CI: 0.89–1.17).

Our study also revealed sex differences in in-hospital mortality depending upon the care settings whereby lower access to ICU for women correlated with increase in mortality. Women were 20% less likely to receive intensive care during hospitalization compared with men. This gap in the intensity of care translated into higher numbers of women experiencing AHF in GW compared with ICU ($p_{interaction} = 0.04$), which, in turn, may have contributed to equalize the total in-hospital mortality rates among women and men. This interpretation is supported by the results of our sex stratified analysis. A central finding of this study was that in GW, there was a 13% increase in risk of death in women compared with men whereas in the intensive care there was a 14% reduction in risk of death with significant interaction ($p_{interaction} = 0.04$). The magnitude of the interaction between sex and rates of mortality leads us to believe that the association we identified is clinically significant and probably not a statistical artefact.

The exact reason of sex-related variations in death and its relation with fatal complications was unclear at this point. Previous analyses had limited adjustment for key patient characteristics thought to be associated with COVID-19 outcomes.[21] Such adjustments were possible in this study,

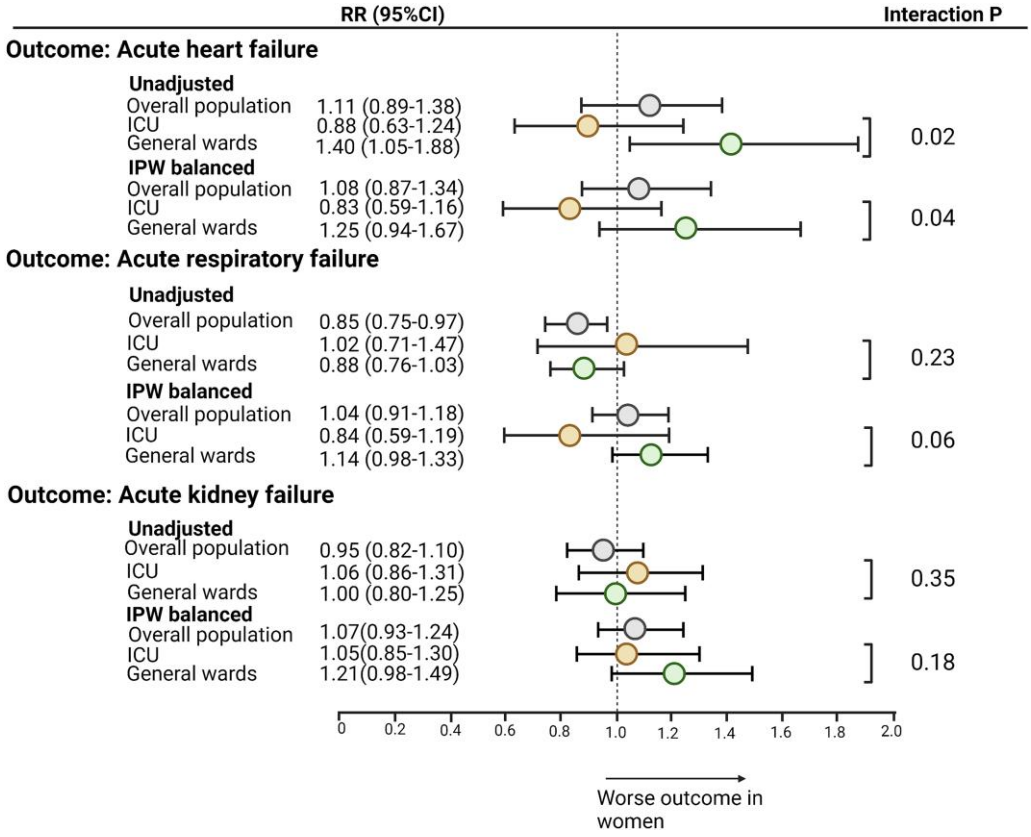


Figure 2 Women to men risk ratios for secondary outcomes. CI, confidence interval; ICU, intensive care unit; IPW, inverse probability weighting; RR, risk ratio. Image created with Biorender.

given the availability of patient-level data on a wide range of exposures and comorbidities. Our modelling approach included specification of 22 variables selected on the basis of established knowledge on conventional risk factors and prior comorbidities and 30 variables describing clinical findings on admission, laboratory test results, and medication records. We examined the associations between sex and main fatal complications using unadjusted and adjusted analyses: an unmet task in prior work.

ARF of varying severity was common in COVID-19 and was strongly associated with in-hospital mortality (OR: 3.95; 95% CI: 3.04–5.14). In the unadjusted analyses, women had a substantially lower rate of ARF (RR: 0.85; 95% CI: 0.75–0.97; *Table 1*). In the adjusted analyses, the female sex specificity for the observed reduced risk of ARF did not replicate (women to men RR: 1.04; 95% CI: 0.91–1.18; *Table 3*). This implies that the reported crude sex differences in the rates of ARF are explained by some factors represented as baseline covariates in the unadjusted analyses. Of note, fewer women than men had radiological evidence of interstitial pneumonia on hospital presentation (63.4% vs. 69.4%). Similar pattern was seen with CRP [9.9 (SD 9.5) vs. 11.4 (SD 9.9) mg/dL] and LDH [532.2 (SD 502.2) vs. 613.7 (SD 769.2) U/L] serum levels, which may reflect the severity of the underlying lung disease.[22] In summary, hospitalized women are less likely to have severe interstitial pneumonia from COVID-19.[23,24] Nevertheless, higher vulnerability to pneumonia of male patients does not necessarily translate into worse outcomes for men as mortality from COVID-19 can be related to other life-threatening complications as documented by the current study.

Preliminary analyses on COVID-19 found that a number of patients died of AKI.[25] In our study, AKI represented one of the most frequent complication during hospitalization (20.5% in women and 21.3% in men) and was associated with a high risk of mortality (OR: 3.85; 95% CI: 3.21–4.63). Based on experimental data, recent work has proposed that women are more protected from AKI than men and that this female renal protection is mediated by the effects of sexual hormones on the synthesis of nitric oxide mediating the pathogenesis of the disease.[26] We found a different pattern: the incidence of AKI was equivalent in women and men either in GW (12.0% vs. 12.0%) or ICU (39.5% vs. 38.1%). Women in our cohort were predominantly in the post-menopausal age range, and, as so, the protective role of sexual hormones may have been attenuated.

Cardiovascular complications have been described in the acute phase of COVID-19.[24,27] The pathogenesis of such complications is still not completely understood and likely involves multiple pathways (*Figure 5*). A direct damage may be mediated by high levels of cytokines that can injure multiple tissues including cardiac myocytes. A small number of case reports have indicated that SARS-CoV-2 might also infect the myocardium, causing viral myocarditis. However, in most cases, myocardial damage appeared to be caused by fever and hypoxemia causing tachycardia with consequent increase in myocardial oxygen consumption.

Our analysis extends this observation by demonstrating a significant interaction between intensity of care and sex-related rates of AHF ($p_{\text{interaction}} = 0.04$) with higher incidence of AHF for women compared with men in GW. The exact cause of such disparity remains unknown, but this information may have important clinical implications. First, this finding may reflect the fact that women in GW were actually sicker than men. The failure to recognize symptoms of AHF in women may have contributed to lack of admission to ICU. The fact that women in GW had also higher mortality rate than men after adjustment for baseline variables lends support to this hypothesis. Although this finding raises concerns about sex disparities in care, it should be interpreted with some caution. At hospital admission, men with COVID-19 have higher C-reactive protein, LDH and creatinine and lower troponin serum levels compared with women.

Table 4 Inverse probability weighting: clinical factors stratified by sex and admission to ICU in patients hospitalized with COVID-19

Characteristics	ICU			General wards		
	Women (*n* = 574)	Men (*n* = 950)	Standardized difference	Women (*n* = 1277)	Men (*n* = 1698)	Standardized difference
Mean age (SD), years	66.8 (13.5)	66.7 (12.6)	0.81	64.8 (17.1)	64.6 (16.1)	0.01
Cardiovascular risk factors (%)						
Diabetes	32.4	32.8	0.91	23.9	23.1	0.02
Hypertension	72.6	71.8	0.82	62.4	61.2	0.03
Hypercholesterolaemia	28.7	28.7	0.82	26.8	26.3	0.01
Current smokers	14.4	13.8	0.85	9.2	10.0	−0.03
Former smokers	15.2	17.0	0.58	14.2	14.6	−0.01
Obesity	24.8	24.4	0.91	19.8	20.1	−0.006
History of comorbidities (%)						
Cardiovascular disease	38.8	39.5	0.85	34.2	33.3	0.02
Asthma	3.8	3.8	1.00	2.8	2.7	0.003
COPD	8.4	8.5	0.97	9.2	8.9	0.01
CKD	15.7	17.0	0.69	10.3	9.6	0.02
Major cognitive disorder	9.1	9.3	0.94	11.5	12.0	−0.01
Active cancer	10.5	10.6	0.97	16.3	14.7	0.04
Immunosuppressive condition	4.5	5.1	0.81	2.7	2.8	−0.005
Laboratory findings on admission						
Mean blood leucocyte count, 10^9/L (SD)	10.3 (5.8)	10.3 (5.2)	0.94	9.7 (9.8)	9.1(6.8)	0.07
Mean blood platelet count, 10^9/L (SD)	231.3 (105.9)	234.7 (133.2)	0.31	231.1 (100.6)	233.8 (110.9)	−0.03
Mean serum creatinine level, mg/dL (SD)	1.5 (1.6)	1.4 (1.4)	0.20	1.3 (1.7)	1.1 (1.1)	0.05
Mean serum C-reactive protein, mg/dL (SD)	13.6 (10.6)	13.7 (10.6)	0.64	9.4 (9.7)	9.3 (8.5)	0.02
Mean serum AST, U/L (SD)	166.8 (485.0)	68.3 (534.3)	0.59	78.1 (139.3)	70.0 (117.3)	0.05
Mean serum ALT, U/L (SD)	140.0 (414.2)	136.3 (354.5)	0.60	82.6 (92.4)	72.4 (88.3)	0.06
Mean serum LDH, U/L (SD)	851.6 (803.1)	863.1 (938.7)	0.23	437.7 (392.2)	434.5 (281.6)	0.01
Clinical findings on admission (%)						
X-ray/CT with signs of interstitial pneumonia	78.8	78.8	1.00	60.4	60.5	−0.002
Myocardial injury during hospitalization	84.3	82.5	0.58	79.9	78.8	0.03
Country income level (%)						
Middle-income countries	82.4	82.0	0.90	63.8	63.9	−0.001
Outcomes						
Primary outcome: death (%)	48.3	52.2	0.14	11.8	10.6	0.31
Risk ratio (95% CI)	0.86 (0.70–1.05)		0.14	1.13 (0.90–1.42)		0.31
Secondary outcome: AHF (%)	10.0	11.8	0.27	7.5	6.1	0.14
Risk ratio (95% CI)	0.83 (0.59–1.16)		0.28	1.25 (0.94–1.67)		0.13
Secondary outcome: ARF (%)	89.8	91.3	0.33	63.0	59.8	0.08
Risk ratio (95% CI)	0.84 (0.59–1.19)		0.32	1.14 (0.98–1.33)		0.08
Secondary outcome: AKI (%)	39.4	38.2	0.66	14.8	12.5	0.08
Risk ratio (95% CI)	1.05 (0.85–1.30)		0.66	1.21 (0.98–1.49)		0.80

Data are % or means (standard deviation), unless otherwise specified.
AHF, acute heart failure; ALT, alanine aminotransferase; AKI, acute kidney injury; ARF, acute respiratory failure; AST, aspartate aminotransferase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography, ICU, intensive care unit; LDH, lactate dehydrogenase.

Among healthy individuals, baseline levels of cardiac biomarkers significantly differ by sex, and women have lower troponin levels compared with men.[28] Taken together, these data would suggest excess myocardial injury in women. However, data pertaining to the effect of sex on the relationship between biomarkers and COVID-19 disease outcomes are still scarce. As so, these findings underscore the difficulties that clinicians may have had in recognizing the subset of patients who would develop AHF.

At least another source of uncertainty merits attention. In our study population, women with active cancer had higher AHF rates than men with active cancer even after adjusting for age and concurrent comorbidities (RR: 1.77; 95% CI: 1.03–3.06; Supplementary material online, *Table S11*). Patients with active cancer are thought to have a poor prognosis and while they may have a need for ICU, they may not be seen to have a need for ICU for a perceived futility of intensive support in patients just affected by concurrent critical illness. This perspective is supported by the data of the current study. Our analysis of people with active cancer and COVID-19 revealed that these patients were more likely to be hospitalized in GW (16.5% vs. 12.0% in women and 11.7 vs. 8.9% in men). Notably, active cancer was associated with increased mortality in women (OR: 2.02; 95% CI: 1.42–2.88), but not in men (OR: 1.14; 95%

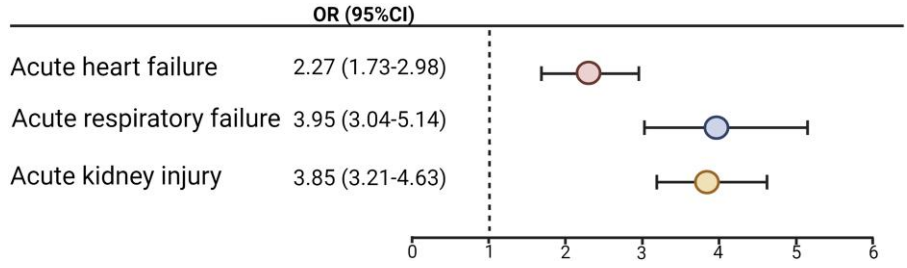


Figure 3 Multivariable logistic regression analysis: associations between major complications and in-hospital mortality. Full model was adjusted for age, sex, cardiovascular risk factors (diabetes mellitus, hypertension, hypercholesterolaemia, smoking status), comorbidities (cardiovascular disease, asthma, chronic obstructive pulmonary disease, chronic kidney disease, major cognitive disorder, active cancer, immunosuppressive condition), laboratory findings on admission (blood leucocyte and platelet count, serum creatinine levels, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase levels), chest X-ray/CT signs of interstitial pneumonia on admission, and myocardial injury during hospitalization. Image created with Biorender. CI, confidence interval; OR, odds ratio.

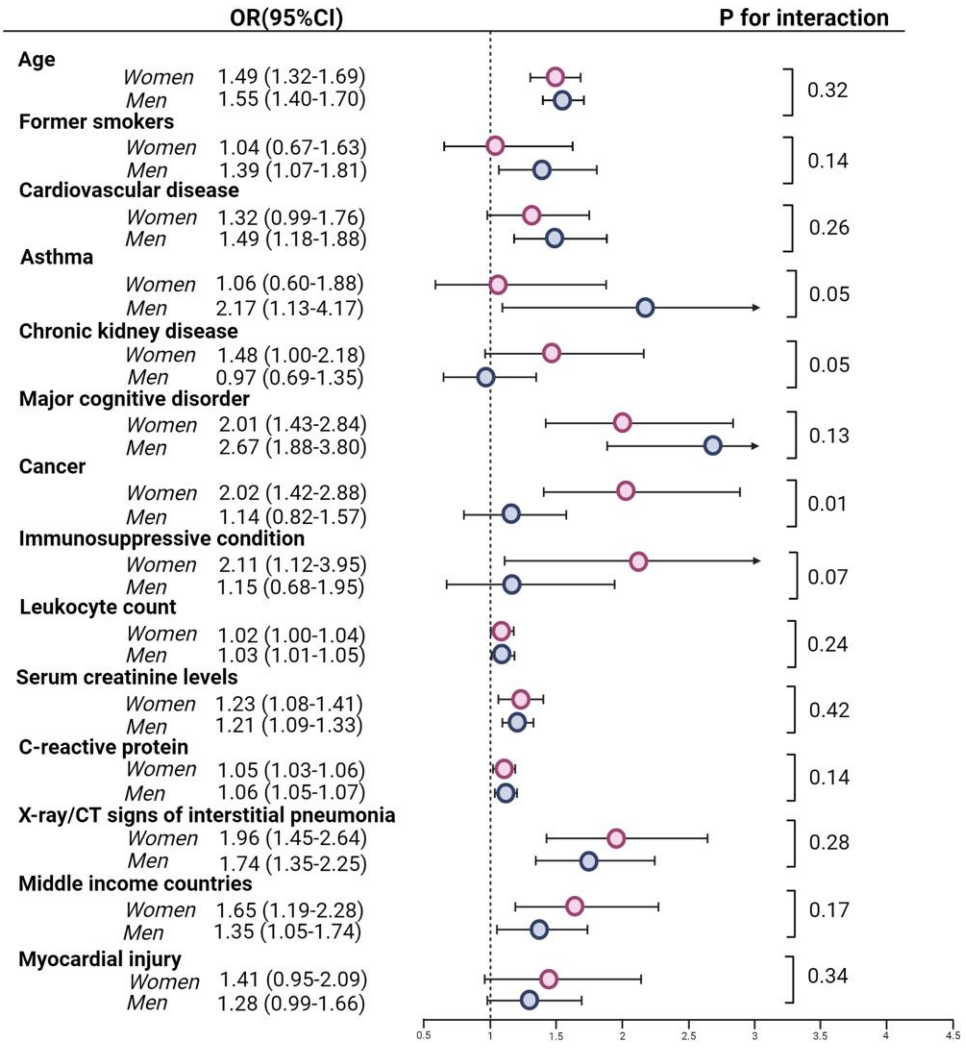


Figure 4 Multivariable logistic regression analysis of factors associated with in-hospital mortality stratified by sex. Full model was adjusted for age, sex, cardiovascular risk factors (diabetes mellitus, hypertension, hypercholesterolaemia, smoking status), comorbidities (cardiovascular disease, asthma, chronic obstructive pulmonary disease, chronic kidney disease, major cognitive disorder, active cancer, immunosuppressive condition), laboratory findings on admission (blood leucocyte and platelet count, serum creatinine levels, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase levels), chest X-ray/CT signs of interstitial pneumonia on admission, Myocardial injury during hospitalization. Image created with Biorender. CI, confidence interval; OR, odds ratio.

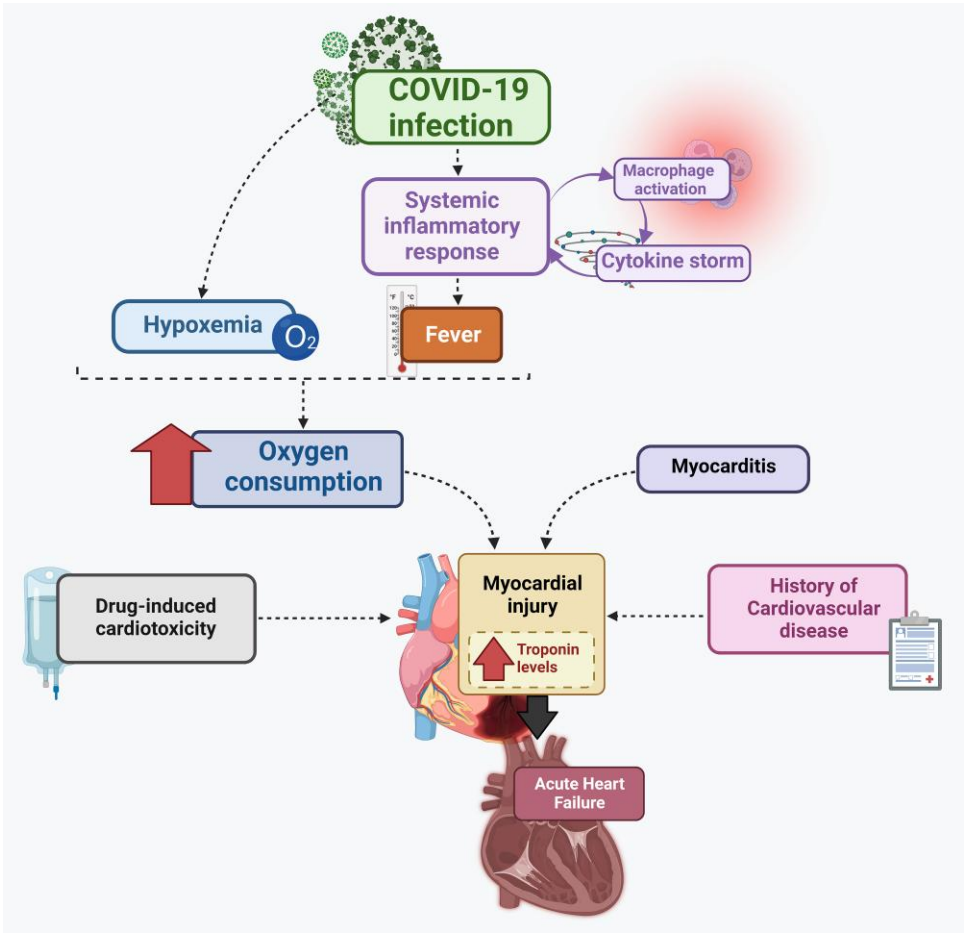


Figure 5 COVID-19 and acute heart failure: mechanisms of myocardial damage in COVID-19. Image created with Biorender.

CI: 0.82–1.57). Thus, one could reasonably conclude that concurrence of COVID-19 and active cancer had significant negative effects especially in women. Yet, we do not know, with the data available, whether the observed sex difference in the development of AHF will be the case.

Evidence obtained from clinical practice is an important source of information about population endpoints for which randomized clinical trials are infeasible, and sex cannot be randomized. To control for confounding, various statistical methods have been developed that allow researchers to assess relationships between an exposure and the outcome of interest. In the present study, the exposure was female sex and outcomes of interest were AHF, ARF, and AKI, and their relationship with death. It is difficult to draw firm conclusions using regression adjustments as development of AHF, ARF, and AKI are mechanisms of death. A confounder must not be an intermediate step in the causal pathway linking the exposure to death, because it may reduce the association between the factor of interest and the outcome. An alternative to regression adjustment is to utilize inverse probability weighting.[11] Inverse probability weighting is calculated using the propensity score and creates a sample in which the distribution of measured baseline covariates is balanced and independent of the sex category, a property that would be expected under randomization.

We acknowledge limitations to the current study. First, residual confounding might exist even if mitigated by matching using propensity-based methods. Our empirical approach did not account for all sources of biases, which could result in unmeasured variables. Second, all patients in our cohort are Caucasians, so racial variations in response to SARS-Cov-2 infection cannot be assessed. Third, some of the risk factors were ascertained by the general practitioners, which might have led to errors in the dataset. Nonetheless, it is unlikely that these misclassifications differentially affect women over men and, thus, are unlikely to modify the sex differences that we found. Fourth, the virus continues to mutate and as new variants emerge, the epidemiology of cardiovascular manifestations in COVID-19 might change over time.

In conclusion, this study reveals that outcomes for patients with COVID-19 rely not only on individual-level comorbidities and risk factors, but also on the type of fatal complications developed during hospitalization. This study also shows increased risk of AHF and in-hospital mortality for women compared with men although this was limited to patients admitted to the GW. The 'one size fits all' assumption that men are more likely than women to die of COVID-19 can hide how there are groups of women that are more vulnerable to poor outcomes than men. Care pathways of women with COVID-19 should include attention to cardiovascular health.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Authors' contributions

Study conceptualisation was led by R.B. All authors contributed to the development of the research question and study design, with development of advanced statistical aspects led by J.Y. All authors contributed to the interpretation of the results. R.B. wrote the first draft of the paper. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. R.B., and J.Y.

had full access to all data in the study, take responsibility for the integrity of the data, and affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. The corresponding author had final responsibility for the decision to submit for publication.

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Conflicts of interests: The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

To guarantee the confidentiality of personal and health information, only the authors have had access to the data during the study. Access to the ISACS COVID-19 data is according to the information on the ISACS-Archives (NCT01218776) website. The source codes for this manuscript are uploaded on GitHub.

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Translational perspective

Early analyses at population-level data have suggested that COVID-19 might be associated with a higher risk of mortality in men compared with women, but these analyses had either limited ability to adjust for key confounding variables or did not consider the type of complications leading to death. In this register-based cohort study with matched propensity-based design of vaccine-naïve patients hospitalized with positive SARS-CoV-2 test prior to or during hospitalization, we estimated at patient-level data the sex-specific risks of organ dysfunctions and in-hospital death. In women, the estimated intensive care unit treatment benefit was a 14% reduction in risk of death compared with men, whereas the estimated effect in general wards was a 13% increase in risk for women compared with men. We showed that the adjusted risks for acute respiratory failure and acute kidney injury were comparable among women and men, regardless of the intensity of care. In contrast, female sex was associated with higher odds for acute heart failure, although this was limited to patients admitted to the general wards. Our results provide evidence that the risk and burden of acute heart failure in women with COVID-19 are substantial. Care pathways of women with COVID-19 should include attention to cardiovascular health. Results may inform future research and current guidelines.