Sex Differences in Clinical Outcomes Among Patients With COVID-19 and Cardiovascular Disease
— Insights From the CLAVIS-COVID Registry —

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E
vidence suggests that clinical outcomes in patients with COVID-19 depend on sex.1-4 Sex influences the outcomes of COVID-19, with men having higher mortality rates than women, especially among older adults.1-5 The sex-specific outcomes of COVID-19 result from the pathophysiological background that women mount stronger immune responses against viruses and vaccines and exhibit superior immune-mediated tissue repair capacities.5 In addition, the effect of sex on outcomes seems to be greater in COVID-19 than in other viral infections.3 Sex also plays a key role in cardiovascular disease and/or risk factors (CVDRF), which are common risk factors of COVID-19.6-8 For example, acute coronary syndrome due to atherosclerosis is more common among men, although coronary artery spasm or microvascular dysfunction, which are presumed to be caused by endothelial dysfunction, are more common among women.9 The sex difference in CVDRF may be attributed to multiple factors, such as genetic mechanisms, epigenetic mechanisms, and sex hormones.10

Sex difference is a pivotal prognostic factor for both COVID-19 and CVDRF; however, the effect of sex on...
outcomes in patients with COVID-19 and CVDRF has not been fully investigated. A better understanding of the role of sex in prognosis in a specific population would contribute to appropriate management of COVID-19. In addition, the prognosis of COVID-19 has been scarcely reported in Japan, where the distribution of CVDRF is known to differ significantly from that in Western countries.\textsuperscript{11}

In this study, we investigated the effect of sex on outcomes in patients with COVID-19 and CVDRF through a post hoc analysis of the Clinical Outcomes of COVID-19 Infection in Hospitalized Patients with Cardiovascular Diseases and/or Risk Factors (CLAVIS-COVID) registry, a Japanese nationwide study focusing on patients with COVID-19 and CVDRF.

Methods

IRB Information
This investigation conformed to the principles outlined in the Declaration of Helsinki. The study protocol, including the use of an opt-out consent method, was approved by the ethics committee of Toho University Omori Medical Center (No. M20253) and the local ethics committees of all participating institutions. Furthermore, this clinical study was registered with the University Hospital Medical Information Network (UNIM) Clinical Trial Registry (UMIN40,598) before the first patient was enrolled.

Study Design and Data Collection
The CLAVIS-COVID was a Japanese nationwide multicenter retrospective study sponsored by the Japanese Circulation Society. The registry investigated the characteristics and outcomes of patients hospitalized with COVID-19 between January 1, 2020 and May 31, 2020. For all patients, the presence of COVID-19 was defined as a positive polymerase chain reaction test result on nasal or pharyngeal swab specimens. All patients enrolled in this study were discharged by November 8, 2020, which was the deadline for data transfer.

The CLAVIS-COVID registry enrolled 1,518 patients with COVID-19, including 693 patients with underlying CVDRF.

In the present study, we analyzed 693 patients with COVID-19 and CVDRF. The study population was divided into 2 groups according to sex. The patient characteristics and in-hospital outcomes were evaluated according to sex. Underlying cardiovascular diseases included heart failure, coronary artery disease, myocardial infarction, peripheral artery disease, valvular heart disease, cardiac arrhythmia, pericarditis, myocarditis, congenital heart disease, pulmonary hypertension, deep vein thrombosis, pulmonary embolism, aortic dissection, aortic aneurysm, cerebral infarction/transient ischemic attack, use of cardiac devices (pacemaker, implantable cardioverter defibrillator, cardiac resynchronization therapy, and left ventricular assist device), heart transplantation, and cardiac arrest. Cardiovascular risk factors included hypertension, diabetes, and dyslipidemia.

Statistical Analysis
Patients with CVDRF were divided into 2 groups (men and women), and their baseline characteristics were compared. Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as the mean±SD or median with interquartile range. To evaluate significant difference between groups, Fisher’s exact test was used for categorical variables, and Student’s t-test or the Mann-Whitney test was used for continuous variables. Logistic regression analysis was used to estimate sex-specific differences in in-hospital outcomes. All analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA).
Sex and Outcomes in Patients With COVID-19

Results

Patient Characteristics

Of 1,518 patients with COVID-19, 693 (45.7%) patients with a history of CVDRF were selected for the analysis in the present study (Figure 1). Of the 693 patients with CVDRF, 64.8% were men and 96.1% were Japanese. The mean age of the 693 patients was 68 years.

Table 1 presents the baseline characteristics of patients with CVDRF stratified by sex. The mean age was significantly higher among women than men.

The most common symptom at the time of admission was cough, which was confirmed in 48.1% of patients; 6.8% of patients did not present any symptoms on admission. The proportions of typical symptoms of COVID-19, such as cough, the presence of sputum, fatigue, dyspnea, and anosmia, did not differ between men and women.

Maximum body temperature during hospitalization and baseline heart rate were significantly higher in men, whereas systolic blood pressure, respiratory rate, and peripheral oxygen saturation did not show significant differences according to sex (Table 1).

Laboratory Findings

Table 2 shows laboratory and imaging findings at the time of admission. There was no significant difference in the white blood cell count between men and women, although the proportion of lymphocytes and neutrophils were sig-

| Table 1. Patient Characteristics on Admission According to Sex |
|---------------------------------|---------|---|---|
|                                 | No. patients with data | Male (n=449) | Female (n=244) | P value |
| Age (years)                     | 693 | 66.2±14.3 | 72.2±15.0 | <0.001 |
| BMI (kg/m²)                     | 580 | 24.5±4.8 | 24.0±5.5 | 0.28 |
| Smoking                         | 655 | 237 (55.2) | 33 (14.6) | <0.001 |
| Comorbidities                   |        |        |        |        |
| Hypertension                    | 693 | 327 (72.8) | 186 (76.2) | 0.37 |
| Diabetes                        | 693 | 185 (41.2) | 81 (33.2) | 0.041 |
| Dyslipidemia                    | 693 | 172 (38.3) | 97 (39.8) | 0.74 |
| Heart failure                   | 693 | 37 (8.2) | 23 (9.4) | 0.67 |
| Ischemic heart disease          | 693 | 64 (14.3) | 21 (8.6) | 0.039 |
| Cardiac arrhythmia              | 693 | 44 (9.8) | 26 (10.7) | 0.79 |
| CI/TIA                          | 693 | 31 (6.9) | 21 (8.6) | 0.45 |
| Chronic lung disease            | 693 | 30 (6.7) | 5 (2.0) | 0.006 |
| CKD                             | 693 | 30 (6.7) | 18 (7.4) | 0.76 |
| Cancer                          | 693 | 49 (10.9) | 18 (7.4) | 0.14 |
| Baseline medication             |        |        |        |        |
| ACEI/ARB                        | 693 | 165 (36.8) | 100 (41.0) | 0.29 |
| β-blocker                       | 693 | 76 (16.9) | 35 (14.3) | 0.39 |
| Loop diuretic                   | 693 | 28 (6.2) | 28 (11.5) | 0.019 |
| Anticoagulants                  | 693 | 36 (8.0) | 16 (6.6) | 0.55 |
| Corticosteroids                 | 693 | 23 (5.1) | 14 (5.7) | 0.73 |
| Symptoms                        |        |        |        |        |
| Cough                           | 693 | 212 (47.2) | 121 (49.6) | 0.58 |
| Sputum                          | 693 | 79 (17.6) | 46 (18.9) | 0.68 |
| Fatigue                         | 693 | 157 (35.0) | 71 (29.1) | 0.13 |
| Dyspnea                         | 693 | 155 (34.5) | 71 (29.1) | 0.15 |
| Anosmia                         | 693 | 33 (7.3) | 16 (6.6) | 0.76 |
| No symptoms                     | 693 | 26 (5.8) | 21 (8.6) | 0.21 |
| Physical findings               |        |        |        |        |
| Maximum body temperature (°C)   | 644 | 38.1±0.9 | 37.9±0.9 | 0.002 |
| Heart rate (beats/min)          | 687 | 87.9±19.0 | 83.6±14.9 | 0.002 |
| Systolic BP (mmHg)              | 688 | 132.9±21.8 | 133.3±21.7 | 0.85 |
| Respiratory rate (/min)         | 540 | 21.0±6.2 | 20.6±6.0 | 0.44 |
| SpO₂ (%)                        | 689 | 94.8±4.6 | 95.2±5.0 | 0.28 |
| Oxygen on administration        | 672 | 174 (40.4) | 88 (36.5) | 0.36 |

Data are given as the mean±SD or n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CI, cerebral infarction; CKD, chronic kidney disease; SpO₂, peripheral oxygen saturation; TIA, transient ischemic attack.
significantly higher in men than in women. Hemoglobin and hematocrit were higher in men than in women, whereas the platelet count was significantly higher in women. The values of circulating inflammatory biomarkers, such as lactate dehydrogenase, C-reactive protein, and ferritin, were significantly higher in men than in women. Baseline serum albumin concentrations and estimated glomerular filtration rate were comparable between the 2 groups.

Table 2. Examination Findings on Admission According to Sex

| Laboratory findings                                      | No. patients with data | Male (n=449) | Female (n=224) | P value |
|---------------------------------------------------------|------------------------|--------------|----------------|---------|
| White blood cells (/μL)                                 | 678                    | 5,800 [4,400–7,430] | 5,570 [4,260–7,800] | 0.66    |
| Lymphocytes (%)                                         | 646                    | 15.3 [10–22.2] | 18.6 [12–28.2] | <0.001  |
| Neutrophils (%)                                         | 602                    | 76.0 [65.9–83.0] | 73.5 [62.3–81.4] | 0.007   |
| Hemoglobin (g/dL)                                       | 679                    | 14.0 [12.2–15.2] | 12.3 [11.3–13.6] | <0.001  |
| Hematocrit (%)                                          | 667                    | 41.0 [36.2–44.2] | 37.2 [33.8–40.8] | <0.001  |
| Platelets (×10^9/μL)                                    | 676                    | 17.7 [14.0–24.4] | 20.1 [16.1–25.6] | <0.001  |
| LDH (IU/L)                                              | 617                    | 297 [233.0–423.5] | 269 [211.3–379.8] | 0.004   |
| CRP (mg/L)                                              | 667                    | 6.7 [2.7–12.4] | 3.8 [0.7–10.2] | <0.001  |
| Ferritin (ng/mL)                                        | 317                    | 701.5 [377.8–1,333.5] | 232.0 [139.0–568.0] | <0.001  |
| Albumin (g/dL)                                          | 639                    | 3.3 [2.8–3.7] | 3.3 [3.0–3.8] | 0.61    |
| eGFR (mL/min/1.73 m²)                                   | 679                    | 85.3 [64.8–105.3] | 89.0 [66.7–107.4] | 0.39    |
| Positive cTn                                            | 147                    | 56 (52.3) | 23 (57.5) | 0.71    |
| BNP (pg/mL)                                             | 217                    | 28.8 [10.3–111.2] | 70.7 [16.9–170.7] | 0.027   |

Imaging findings

| Chest X-ray | GGO/consolidation/alveolar opacity | 630 | 325 (78.1) | 150 (70.1) | 0.032 |
|-------------|------------------------------------|-----|------------|------------|-------|
| Chest CT    | GGO/consolidation                  | 543 | 344 (93.2) | 154 (88.5) | 0.068 |
|             | GGO                                | 543 | 271 (73.4) | 121 (69.5) | 0.36  |
|             | Consolidation                      | 543 | 170 (46.1) | 71 (40.8)  | 0.27  |
|             | Pleural effusion                   | 543 | 52 (14.1)  | 24 (13.8)  | 0.99  |

Data are given as the median [interquartile range] or n (%). BNP, brain natriuretic peptide; CRP, C-reactive protein; CT, cardiac tomography; cTn, cardiac troponin; eGFR, estimated glomerular filtration rate; GGO, ground-glass opacity; LDH, lactate dehydrogenase.

Table 3. Treatments and In-Hospital Outcomes According to Sex

| Treatments                          | No. patients with data | Male (n=449) | Female (n=224) | P value |
|-------------------------------------|------------------------|--------------|----------------|---------|
| Mechanical ventilation              | 693                    | 125 (27.8)   | 27 (11.1)      | <0.001  |
| Renal replacement therapy           | 693                    | 24 (5.3)     | 2 (0.8)        | 0.002   |
| ECMO                                | 693                    | 23 (5.1)     | 2 (0.8)        | 0.002   |

In-hospital outcomes

| ARDS                                | 693                    | 70 (15.6)    | 27 (11.1)      | 0.11    |
| Sepsis                              | 693                    | 38 (8.5)     | 17 (7.0)       | 0.56    |
| Acute kidney injury                 | 693                    | 48 (10.7)    | 13 (5.3)       | 0.017   |
| MOF                                 | 693                    | 32 (7.1)     | 10 (4.1)       | 0.13    |
| Embolism (any)                      | 693                    | 28 (6.2)     | 2 (0.8)        | <0.001  |
| CI/TIA                              | 693                    | 4 (0.9)      | 1 (0.4)        | 0.66    |
| Pulmonary embolism                  | 693                    | 12 (2.7)     | 0              | 0.011   |
| Total hospital LOS (days)           | 693                    | 24.3±23.7    | 24.1±21.4      | 0.89    |

Data are given as the mean±SD or n (%). ARDS, acute respiratory distress syndrome; CI, cerebral infarction; ECMO, extracorporeal membrane oxygenation; LOS, length of stay; MOF, multiple organ failure; TIA, transient ischemic attack.

A high-sensitivity assay was used to measure cardiac troponin in 129 patients (92.1%). There were no significant difference in cardiac troponin according to sex. Baseline brain natriuretic peptide concentrations were significantly higher in female than male (Table 2).

**Imaging Findings**

Of the 693 patients with CVDRF, 630 (90.9%) underwent chest radiography and 543 (78.4%) underwent cardiac computed tomography (CT) on admission. The proportion

Circulation Reports Vol.4, July 2022
Sex and Outcomes in Patients With COVID-19

Treatments and In-Hospital Outcomes

Table 3 presents the treatment and in-hospital outcomes of patients after admission. There were no missing data on prognosis during the index hospitalization. During the hospital course, mechanical ventilation, renal replacement therapy, and extracorporeal membrane oxygenation were significantly more prevalent among men than women. The incidence rates of acute kidney injury, pulmonary embolism, and other embolisms were significantly higher among men. The presence of GGO/consolidation on cardiac CT at the time of admission was also more common in men, but the difference was not statistically significant (P=0.068).

Table 4. Univariate and Multivariate Analysis Models Evaluating the Effect of Sex on In-Hospital Mortality After Adjusting for Age and Medical Histories in the Overall Population and in Elderly (Age ≥80 Years) Patients Separately

|                      | Univariate analysis | Multivariate analysis |
|----------------------|---------------------|-----------------------|
|                      | OR 95% CI P value   | OR 95% CI P value     |
| Overall population   |                     |                       |
| Male sex             | 1.22 0.74–2.02 0.43 | 2.20 1.23–3.92 0.008  |
| Age                  | 1.10 1.07–1.12 <0.001 | 1.10 1.07–1.13 <0.001  |
| Hypertension         | 1.46 0.82–2.60 0.20  | 0.88 0.46–1.68 0.69   |
| Diabetes             | 0.70 0.43–1.16 0.17  | 0.93 0.53–1.62 0.80   |
| Heart failure        | 2.91 1.54–5.51 0.001 | 0.99 0.47–2.08 0.98   |
| Coronary artery disease | 2.59 1.40–4.79 0.002 | 1.63 0.81–3.28 0.17   |
| Chronic lung disease | 2.41 1.06–5.51 0.037 | 1.19 0.48–2.99 0.71   |
| Chronic kidney disease | 3.20 1.62–6.36 0.001 | 1.96 0.90–4.24 0.09   |
| Elderly patients     |                     |                       |
| Male sex             | 2.21 1.11–4.41 0.024 | 2.55 1.22–5.36 0.01   |
| Age                  | 1.05 0.98–1.12 0.19  | 1.07 0.99–1.15 0.09   |
| Hypertension         | 1.35 0.51–3.59 0.55  | – – –                  |
| Diabetes             | 0.45 0.19–1.06 0.07  | – – –                  |
| Heart failure        | 0.87 0.37–2.02 0.75  | 0.76 0.30–1.89 0.55   |
| Coronary artery disease | 1.28 0.53–3.06 0.59  | 1.16 0.45–2.95 0.76   |
| Chronic lung disease | 0.93 0.28–3.09 0.91  | 0.73 0.21–2.56 0.62   |
| Chronic kidney disease | 1.75 0.64–4.83 0.28  | 1.64 0.56–4.80 0.36   |

CI, confidence interval; OR, odds ratio.
men than women. In the overall population with COVID-19 and CVDRF (n=693), univariate analysis showed that sex was not significantly associated with in-hospital mortality (odds ratio [OR] 1.22; 95% confidence interval [CI] 0.74–2.02; P=0.43), whereas male sex was significantly associated with higher mortality than female sex in a multivariate analysis model adjusting for age and medical histories (Table 4). Figure 2 shows that the effect of sex on in-hospital mortality differed according to age, and male sex was significantly associated with worse outcomes in older (age ≥80 years) patients. Univariate and multivariate analysis models focusing on older (age ≥80 years) patients showed that male sex was an independent predictor of higher in-hospital mortality (Table 4).

Discussion

This study demonstrated sex-specific features and outcomes of patients with COVID-19 and CVDRF using post hoc analysis of CLAVIS-COVID, a nationwide Japanese registry focusing on individuals with COVID-19 and CVDRF. We found that male sex, especially in older (age ≥80 years) patients, was an independent predictor of higher in-hospital mortality in patients with COVID-19 and CVDRF after adjusting for age and medical histories, which are widely acceptable predictors of worse outcomes in COVID-19. 2,3,12,14

According to previous reports, approximately 60% of patients with COVID-19 are men, and the fatality rate is higher for men than women (2.8% and 1.7%, respectively). 2,3,7,12,14 Furthermore, men require intensive care more frequently than women. 12 In the present study, men had higher requirements for intensive care, such as mechanical ventilation, renal replacement therapy, and extracorporeal membrane oxygenation. A higher proportion of comorbidities, including cardiovascular diseases, may be associated with worse clinical courses and outcomes in men than in women, similar to findings reported previously. 1,17

We could not reveal the reason behind the increased death rate in older men with COVID-19 and CVDRF than in women; however, some previous studies proposed hypotheses related to the occurrence of COVID-19. 1–3,8 Of these hypotheses, differences in the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are considered one of the important factors contributing to the clinical course in each sex. In general, women have more robust immune systems than men. Estrogen and X chromosomes in women play a key role in the development of a stronger response to infectious disease. 18 Women are protected by stronger immune responses against viruses and exhibit superior immune-mediated tissue repair capacities than men. 5,10 Similarly, proinflammatory innate immunity chemokines and cytokines, such as interleukin (IL)-8, IL-18, and chemokine (C-C motif) ligand 5 (CCL5), are higher in men than women with COVID-19. 19 The T cell response to SARS-CoV-2 is more robust in women, and an increase in CD8 T cells compared with that in healthy volunteers is observed only in women. 20 These immunological differences between men and women may be associated with the different clinical courses and outcomes of COVID-19. Furthermore, the men had higher levels of C-reactive protein, lactate dehydrogenase, and ferritin, as well as higher rates of pulmonary complications at the time of admission, suggesting higher inflammation status in men than in women.

The T cell response to SARS-CoV-2 is negatively correlated with patient age in men, whereas the association between immune response and aging is not observed in women. 20 In addition, men aged >65 years have a relative deficiency of proinflammatory genomic signatures and plasma concentrations of inflammatory cytokines, such as IL-6. 21 The immunological background of vulnerability in older men leads to significantly higher in-hospital mortality. The weak response to SARS-CoV-2 supports the hypothesis that older men are expected to be good therapeutic targets for vaccines and therapies to increase their immune responses to SARS-CoV-2. Furthermore, given that the COVID-19 mortality rate is higher in patients with than without CVDRF, 2,12,14 these specific prevention and treatment strategies for COVID-19 may be more beneficial in older men with CVDRF, which is a more vulnerable population.

Study Limitations

This was a retrospective study, therefore we could not assess a considerable number of baseline serum biomarkers. The relatively small sample size compared with other nationwide registries in other countries 6,8,22 may have led to statistical non-significance in the univariate analysis model that evaluated the effect of sex on outcomes in patients with CVDRF. In addition, the Japanese government mandated the hospitalization of all patients with COVID-19 regardless of disease severity during patient enrollment, which may have consequently been associated with different prognoses in Japan. 24

Conclusions

This post hoc analysis of the CLAVIS-COVID registry revealed that male sex, especially among older patients, was an independent predictor of higher in-hospital mortality. Older men constitute a specific population that is vulnerable to COVID-19; therefore, strict prevention and management strategies against COVID-19 are needed for this group.

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Data Availability

The deidentified participant data will not be shared.

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