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ORIGINAL ARTICLE
Epidemiology

Sex Differences in Clinical Outcomes Among Patients With COVID-19 and Cardiovascular Disease

— Insights From the CLAVIS-COVID Registry —

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Background: Male sex is associated with a worse clinical course and outcomes of COVID-19, particularly in older patients. However, studies on COVID-19 patients with cardiovascular disease and/or risk factors (CVDRF), which are representative risk factors of COVID-19, are limited. In this study, we investigated the effect of sex on the outcomes of hospitalized COVID-19 patients with CVDRF.

Methods and Results: We analyzed 693 COVID-19 patients with CVDRF. Patients were divided into 2 groups based on sex, and baseline characteristics and in-hospital outcomes were compared between the 2 groups. The mean age of the 693 patients was 68 years; 64.8% were men and 96.1% were Japanese. In a univariate analysis model, 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). However, men had higher in-hospital mortality than women, especially among older (age ≥80 years) patients (OR 2.21; 95% CI 1.11–4.41; P=0.024). After adjusting for age and pivotal risk factors (hypertension, diabetes, heart failure, coronary artery disease, chronic lung disease, and chronic kidney disease), multivariate analysis suggested that male sex was an independent predictor of in-hospital mortality (OR 2.20; 95% CI 1.23–3.92; P=0.008).

Conclusions: In this post hoc analysis of a nationwide registry focusing on patients with COVID-19 and CVDRF, men had higher in-hospital mortality than women, especially among older patients.

Key Words: Cardiovascular diseases; COVID-19; Gender; Sex

Evidence suggests that clinical outcomes in patients with COVID-19 depends 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 results 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

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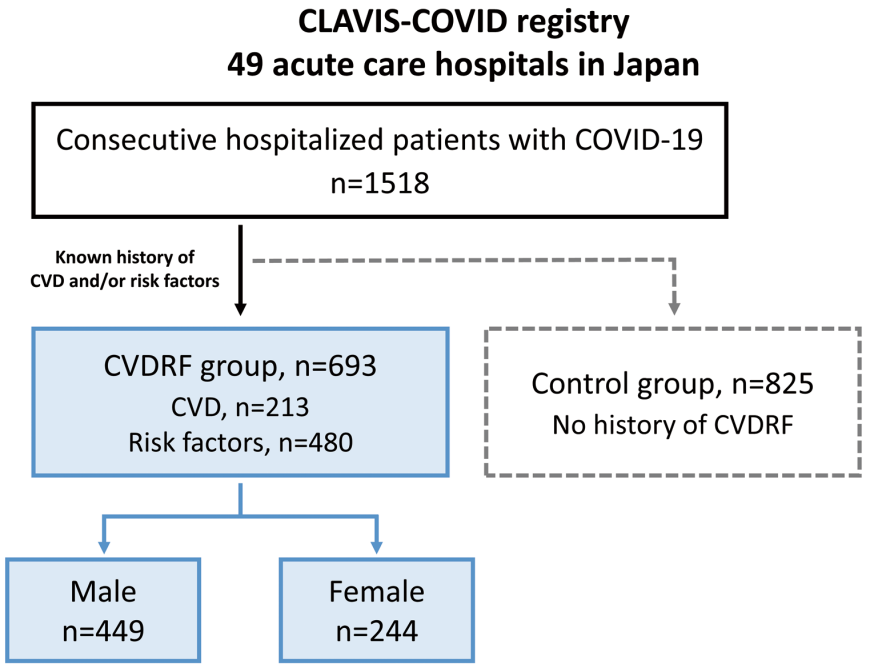

Figure 1. Clinical Outcomes of COVID-19 Infection in Hospitalized Patients with Cardiovascular Diseases and/or Risk Factors (CLAVIS-COVID) registry flow chart. CVD, cardiovascular disease; CVDRF, cardiovascular disease and/or risk factors.

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.[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).

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
SpO_2 (%)	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; SpO_2, peripheral oxygen saturation; TIA, transient ischemic attack.

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. Men were more likely than women to have a history of smoking, diabetes, ischemic heart disease, and chronic lung disease. The prevalence of hypertension and dyslipidemia did not differ significantly according to sex. The use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, and antiplatelet agents was comparable between men and women; however, loop diuretic use 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 2. Examination Findings on Admission According to Sex

	No. patients with data	Male (n=449)	Female (n=224)	P value
Laboratory findings				
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 (×10⁴/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

	No. patients with data	Male (n=449)	Female (n=224)	P value
Treatments				
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.

nificantly 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.

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

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 (n=693, in-hospital deaths, n=108)						
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 (n=172; in-hospital deaths, n=48)						
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.

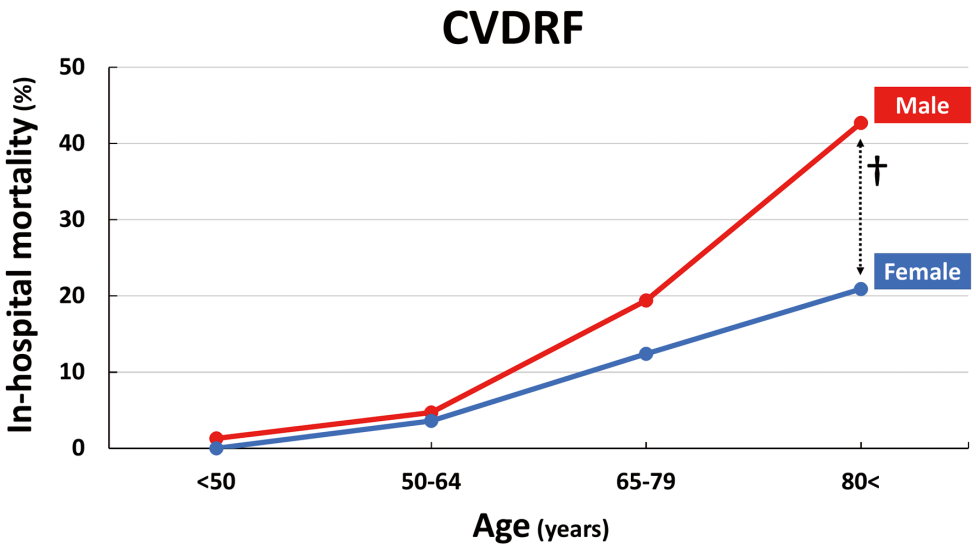

Figure 2. In-hospital mortality according to sex and age in patients with cardiovascular disease and/or risk factors (CVDRF). †P<0.05.

of patients with ground-glass opacity (GGO)/consolidation/alveolar opacity on chest radiography and cardiac CT was 75.4% and 91.7%, respectively. The proportion of patients with GGO/consolidation/alveolar opacity on chest X-ray was significantly higher among men than women. 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).

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 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).[2,7,12] Furthermore, men require intensive care more frequently than women.[15,16] 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.[1,18] 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.[5,19] 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.[20] 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 prognosis in Japan.[23]

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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