CLINICAL RESEARCH

Characteristics and impact of cardiovascular comorbidities on coronavirus disease 2019 in women: A multicentre cohort study[☆]

Caractéristiques et impact des comorbidités cardiovasculaires sur le COVID-19 chez les femmes : étude de cohorte multicentrique

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Summary
Background. — Although women account for up to half of patients hospitalized for coronavirus disease 2019 (COVID-19), no specific data have been reported in this population.
Aims. — To assess the burden and impact of cardiovascular comorbidities in women with COVID-19.
Methods. — All consecutive patients hospitalized for COVID-19 across 24 hospitals from 26 February to 20 April 2020 were included. The primary composite outcome was transfer to an intensive care unit or in-hospital death.
Results. — Among 2878 patients, 1212 (42.1%) were women. Women were older (68.3 ± 18.0 vs. 65.4 ± 16.0 years; $P < 0.001$), but had less prevalent cardiovascular comorbidities than men. Among women, 276 (22.8%) experienced the primary outcome, including 161 (13.3%) transfers to an intensive care unit and 115 (9.5%) deaths without transfer to intensive care unit. The rate of in-hospital death or transfer to an intensive care unit was lower in women versus men (crude hazard ratio [HR]: 0.62, 95% confidence interval [CI]: 0.53—0.72). Age (adjusted HR: 1.05 per 5-year increase, 95% CI: 1.01—1.10), body mass index (adjusted HR: 1.06 per 2-unit increase, 95% CI: 1.02—1.10), chronic kidney disease (adjusted HR: 1.57, 95% CI: 1.11—2.22) and heart failure (adjusted HR: 1.52, 95% CI: 1.04—2.22) were independently associated with the primary outcome in women. Elevated B-type natriuretic peptide/N-terminal prohormone of B-type natriuretic peptide (adjusted HR: 2.41, 95% CI: 1.70—3.44) and troponin (adjusted HR: 2.00, 95% CI: 1.39—2.88) concentrations at admission were also associated with the primary outcome, even in women free of previous coronary artery disease or heart failure.
Conclusions. — Although female sex was associated with a lower risk of transfer to an intensive care unit or in-hospital death, COVID-19 remained associated with considerable morbimortality in women, especially in those with cardiovascular diseases.
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Résumé
Justification. — Bien que les femmes constituent près de la moitié des patients hospitalisés pour une infection COVID-19, il n'a pas été reporté de données spécifiques dans cette population.
Objectifs. — Évaluer la fréquence et l'impact des comorbidités cardiovasculaires chez les femmes atteintes de la COVID-19.

Méthode. — Tous les patients hospitalisés de façon consécutive pour une infection COVID-19 dans 24 hôpitaux ont été inclus consécutivement entre le 29 février et le 20 avril 2020. Le critère de jugement principal est le transfert en unité de soins intensifs ou al survenue d'un décès intra-hospitalier.

Résultats. — Parmi les 2878 patients, 1212 (42,1 %) étaient des femmes. Les femmes étaient plus âgées (68,3 ± 18,0 vs 65,4 ± 16,0 ans, *p* < 0,001) mais présentaient moins de comorbidités cardiovasculaires par rapport aux hommes. Parmi les femmes, 176 (22,8 %) ont présenté un évènement incluant 161 patients (13,3 %) ont dû être transférées en unité de soins intensifs et 115 (9,5%) sont décédées, sans transfert dans une unité de soins intensifs. Le taux de décès intra-hospitaliers ou de transferts dans une unité de soins intensifs était moindre chez les femmes comparativement aux hommes (HR brut : 0,62, IC95 % : 0,53—0,72). L'âge (HR ajusté : 1,05 par tranche de 5 ans, IC95 %: 1,02—1,1), l'insuffisance rénale chronique (HR ajusté : 1,57, IC95 % : 1,11—2,22) et l'insuffisance cardiaque (HR ajusté: 1,52, IC95 % : 1,02—2,22) étaient indépendamment associés avec la survenue du critère de jugement principal chez la femme. Une élévation du peptide natriurétique (BNP) ou du NT-pro-BNP (HR ajusté : 2,41, IC95 % : 1,73—3,44) et une élévation de la troponine (HR ajusté : 2,00, IC95 % : 1,39—2,88) à l'admission étaient également associés avec la survenue du critère de jugement principal, y compris chez les femmes n'ayant pas de maladie coronaire ou d'insuffisance cardiaque avérée.

Conclusion. — Bien que le sexe féminin soit associé avec un risque moindre de transfert en unité de soins intensifs ou de survenue de décès hospitalier, la COVID-19 associée à une augmentation de la morbi-mortalité chez la femme en particulier chez celle ayant une maladie cardiovasculaire sous-jacente.

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Background

The world is facing the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Despite unprecedented reorganization of health resources and sanitary measures in most countries, hundreds of thousands of people have already died worldwide, and new wave(s) and seasonal re-emergence are feared [1—3].

The main characteristics and profiles of patients hospitalized for COVID-19 have been reported in case series from China [4,5], Europe [6—9] and the USA [10—12]. The association between cardiovascular comorbidities and the prognosis of COVID-19 was soon demonstrated [13—16]. Hypertension, diabetes, chronic kidney disease and other cardiovascular diseases have been associated with a significantly increased risk of death [17—20]. Furthermore, male sex has been identified as a risk for severe clinical presentation of COVID-19, with men representing up to 80% of patients admitted to an intensive care unit (ICU) [8,9]. However, although women accounted for 40—50% of patients in main series [4,11,12,21], no specific data have been reported so far in this population.

Through a large multicentre cohort of patients hospitalized for COVID-19, we aimed to describe the burden and impact of cardiovascular comorbidities in women.

Methods

Study settings

The Critical COVID-19 France study is a retrospective observational multicentre study initiated by the French Society of Cardiology, including all consecutive adult patients admitted to hospital with a diagnosis of SARS-CoV-2 infection in 24 centres between 26 February and 20 April 2020 (ClinicalTrials.gov identifier: NCT04344327). A complete list of the Critical COVID-19 France Investigators is provided in the Appendix.

According to World Health Organization criteria, SARS-CoV-2 infection is defined as a positive result of real-time reverse transcriptase polymerase chain reaction of nasal and pharyngeal swabs or lower respiratory tract aspirates (confirmed case), or as typical chest computed tomography patterns when laboratory testing results were inconclusive (probable case) [22]. Patients admitted directly to an ICU were excluded.

The Critical COVID-19 France study was declared to and authorized by the French data protection committee (Commission Nationale Informatique et Liberté [CNIL]; authorization No. 2207326v0), and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The

authors had full access to and take full responsibility for the integrity of the data. All authors have read and approved the manuscript as written.

Data collection

All data were recorded by local investigators on an electronic case report form via REDCap software (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA). Patient baseline information included demographic characteristics, main comorbidities and chronic medications. Heart failure was defined as history of heart failure with reduced or preserved left ventricular ejection fraction [23]. A glomerular filtration rate < 60 mL/min/1.73 m^2 (Modification of Diet in Renal Disease study equation) was considered to define chronic kidney disease [24]. Clinical variables, blood test results and chest computed tomography characteristics (when performed) were also recorded at admission. A cut-off value of B-type natriuretic peptide (BNP) > 50 pg/mL or N-terminal prohormone of BNP (NT-proBNP) > 300 pg/mL was used, and troponin elevation was defined as any value above each centre's threshold [25]. According to European guidelines, the degree of computed tomography lesions was based on visual assessment of parenchymal involvement, and categorized as limited (< 25%), moderate (25—50%) or severe (> 50%) [26]. Data on pharmacological therapies, mode of respiratory support and final vital status were also collected during hospitalization. The date of final follow-up for patients still hospitalized was 21 April 2020.

Outcomes

The primary composite outcome was transfer to an ICU or in-hospital death. An ICU was defined as a specialized hospital unit providing intensive care for critically ill or injured patients, staffed by specially trained medical personnel, and with equipment allowing for continuous monitoring and life support, including, if needed, invasive ventilation and haemodynamic and renal support. The secondary outcome was in-hospital death, including all deaths occurring during hospital stay (with or without transfer to an ICU). All medical interventions (including pharmacological agents to treat SARS-CoV-2) were left to the discretion of the referring medical team.

Statistical analysis

This report was prepared in compliance with the STROBE checklist for observational studies [27]. Categorical data are reported as counts and percentages. Continuous data are reported as means ± standard deviations for normally distributed data, and as medians (interquartile ranges) for non-normally distributed data. Comparisons used the χ^2 test or Fisher's exact test for categorical variables, and Student's t-test or the Mann—Whitney—Wilcoxon test, as appropriate, for continuous variables. Survival curves were plotted by the Kaplan—Meier method, and adjusted on main confounders. Censoring occurred when patients were still hospitalized without a primary outcome event at the end of follow-up. Cox proportional hazard models were used to identify factors associated with the primary and secondary

outcomes. Variables with probability values < 0.20 in univariate analyses were considered in multivariable models, with final selection based on the most favourable goodness-of-fit measures (Bayesian information criterion). The amount of missing data for each variable is presented in Table 1. A two-tailed P-value < 0.05 was considered statistically significant. All data were analysed using R software, version 3.6.3 (R Project for Statistical Computing, Vienna, Austria).

Results

Population

Among 2878 consecutive patients hospitalized for COVID-19, 1212 (42.1%) were women (Fig. 1). The main baseline characteristics of patients are compared according to sex in Table 1. Women were significantly older than men (68.3 ± 18.0 vs. 65.4 ± 16.0 years; $P < 0.001$), but had less prevalent cardiovascular comorbidities, including smoking (7.8% vs. 17.6%; $P < 0.001$), diabetes (21.1% vs. 25.6%; $P = 0.006$), heart failure (9.3% vs. 12.4%; $P = 0.013$), coronary artery disease (6.7% vs. 16.9%; $P < 0.001$) and peripheral artery disease (3.2% vs. 6.6%; $P < 0.001$). Women, however, more frequently presented with a history of asthma (8.5% vs. 5.2%; $P < 0.001$) and venous thromboembolic disease (9.1% vs. 6.1%; $P = 0.003$).

At hospital admission, women had lower blood concentrations of C-reactive protein (80.6 ± 76.9 vs. 97.4 ± 76.5 mg/L; $P < 0.001$), fibrinogen (5.6 ± 1.5 vs. 6.2 ± 1.7 g/L; $P < 0.001$) and ferritin (783 ± 1208 vs. 1313 ± 2217 μg/L; $P < 0.001$) compared with men. An elevated BNP or NT-proBNP concentration was more frequently observed in women (57.5% vs. 49.8%; $P = 0.002$), whereas troponin elevation tended to be less frequent compared with men (29.7% vs. 34.2%; $P = 0.06$). Severe pulmonary infiltration (16.3% vs. 21.0%; $P = 0.006$) and pulmonary embolism (3.7% vs. 6.3%; $P = 0.03$) were also less frequently found on the computed tomography scan in women.

High-concentration oxygen therapy (13.3% vs. 16.9%; $P = 0.01$), high-flow nasal cannula therapy (3.3% vs. 6.8%; $P < 0.001$) and invasive ventilation (9.2% vs. 15.5%; $P < 0.001$) were less frequently required in women (Table A.1), The prescription of antibiotics was also less frequent in women (70.8% vs. 77.1%; $P < 0.001$).

Sex differences in outcomes

Overall, 276/1210 (22.8%) women experienced the primary outcome ($n = 562/1663$, 33.8% in men; $P < 0.001$), including 161 (13.3%) transfers to an ICU and 115 (9.5%) deaths without transfer to an ICU. In addition, 24 women died in an ICU, giving a total of 139 (11.5%) deaths ($n = 223$, 13.4% in men; $P = 0.14$). The rate of in-hospital death or transfer to an ICU was lower in women versus men (adjusted hazard ratio [HR]: 0.62, 95% confidence interval [CI]: 0.53—0.72; $P < 0.001$), whereas the observed difference in overall in-hospital deaths did not reach statistical significance ($P = 0.41$) (Fig. 2). Table A.2 shows the factors associated with death among women in the univariate analysis. After adjustment on age, body mass index, diabetes, chronic kidney disease and heart failure, female sex

Table 1 Baseline characteristics of patients (n = 2878) according to sex.

Variables	n	Women (n = 1212)	Men (n = 1666)	P
Demographics				
Age (years)	2878	68.3 ± 18.0	65.4 ± 16.0	< 0.001
BMI (kg/m^2)	2493	28.0 ± 6.9	27.7 ± 5.3	0.32
Time from illness onset to hospitalization (days)	2777	6.6 ± 4.6	6.9 ± 4.7	0.05
Positive SARS-CoV-2 RT-PCR	2878	1131 (93.3)	1540 (92.4)	0.41
Cardiovascular risk factors				
Smoking	2810	93 (7.8)	285 (17.6)	< 0.001
Hypertension	2859	632 (52.4)	821 (49.7)	0.16
Diabetes	2860	254 (21.1)	423 (25.6)	0.006
Dyslipidaemia	2859	315 (26.2)	485 (29.3)	0.07
Family history of premature CVD	2713	11 (0.9)	33 (2.1)	0.03
Comorbidities				
Heart failure	2850	112 (9.3)	204 (12.4)	0.013
Coronary artery disease	2878	81 (6.7)	281 (16.9)	< 0.001
Atrial fibrillation	2852	170 (14.2)	246 (14.9)	0.62
Stroke	2837	114 (9.6)	139 (8.4)	0.32
Peripheral artery disease	2838	38 (3.2)	109 (6.6)	< 0.001
Asthma	2842	103 (8.5)	86 (5.2)	< 0.001
COPD	2878	48 (4.0)	116 (7.0)	< 0.001
Chronic kidney disease	2838	158 (13.2)	247 (15.0)	0.20
Malignancy	2878	182 (15.0)	233 (14.0)	0.47
Venous thromboembolic disease	2878	110 (9.1)	102 (6.1)	0.003
Treatment before hospitalization				
Anticoagulation	2878	162 (13.4)	256 (15.4)	0.15
Platelet antiaggregant	2878	213 (17.6)	414 (24.8)	< 0.001
Statins	2878	236 (19.5)	417 (25.0)	0.001
ACE inhibitors	2878	197 (16.3)	309 (18.5)	0.12
ARBs	2878	192 (15.8)	277 (16.6)	0.61
Diuretics	2878	241 (19.9)	323 (19.4)	0.78
Beta-blockers	2878	317 (26.2)	418 (25.1)	0.55
Aldosterone antagonists	2878	40 (3.3)	39 (2.3)	0.15
Oral antidiabetics	2878	156 (12.9)	295 (17.7)	0.001
Laboratory				
Leucocytes (G/L)	2827	7.30 ± 5.94	7.36 ± 4.46	0.77
Lymphocytes (G/L)	2785	1.44 ± 4.05	1.21 ± 2.95	0.11
Haemoglobin (g/dL)	2835	12.6 ± 1.8	13.5 ± 2.0	< 0.001
Platelets (G/L)	2807	231 ± 102	213 ± 96	< 0.001
C-reactive protein (mg/L)	2758	80.6 ± 76.9	97.4 ± 76.5	< 0.001
Fibrinogen (g/L)	1379	5.59 ± 1.52	6.23 ± 1.68	< 0.001
Ferritin (µg/L)	722	783 ± 1208	1313 ± 2217	< 0.001
Lactate dehydrogenase (U/L)	922	346 ± 178	385 ± 409	0.05
Glomerular filtration rate (mL/min/m^2)	2829	81.6 ± 30.2	81.6 ± 29.0	1.000
Elevated BNP or NT-proBNP[a]	1778	429 (57.5)	514 (49.8)	0.002
Troponin elevation[b]	1763	200 (29.7)	372 (34.2)	0.06
Abnormalities on chest CT				
Parenchymal involvement assessed on CT	2247			< 0.001
Minimal < 25%		439 (48.4)	514 (38.3)	
Moderate 25−50%		320 (35.3)	544 (40.6)	
Severe > 50%		148 (16.3)	282 (21.0)	
Pulmonary embolism on CT	1527	23 (3.7)	57 (6.3)	0.03

Data are expressed as mean ± standard deviation or number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; BNP: B-type natriuretic peptide; COPD: chronic obstructive pulmonary disease; CT: computed tomography; CVD: cardiovascular disease; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; RT-PCR: reverse transcriptase polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

[a] BNP > 50 pg/mL or NT-proBNP > 300 pg/mL
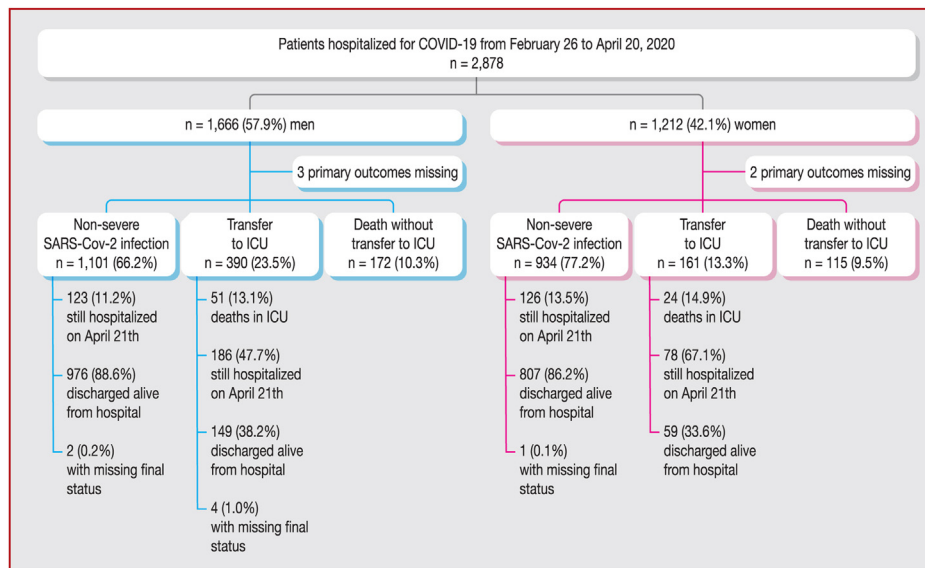
[b] Above each centre's threshold.

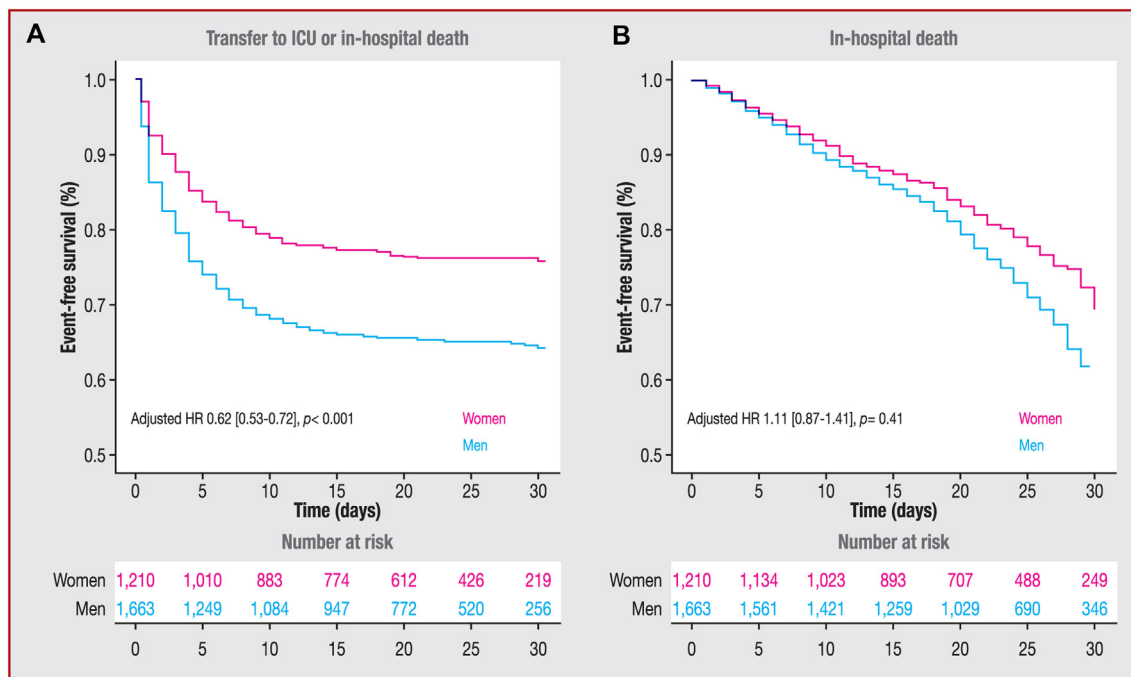**Figure 1.** Study flow chart. ICU: intensive care unit.

Figure 2. A. Survival without transfer to intensive care unit (ICU) or in-hospital death (adjusted on age, body mass index, chronic kidney failure, diabetes, hypertension, coronary artery disease, heart failure and dyslipidaemia). B. Survival without in-hospital death in women versus men (adjusted on age, chronic kidney failure, diabetes and heart failure).

remained significantly associated with a lower risk of experiencing the primary outcome (adjusted HR: 0.62, 95% CI: 0.52—0.71; $P < 0.001$; Table A.3). Women represented 29.2% of patients transferred to an ICU. As of 21 April 2020, 204 (16.8%) women were still hospitalized. The median length of hospitalization among the 866 (71.6%) women discharged alive was 7.0 (4—12) days, versus 8.9 (5—12) days in men ($P = 0.003$).

Impact of cardiovascular comorbidities

Factors associated with primary and secondary outcomes are presented in Table 2 and Table A.2, respectively. The proportion of women who experienced the primary outcome or died were, respectively, 37.8% and 25.9% in women with heart failure ($n = 112$), 30.9% and 24.7% in women with coronary artery disease ($n = 81$), 29.1% and 17.7% in women with

Table 2 Factors associated with primary outcome in women: univariate analysis.

Variables	Women				Men			
	Presence of primary composite outcome[a]		Univariate analysis HR (95% CI)	P	Presence of primary composite outcome[a]		Univariate analysis HR (95% CI)	P
	Yes (n = 276)	No (n = 934)			Yes (n = 559)	No (n = 1101)		
Demographics								
Age (years)	72.3 ± 16.3	67.1 ± 18.4	1.07 (1.03−1.11)[b]	< 0.001	68.2 ± 15.2	63.9 ± 16.3	1.05 (1.03−1.08)[b]	< 0.001
BMI (kg/m²)	29 ± 7.3	28 ± 6.8	1.15 (1.06−1.22)[c]	< 0.001	28.1 ± 5.5	27.5 ± 5.2	1.04 (1.01−1.07)[c]	0.02
Time from illness onset to hospitalization (days)	6.2 ± 4.2	6.7 ± 4.7	0.98 (0.96−1.01)	0.19	6.6 ± 4.5	7.1 ± 4.8	0.99 (0.97−1.01)	0.21
Cardiovascular risk factors								
Smoking	24 (8.9)	69 (7.5)	1.20 (0.79−1.82)	0.40	93 (17.2)	190 (17.7)	1.02 (0.81−1.27)	0.88
Hypertension	164 (59.6)	467 (50.3)	1.41 (1.10−1.79)	0.006	317 (57.2)	501 (45.8)	1.39 (1.18−1.65)	< 0.001
Diabetes	74 (26.9)	180 (19.4)	1.43 (1.10−1.87)	0.008	172 (31.0)	249 (22.8)	1.40 (1.17−1.68)	< 0.001
Dyslipidaemia	82 (30.0)	232 (25.0)	1.25 (0.97−1.62)	0.09	193 (34.6)	289 (26.5)	1.33 (1.12−1.58)	0.001
Familial premature CVD	3 (1.2)	8 (0.9)	1.15 (0.37−3.60)	0.81	14 (2.75)	19 (1.83)	1.33 (0.78−2.26)	0.29
Comorbidities								
Heart failure	42 (15.4)	69 (7.5)	1.98 (1.43−2.76)	< 0.001	84 (15.2)	117 (10.7)	1.33 (1.05−1.68)	0.02
Coronary artery disease	25 (9.1)	56 (6.0)	1.47 (0.97−2.21)	0.07	106 (19.0)	175 (15.9)	1.11 (0.90−1.37)	0.31
Atrial fibrillation	35 (12.7)	134 (14.5)	0.89 (0.62−1.26)	0.50	84 (15.2)	159 (14.5)	0.97 (0.77−1.22)	0.82
Stroke	29 (10.8)	85 (9.3)	1.14 (0.77−1.67)	0.64	53 (9.60)	85 (7.8)	1.15 (0.86−1.52)	0.33
Peripheral artery disease	11 (4.0)	27 (2.9)	1.32 (0.72−2.42)	0.36	40 (7.3)	69 (6.3)	1.12 (0.81−1.55)	0.47
Asthma	27 (9.8)	76 (8.1)	1.17 (0.79−1.75)	0.43	24 (4.3)	62 (5.6)	0.82 (0.54−1.23)	0.33
COPD	16 (5.8)	39 (4.2)	1.34 (0.81−2.23)	0.25	46 (8.2)	67 (6.1)	1.25 (0.93−1.70)	0.14
Chronic kidney disease	60 (22.2)	98 (10.6)	2.04 (1.53−2.72)	< 0.001	116 (21.1)	127 (11.7)	1.54 (1.25−1.89)	< 0.001
Malignancy	46 (16.7)	136 (14.6)	1.16 (0.85−1.60)	0.35	83 (14.8)	148 (13.4)	1.05 (0.83−1.33)	0.63
Venous thromboembolic disease	25 (9.1)	85 (9.1)	1.00 (0.67−1.51)	0.99	40 (7.2)	62 (5.6)	1.18 (0.86−1.63)	0.30
Immunodeficiency	18 (6.5)	61 (6.5)	0.94 (0.58−1.51)	0.79	25 (4.47)	43 (3.91)	1.06 (0.71−1.58)	0.76

Table 2 (*Continued*)

Variables	Women				Men			
	Presence of primary composite outcome[a]		Univariate analysis HR (95% CI)	P	Presence of primary composite outcome[a]		Univariate analysis HR (95% CI)	P
	Yes (n = 276)	No (n = 934)			Yes (n = 559)	No (n = 1101)		
Treatment before hospitalization								
Anticoagulation	32 (11.6)	129 (13.8)	0.87 (0.60—1.25)	0.44	91 (16.3)	162 (14.7)	1.03 (0.83—1.30)	0.73
Platelet antiaggregant	66 (23.9)	147 (15.7)	1.57 (1.19—2.07)	0.001	152 (27.2)	261 (23.7)	1.11 (0.92—1.34)	0.24
Statins	55 (19.9)	181 (19.4)	1.04 (0.78—1.40)	0.79	158 (28.3)	258 (23.4)	1.19 (0.99—1.44)	0.05
ACE inhibitors	49 (17.8)	149 (15.8)	1.15 (0.85—1.57)	0.36	117 (20.9)	191 (17.3)	1.19 (0.97—1.46)	0.09
ARBs	54 (19.6)	137 (14.7)	1.31 (0.97—1.77)	0.07	101 (18.1)	176 (16.0)	1.13 (0.91—1.40)	0.26
Diuretics	71 (25.7)	169 (18.1)	1.51 (1.15—1.98)	0.003	121 (21.6)	200 (18.2)	1.17 (0.96—1.44)	0.11
Beta-blockers	81 (29.3)	235 (25.2)	1.22 (0.94—1.58)	0.13	159 (28.4)	256 (23.3)	1.17 (0.97—1.41)	0.08
Aldosterone antagonists	15 (5.4)	25 (2.7)	1.79 (1.06—3.01)	0.03	10 (1.8)	29 (2.6)	0.72 (0.39—1.35)	0.32
Oral antidiabetics	45 (16.3)	111 (11.9)	1.34 (0.97—1.84)	0.08	123 (22.0)	171 (15.5)	1.41 (1.15—1.72)	0.01
Laboratory								
Leucocytes (G/L)	8.64 ± 8.20	6.89 ± 5.02	1.06 (1.03—1.09)	0.001	7.9 ± 4.2	7.1 ± 4.6	1.02 (1.01—1.03)	< 0.001
Lymphocytes (G/L)	1.67 ± 7.30	1.35 ± 2.28	1.02 (0.99—1.05)	0.48	1.1 ± 1.9	1.27 ± 3.4	0.96 (0.90—1.04)	0.34
Haemoglobin (g/dL)	12.2 ± 1.98	12.7 ± 1.70	0.88 (0.82—0.95)	0.002	13.5 ± 2.03	13.6 ± 2.0	0.99 (0.95—1.03)	0.63
Platelets (G/L)	223 ± 113	234 ± 99	1.00 (1.00—1.00)	0.17	204 ± 99.3	218 ± 94.4	0.99 (0.98—1.00)[d]	< 0.001
C-reactive protein (mg/L)	121 ± 85.8	68.4 ± 69.0	1.06 (1.05—1.07)[d]	< 0.001	120 ± 84.8	85.9 ± 69.2	1.05 (1.04—1.06)[d]	< 0.001
Fibrinogen (g/L)	6.11 ± 1.51	5.39 ± 1.48	1.38 (1.21—1.57)	< 0.001	6.4 ± 1.6	6.1 ± 1.7	1.11 (1.04—1.19)[e]	0.001
Ferritin (μg/L)	1064 ± 1369	692 ± 1140	1.21 (1.04—1.39)[e]	0.01	1832 ± 3396	1034 ± 1057	2.20 (1.63—1.95)[e]	< 0.001
Lactate dehydrogenase (U/L)	451 ± 274	314 ± 120	1.55 (1.39—1.72)[e]	< 0.001	484 ± 626	323 ± 133	1.16 (1.10—1.22)[e]	< 0.001
Glomerular filtration rate (mL/min/m²)	71.5 ± 33.1	84.7 ± 28.6	0.99 (0.98—0.99)	< 0.001	75.0 ± 29.9	85.1 ± 27.9	0.92 (0.90—0.95)[d]	< 0.001
Elevated BNP or NT-proBNP[f]	146 (72.3)	282 (51.9)	2.41 (1.70—3.44)	< 0.001	218 (56.8)	293 (45.5)	1.01 (0.86—1.18)	0.49

Table 2 (*Continued*)

Variables	Women				Men			
	Presence of primary composite outcome[a]		Univariate analysis HR (95% CI)	P	Presence of primary composite outcome[a]		Univariate analysis HR (95% CI)	P
	Yes (n = 276)	No (n = 934)			Yes (n = 559)	No (n = 1101)		
Troponin elevation[g]	70 (41.2)	130 (25.9)	2.00 (1.39—2.88)	< 0.001	172 (42.3)	198 (29.2)	0.84 (0.71—0.99)	0.03
Abnormalities on chest CT Parenchymal involvement assessed on CT				< 0.001				0.005
Minimal < 25%	42 (20.5)	397 (56.6)	Ref.		106 (24.3)	406 (45.1)	Ref.	
Moderate 25—50%	88 (42.9)	232 (33.1)	3.57 (2.40—5.38)		175 (40.0)	368 (40.9)	0.88 (0.76—1.01)	
Severe > 50%	75 (36.6)	72 (10.3)	9.77 (6.24—15.5)		156 (35.7)	126 (14.0)	1.15 (0.94—1.41)	
Pulmonary embolism on CT	4 (3.0)	19 (39)	0.80 (0.22—2.18)	0.80	18 (5.77)	39 (6.61)	1.00 (0.72—1.39)	0.68

Data are expressed as mean ± standard deviation or number (%), unless otherwise indicated. ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; BNP: B-type natriuretic peptide; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CT: computed tomography; CVD: cardiovascular disease; HR: hazard ratio; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide.

[a] Two women and three men with missing outcomes were excluded.
[b] Increment of 5.
[c] Increment of 2.
[d] Increment of 10.
[e] Increment of 1 standard deviation.
[f] BNP > 50 pg/mL or NT-proBNP > 300 pg/mL.
[g] Above each centre's threshold.

diabetes (n = 254), 26.1% and 15.2% in women with dyslipidaemia (n = 315) and 26.0% and 15.5% in women with hypertension (n = 632) (Fig. 3; respective proportions in men are shown in Panel B).

In women, age (adjusted HR: 1.05 per 5-year increment, 95% CI: 1.01—1.10; P = 0.02), body mass index (adjusted HR: 1.06 per 2-unit increment, 95% CI: 1.02—1.10; P = 0.001), chronic kidney disease (adjusted HR: 1.57, 95% CI: 1.11—2.22; P = 0.01) and history of heart failure (adjusted HR: 1.52, 95% CI: 1.04—2.22; P = 0.03) remained independently associated with the primary outcome. Age (adjusted HR: 1.28 per 5-year increment, 95% CI: 1.13—1.45; P < 0.001), diabetes (adjusted HR: 1.86, 95% CI: 1.02—3.38; P = 0.04) and history of heart failure (adjusted HR: 2.05, 95% CI: 1.09—3.84; P = 0.03) were independently associated with in-hospital death (Fig. 4).

Among men, body mass index (adjusted HR: 1.03, 95% CI: 1.001—1.07 per 2-unit increase; P = 0.04) was the only factor that remained independently associated with the primary outcome (Fig. A.1). Age (adjusted HR: 1.41. 95% CI: 1.33—1.50 per 2-year increase; P = 0.04) and chronic kidney disease (adjusted HR: 1.43, 95% CI: 1.05—1.95; P = 0.025) were independently associated with in-hospital death.

Prognostic value of cardiac biomarkers

Elevated BNP or NT-proBNP (crude HR 2.41, 95% CI 1.70—3.44; P < 0.001) and troponin elevation (crude HR 2.00, 95% CI 1.39—2.88; P < 0.001) at admission were strongly associated with outcomes in women (Table 2 and Table A.2). Among tested patients, 34.0% (146/429) of women with elevated BNP or NT-proBNP and 35.0% (70/200) of women with troponin elevation experienced the primary outcome, whereas 23.4% (100/428) and 22.5% (45/200) presented in-hospital death, respectively.

BNP and NT-proBNP concentrations remained significantly associated with the primary outcome (adjusted HR: 1.96, 95% CI: 1.42—2.70; P < 0.001) and in-hospital death (adjusted HR: 7.92, 95% CI: 4.10—15.31; P < 0.001) after adjustment on heart failure and coronary artery disease status. Troponin elevation remained associated with the primary outcome (adjusted HR: 1.64, 95% CI: 1.19—2.27;
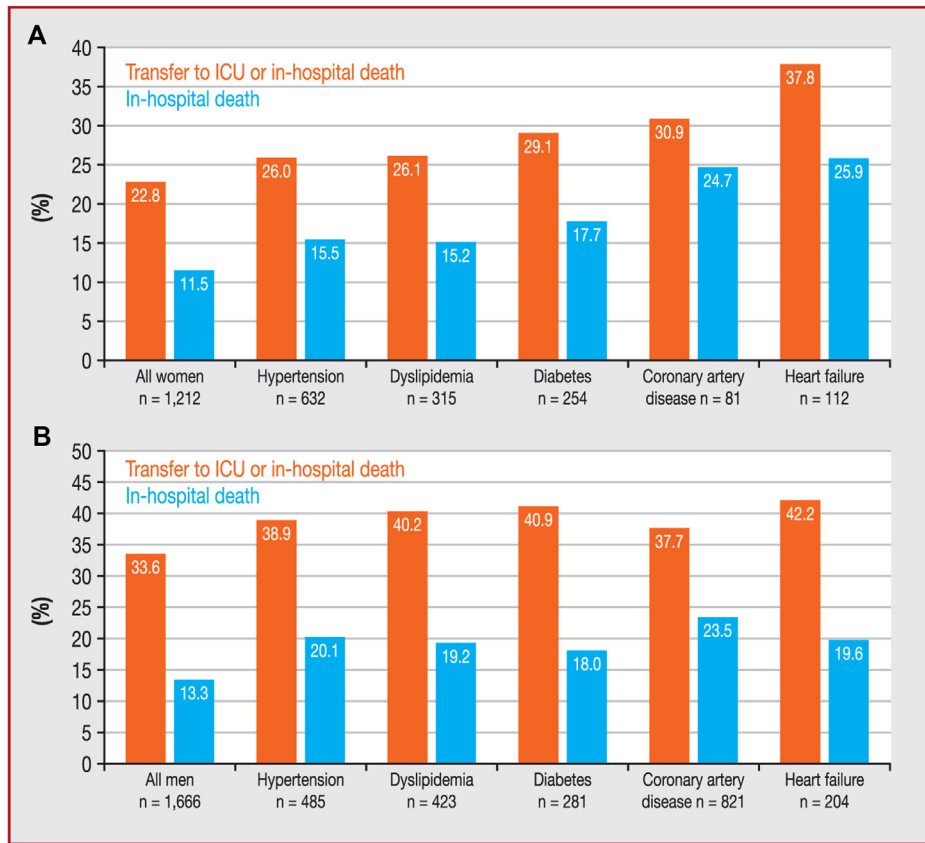
Figure 3. A. Impact of cardiovascular comorbidities on outcomes in women hospitalized for coronavirus disease 2019 (COVID-19). B. Impact of cardiovascular comorbidities on outcomes in men hospitalized for COVID-19. ICU: intensive care unit.
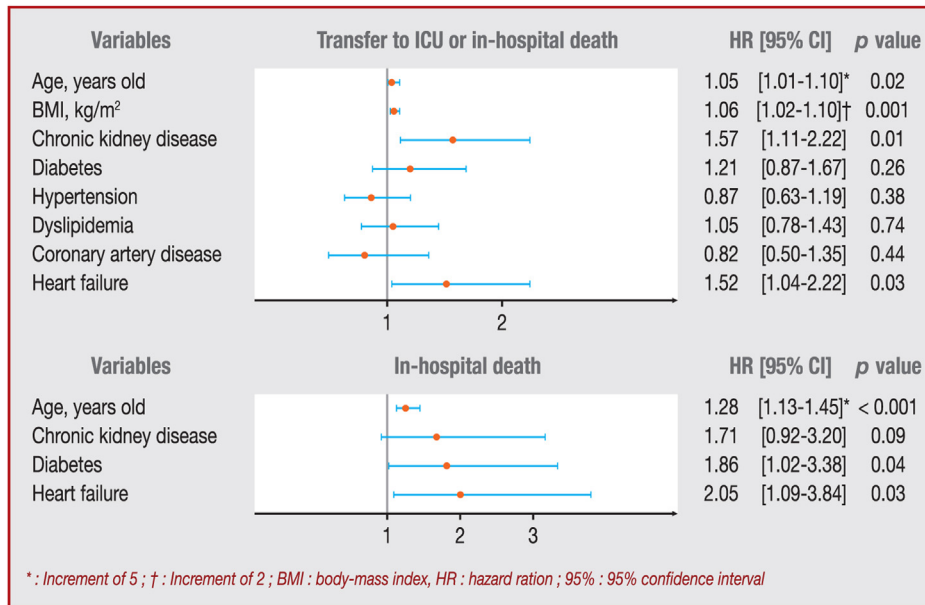

Figure 4. Forest plot of primary outcome and in-hospital death in women in the multivariable analysis. [a] Increment of 5. [b] Increment of 2.

$P = 0.003$) and in-hospital death (adjusted HR: 3.61, 95% CI: 2.16—6.01; $P < 0.001$) after adjustment on heart failure and coronary artery disease.

Discussion

In this multicentre cohort study, women hospitalized for COVID-19 were older than men, but presented less prevalent cardiovascular comorbidities. Although female sex was associated with a lower risk of a composite outcome (transfer to an ICU or in-hospital death), COVID-19 remained associated with high morbimortality in women with pre-existing cardiovascular diseases.

All published series reported a predominance of men among patients hospitalized for COVID-19, particularly among those with severe presentation; 50—60% of patients were men [4,11,12,21], and up to 80% of patients admitted to an ICU [8]. In this study, women accounted for 42% of patients hospitalized, and presented with a significantly lower prevalence of cardiovascular comorbidities. The primary outcome was less frequently experienced in women, mainly driven by fewer transfers to an ICU. In-hospital mortality between women and men was, however, similar.

Data regarding sex disparities in COVID-19 remain mostly speculative. Different mechanisms have been hypothesized to explain the lower propensity to develop severe forms in women. The higher prevalence of co-existing cardiovascular diseases in men probably partly underlies these differences. Our data, however, demonstrated that women less frequently experienced the primary outcome, even after consideration of main comorbidities. Another interesting potential explanation recently emerged from two independent cohorts of patients with heart failure, where plasma concentrations of angiotensin-converting enzyme 2 were higher in men than in women [28]. Angiotensin-converting enzyme 2 is not only an enzyme, but also a functional receptor on cell surfaces for SARS-CoV-2, and is highly expressed in the heart, testis, kidneys and lungs [29]. These increased plasma concentrations might reflect higher tissue expression, which may explain why men are more vulnerable to infection with or the consequences of SARS-CoV-2. This assumption may underly the lower levels of inflammation observed in our study in women, with lower blood concentrations of C-reactive protein, fibrinogen and ferritin, and less severe pulmonary infiltration on initial computed tomography scan. Hormonal factors have also been identified from preliminary studies. In an animal model, oophorectomy or treating female mice with an oestrogen receptor antagonist resulted in increased mortality as a result of SARS-CoV2 infection [30]. Sex chromosome genes and sex hormones contribute to the differential regulation of immune responses between the sexes, and these findings suggest that oestrogen signalling may protect females. Lastly, other behavioural and social differences that may favour women have been suggested, with previous studies reporting that women are more likely than men to follow hand hygiene practices and seek preventive care [31,32].

Our findings furthermore demonstrated that an elevation of BNP/NT-proBNP or troponin concentrations in women was associated with poorer outcomes, even after adjustment on heart failure or coronary artery disease status. Troponin concentration has already been highlighted as a risk factor for severe COVID-19, and seems rather to reflect a cardio-inflammatory response than an authentic myocardial injury [33—35]. These findings are consistent with previous viral epidemics, such as seasonal influenza infection or Middle East respiratory syndrome coronavirus (MERS-CoV) infection [36,37]. Similar results regarding NT-proBNP have been reported, even in heart failure-naïve patients [38]. The prognostic value of cardiac biomarkers, however, has not been assessed specifically in women. These results support the potential input of cardiac biomarkers in risk stratification of women hospitalized with COVID-19, even in those without known cardiovascular diseases.

Sex disaggregated data are essential for understanding the distributions of risk, infection and disease in the population, and the extent to which sex affects clinical outcomes. Whereas severe forms were less frequent in women, our results emphasized that morbimortality associated with COVID-19 remained considerable, especially in women with cardiovascular diseases. More than one-third of women with a history of heart failure experienced transfer to an ICU or death during hospitalization, and one-quarter died. Other independent factors associated with a higher risk of developing a severe form of COVID-19 included age, body mass index and chronic kidney disease. Identifying specific risk factors for severe COVID-19 presentation in women is essential to help clinical care, optimize early triage of patients and fight against health inequities in preventing bias in treating men and women. The recognition of phenotypical differences in severe case manifestations of COVID-19 in men and women is also a fundamental step towards understanding the effects of this health emergency on different individuals and to provide equitable interventions. Although cardiovascular comorbidities are now well-recognized risk factors for severe COVID-19 [19], no specific data had been reported in women. Poorer outcomes in men should not obscure the substantial morbimortality observed in women with COVID-19. Cardiovascular diseases are important to consider, and should incite careful follow-up and management of women with COVID-19.

Study limitations

We acknowledge some limitations. First, data collection was retrospective. However, the relatively short time between each patient hospitalization and gathering of their data — median 14 (9—19) days — allowed investigators to easily recover a large amount of data of interest. Second, a non-negligible proportion of patients was still hospitalized at the end of follow-up, with similar percentages of women and men (16.8% vs. 18.5%; $P = 0.48$). However, the probability of these hospitalized patients developing a severe form of disease was relatively low, because the primary outcome occurred most commonly during the first few days of hospitalization (median 3 days), whereas these patients were hospitalized for a median of 7 days. Furthermore, the heterogeneous durations of follow-up and censoring were integrated into our statistical approach using Cox regression analysis. Third, some patients with severe clinical presentations might not have been transferred to an ICU because of a lack of space, particularly the elderly. Considering

patients with similar severity, it is, however, very unlikely that men were selected over women to be transferred to an ICU. Furthermore, our results are consistent with the literature demonstrating a higher risk of severe COVID-19 in men [39,40]. Finally, although our results emerge from a large multicentre study, regional disparities may exist, and these findings need to be further investigated in other populations or health systems.

Conclusions

This multicentre study demonstrated that women hospitalized for COVID-19 were older than men and had less prevalent cardiovascular comorbidities. Although female sex was associated with a lower risk of transfer to an ICU or in-hospital death, COVID-19 remained associated with a significant morbimortality in women, especially in those with cardiovascular diseases.

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The other authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2021.04.002.

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