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Sex disparities in patients with suspected COVID-19 presenting at an emergency department in Switzerland

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Summary

AIMS OF THE STUDY: In the global COVID-19 pandemic, female sex is associated with comparable infection rates but better outcome. However, most studies lacked appropriate controls. We investigated whether these sex disparity findings are specific to patients with COVID-19 or generalizable to patients presenting to the emergency room (ER) with similar symptoms but no COVID-19.

METHODS: In this prospective cohort study, consecutive patients presenting with symptoms suggestive of COVID-19 were recruited at the ER of the University Hospital Basel, Switzerland from March to June 2020. Patients were categorized as SARS-CoV-2 positive (cases) or negative (controls) based on nasopharyngeal PCR swab tests. The final clinical diagnosis was determined for all patients. The primary outcome was a composite of intensive care admission, rehospitalization for respiratory distress and all-cause death within 30 days. We used Kaplan–Meier curves and Cox proportional hazards models to explore associations between sex and outcomes.

RESULTS: Among 1,081 consecutive ER patients, 191 (18%) tested positive for SARS-CoV-2, with an even sex distribution (17.9% female vs. 17.5% male, p = 0.855). In COVID-19 patients, female sex was associated with lower risk of hospitalization (51% vs. 66%, p = 0.034), lower necessity of haemodynamic support (8% vs. 20%, p = 0.029), lower rates of intubation (10% vs. 21%, p = 0.037) and the primary outcome (18% vs. 31%, p = 0.045; age-adjusted HR 0.536, 95%CI 0.290–0.989, p = 0.046) compared with male sex. Sex disparities were most prominent in patients ≥55 years (HR for composite primary outcome in women 0.415, 95%CI 0.201–0.855, p = 0.017). In contrast to the COVID-19 patients, no sex-specific differences in outcomes were observed in the unselected overall control group (age-adjusted HR 0.844, 95%CI 0.560–1.273, p = 0.419) or in a subgroup of controls with upper respiratory tract infections or pneumonia (age-adjusted HR 0.840, 95%CI 0.418–1.688, p = 0.624).

CONCLUSION: In this unselected, consecutive cohort study at a tertiary hospital in Switzerland, female sex is associated with better outcome in patients presenting to the ER with COVID-19. These sex disparities seem to be at least partly specific to COVID-19, as they were not observed in comparable controls.

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Introduction

A novel pneumonia-like illness outbreak that started in China in December 2019 resulted in a worldwide pandemic, as declared by the World Health Organization on March 11, 2020. The cause was identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense, single-stranded RNA virus [1]. Several studies have reported an association between male sex and severe outcome, including intensive care unit (ICU) admission and death, in SARS-CoV-2 infected patients [2–5]. On the other hand, there is little data providing information about sex differences in coronavirus disease 2019 (COVID-19) incidence. Recent global data reported by the Global Health 50/50 research initiative show that the infection rates seem to be comparable for both sexes [2, 6]. Regardless, most of these studies only included patients with confirmed SARS-CoV-2 infections and lacked adequate controls of patients with similar symptoms and disease severity but without SARS-CoV-2 infection. Thus, we

aimed to investigate whether sex disparities in outcomes are present in patients with COVID-19, and whether these are specific to COVID-19 or generalizable to all patients with symptoms suggestive of COVID-19 infection upon ER presentation.

Methods

Study design, population and inclusion criteria

The prospective cohort COronaVIrus surviVAl (COVIVA, ClinicalTrials.gov NCT04366765) study included unselected patients aged 18 years or older presenting to the emergency room (ER) of the University Hospital Basel, Switzerland, with clinically suspected or confirmed SARS-CoV-2 infection during the first wave of the COVID-19 pandemic between March and June, 2020. All patients with clinical suspicion of COVID-19 underwent nasopharyngeal SARS-CoV-2 swab tests. Patients were considered SARS-CoV-2 positive (cases) if, in addition to clinical signs and symptoms of COVID-19, one or more SARS-CoV-2 PCR swab tests performed on the day of ER presentation or within 14 days prior to or after the ER presentation were positive. The remaining patients with only negative SARS-CoV-2 swab test results were considered as controls. All participating patients or their legally authorized representatives consented by signing a local general consent form. This study was conducted according to the principles of the Declaration of Helsinki and was approved by the local ethics committee (EKNZ identifier 2020–00566).

The authors designed the study, gathered and analysed the data according to the STROBE guidelines for reporting observational studies [7] (table S1 in the appendix), vouched for the data and analysis, wrote the paper, and decided to submit it for publication.

Clinical assessment

All patients underwent a thorough clinical assessment by the treating ER physician according to local standard operating procedures (SOPs). Vital parameters including heart rate, blood pressure, oxygen saturation and respiratory rate were assessed in every patient. The patients' management was left to the discretion of the attending physicians in accordance with local SOPs, which did not contain any sex-specific recommendations.

Blood sampling

Blood samples were routinely taken at the time of ER presentation in every patient (both cases and controls). Besides routine laboratory parameters, high-sensitivity troponin T (hs-cTn), natriuretic peptides, D-dimers, procalcitonin and ferritin were measured for every patient as part of the local SOP for suspected COVID-19 patients. The timing and type of subsequent laboratory measurements during hospital stay were left to the discretion of the treating physicians and were not part of this study's protocol.

Follow-up

Thirty days after discharge, patients were contacted by telephone or in writing by research physicians or study nurses and information about current health, hospitalizations and adverse events were obtained using a predefined set of questions and item checklists. The records of other hospitals/ICUs and primary care physicians, as well as national death registries, were screened for additional information, if applicable.

Outcome

The primary outcome measure was a composite of ICU admission, rehospitalization due to respiratory complications and all-cause death at 30 days. Secondary outcomes included the components of the composite primary endpoint, case management and length of hospital stay, as well as incidence of intubation, haemodynamic support and acute respiratory distress syndrome during the course of the index hospitalization.

Adjudication of final diagnosis

To determine the final diagnosis that led to the index ER presentation and the clinical suspicion of COVID-19, trained physicians reviewed all medical data available, including 30 days post-discharge follow-up information, and chose from a predefined list the diagnosis which best fitted each patient. The predefined main categories included, but were not limited to, COVID-19, non-SARS-CoV-2 infections (e.g. other respiratory, gastrointestinal or urogenital infections), cardiovascular disease (acute coronary syndrome, rhythm disorder, congestive heart failure, pulmonary embolism), other non-infectious pulmonary disease (e.g. lung tumour, asthma, chronic obstructive pulmonary disease) and neurologic disease (e.g. stroke, seizure).

Statistical analysis

Data are expressed as medians and interquartile ranges (IQR) for continuous variables and as numbers and percentages (%) for categorical variables. All variables were compared using Mann–Whitney U tests for continuous variables and Pearson's chi-squared or Fisher's exact test for categorical variables, as appropriate. In this analysis, COVID-19 patients (cases) were compared to the unselected SARS-CoV-2 negative patients (overall control group, table S2 in the appendix), as well to the subgroup of patients with acute respiratory infections but no COVID-19 (respiratory control group, e.g. viral infection of the upper airways, bronchitis, pneumonia). The composite outcome was plotted in Kaplan–Meier curves and the log-rank test was used to assess differences between groups. The association between sex and the composite outcome was assessed using age-adjusted Cox proportional hazards models. In the case of multiple events, the time to the first event within 30 days was considered. Predefined subgroup analyses were performed for patients under and over 55 years of age and with or without cardiac disease, hypertension, diabetes, obesity, smoking and pneumopathy. The cut-off age of 55 years was chosen to assess sex disparities with respect to hormonal changes before and after menopause [8]. In a second multivariable Cox proportional hazards model, we aimed to further investigate the predictive value of sex if adjusted for age and numerous comorbidities using a stepwise-backward approach. The small

sample size and number of events meant that this was not possible. Prespecified subgroup comparisons were performed using multivariable Cox models, including treatment with a covariable interaction term, and were summarized using a forest plot.

All hypothesis testing was two-tailed and p-values of less than 0.05 were considered significant. No correction for multiple testing was applied. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY).

Results

Baseline

From March 2020 to June 2020, 1,086 patients presented at the ER with symptoms suggesting SARS-CoV-2 infection (e.g. dyspnoea, coughing, fever). Follow-up at 30 days was complete in 1,081 patients, meaning 5 patients were excluded from the analysis (none of them with COVID-19, see figure S1 in the appendix). The baseline characteristics of the unselected study population are listed in table S3 in the appendix. Overall, 43.4% were female and 56.6% male (p <0.001). 191 patients (18%) tested positive for SARS-CoV-2, with a median age of 57 years (IQR 44–69 years; table 1). The prevalence of COVID-19 was similar in women (n = 84, 17.9%) and men (n = 107, 17.5%, p = 0.855).

In the total study population, as well as in those with COVID-19, men had a significantly higher burden of comorbidity, more often had cardiac disease or coronary artery disease (CAD), were more often smokers, and had higher infection parameters (CRP, leucocytes), ferritin and hs-cTn levels compared to women. In contrast, procalcitonin levels were higher only in male SARS-CoV-2 positive patients, which was not the case for controls. Comparable findings were observed in the subgroups of SARS-CoV-2 positive patients <55 and ≥55 years (table S4 in the appendix).

Sex and outcome

SARS-CoV-2 positive female patients were less frequently hospitalized (51% vs. 66%, p = 0.034), intubated (10% vs. 21%, p = 0.037) or received haemodynamic support (8% vs. 20%, p = 0.029) than men. In contrast, no sex differences for the above-mentioned endpoints could be observed in the overall control group or the respiratory control group (table 2).

The composite primary outcome occurred in 144 of 1,081 (13%) patients, with a significantly higher incidence of 25% (48/191 patients) in COVID-19 cases compared to 11% (96/890 patients) in the overall control group (p<0.001) and 10% (33/323) in the respiratory control group.

Importantly, within the SARS-CoV-2 positive population the incidence of the composite outcome was significantly lower in women (18%, 15/84 patients) than in men (31%, 33/107 patients, log-rank p = 0.045; age-adjusted HR for female sex 0.536, 95%CI 0.290–0.989, p = 0.046). Both age and sex were independent predictors of the composite outcome in COVID-19 positive patients. In contrast, no sex-related differences were observed among the SARS-CoV-2 negative patients, neither in the overall control group (age-adjusted HR 0.844, 95%CI 0.560–1.273, p = 0.419) nor in the respiratory control group (age-adjusted HR 0.840, 95%CI 0.418–1.688, p = 0.624). Figure 1 shows the Kaplan–Meier curves for the occurrence of the composite outcome within 30 days for men and women in the SARS-CoV-2 positive and negative groups.

Figure S2 in the appendix shows the same for the respiratory control group.

When stratified by age, in COVID-19 patients under the age of 55 years, no sex differences in the primary outcome could be observed (HR 1.275, 95%CI 0.369–4.405, p = 0.701, figure 2).

In contrast, in COVID-19 patients ≥55 years, female sex was associated with a significantly superior event-free survival (HR 0.415, 95%CI 0.201–0.855, p = 0.017).

In additional subgroup analyses, a consistent trend towards better outcomes in women could be observed in the majority of subgroups without reaching the level of significance (figure 3).

Discussion

In this prospective cohort study of consecutive patients presenting with suspected SARS-CoV-2 infection to the ER of the University Hospital in Basel, Switzerland, we explored the impact of sex on clinical outcome in COVID-19 patients and in comparable controls.

First, the prevalence of confirmed COVID-19 infections in patients presenting to the ER was comparable between women and men. Second, the incidence of adverse clinical outcomes, defined as the composite of ICU admission, rehospitalization for respiratory distress or death within 30 days, was almost halved in women compared to in men with COVID-19, regardless of age. In addition, female patients with SARS-CoV-2 infection were less often hospitalized, intubated or in need of haemodynamic support. Third, sex-related differences in outcome were most prominent in patients aged 55 years and older and were seen across a range of additional subgroup analyses. Fourth, the observed sex disparities were consistently associated with COVID-19 infections and were not found in SARS-CoV-2 negative patients, nor in patients with other upper respiratory infections or pneumonia.

Among patients presenting to the ER with suspected COVID-19, male sex was more prevalent, as had already been observed in patients with similar symptoms before the pandemic [9]. However, in line with the most recent data, our results showed that the prevalence of SARS-CoV-2 infection was similar in men and women [2, 6, 10, 11].

Male sex and older age have been described as predictors of adverse outcome [4, 12–14]. However, whether this is specific to COVID-19 has not yet been clearly established. To the best of our knowledge, this is one of the few studies recruiting consecutive patients presenting to the ER with symptoms suggesting SARS-CoV-2 infection and therefore with parallel enrolment of an adequate control group. Importantly, we could demonstrate that the highest risk was observed in male COVID-19 patients over the age of 55, whose risk was substantially higher compared to their age-matched female counterparts.

Thus, a postulated protective effect of female sex hormones, which are presumably present in patients <55 years, seems to be neglectable regarding disease severity and outcome in symptomatic COVID-19 patients [15, 16]. In contrast, some data in mouse models even suggest a stronger immunological response driven by oestrogen. The sex disparities observed in this analysis could be explained by a plethora of possible reasons, such as differences in cardiovascular comorbidities, genetic factors and immune functions [15–17]. Some influencing factors could also possibly be attributed to gender, which is defined by social and cultural norms, roles and behaviours. As an example, women tend to take over the role of the primary caregiver not only at home, but also in the health care system. Based on our exploratory subgroup analyses, cardiovascular comorbidities and risk factors do not themselves seem to

Table 1:
Clinical characteristics.

	SARS-CoV-2 positive (Cases)			**SARS-CoV-2 negative** (Overall control group)			**SARS-CoV-2 negative with respiratory infection** (Respiratory control group)		
	All (n = 191)	**Female (n = 84)**	**Male (n = 107)**	**All (n = 890)**	**Female (n = 385)**	**Male (n = 505)**	**All (n = 323)**	**Female (n = 142)**	**Male (n = 181)**
Age – years [IQR]	57 [44,69]	57 [41,67]	58 [46,69]	57 [38,74]	61 [43,74]	57 [44,69]	59 [41,74]	57 [38,74]	61 [43,74]
Age ≥55 years	103 (54%)	45 (54%)	58 (54%)	499 (56%)	201 (52%)	298 (59%)	174 (54%)	70 (49%)	104 (58%)
Risk factors and history									
Comorbidity burden – median [IQR]	1 [0,3]	1 [0,3]	2 [0,3]	2 [0,3]	1 [0,3]	2 [1,4]	2 [0,3]	1 [0,3]	2 [1,4]
Cardiac disease	38 (20%)	11 (13%)	27 (25%)	261 (29%)	85 (22%)	176 (35%)	92 (29%)	30 (21%)	62 (34%)
CAD	21 (11%)	2 (2%)	19 (18%)	131 (15%)	26 (7%)	105 (21%)	43 (13%)	11 (8%)	32 (18%)
Hypertension	81 (42%)	33 (39%)	48 (45%)	367 (41%)	146 (37.9%)	221 (44%)	142 (44%)	58 (41%)	84 (46%)
Smoking	58 (30%)	19 (23%)	39 (36%)	361 (41%)	107 (28%)	254 (50%)	159 (49%)	50 (35%)	109 (60%)
COPD	9 (5%)	2 (2%)	7 (7%)	111 (12%)	36 (9%)	75 (15%)	58 (18%)	20 (14%)	38 (21%)
Diabetes	34 (18%)	12 (14%)	22 (21%)	137 (15%)	41 (11%)	96 (19%)	51 (16%)	18 (13%)	33 (18%)
Obesity	74 (39%)	30 (36%)	44 (41%)	278 (31%)	100 (26%)	178 (35%)	91 (28%)	33 (23%)	58 (32%)
Renal insufficiency	26 (14%)	10 (12%)	16 (15%)	145 (16.3%)	52 (14%)	93 (18%)	39 (12%)	16 (11%)	23 (13%)
Stroke/TIA	10 (5%)	3 (4%)	7 (7%)	70 (8%)	25 (7%)	45 (9%)	19 (6%)	5 (4%)	14 (8%)
Symptoms									
Beginning of symptoms in days – median [IQR]	7 [3,11]	7 [3,11]	7 [3,11]	3 [2,8]	3 [2,8]	3 [2,7]	3 [2,8]	3 [2,8]	3 [2,7]
Fever	104 (55%)	42 (50%)	62 (58%)	353 (40%)	155 (40%)	198 (39%)	147 (46%)	67 (47%)	80 (44%)
Chills	31 (16%)	11 (13%)	20 (19%)	165 (18.5%)	84 (22%)	81 (16%)	68 (21%)	38 (27%)	30 (17%)
Cough	126 (66%)	52 (62%)	74 (69%)	465 (52%)	207 (54%)	258 (51%)	242 (75%)	108 (76%)	134 (74%)
Dyspnoea	81 (42%)	38 (45%)	43 (40%)	438 (49%)	192 (50%)	246 (49%)	185 (57%)	82 (58%)	103 (57%)
Clinical parameters – median [IQR]									
Temperature* in °C	37.1 [36.8,38]	37.1 [36.8,38]	37.2 [36.8,38]	37 [36.5,37.7]	37 [36.6,37.5]	37 [36.5,37.7]	37 [36.5,37.7]	37 [36.6,37.5]	37 [36.5,37.7]
Respiratory rate*	20 [16,24]	20 [16,23]	20 [16,25]	18 [16,23]	19 [16,23]	18 [16,22]	18 [16,23]	19 [16,23]	18 [16,22]
SaO_2* in %	97 [95,98]	97 [96,98]	96 [94,98]	97 [95,98]	97 [96,99]	97 [95,98]	97 [95,98]	97 [96,99]	97 [95,98]
Heart rate*	89 [80,103]	89 [76,101]	90 [82,103]	88 [75,103]	89 [75,102]	87 [74,103]	88 [75,103]	89 [75,102]	87 [74,103]
Blood pressure – systolic* in mmHg	135 [122,149]	128 [116,153]	136 [124,148]	137 [121,156]	135 [120,156]	138 [123,155]	137 [121,156]	135 [120,156]	138 [123,155]
Blood pressure – diastolic* in mmHg	82 [71,90]	80 [71,86]	83 [72,90]	81 [72,90]	80 [70,86]	82 [75,91]	81 [72,90]	80 [70,86]	82 [75,91]
BMI in kg/m²	29 [25,32]	29 [25,33]	29 [25,32]	26 [23,30]	25 [22,31]	25 [23,29]	26 [23,30]	25 [22,31]	26 [23,29]
Laboratory parameters – median [IQR]									
Leucocytes in $*10^9$/l	6.27 [4.95,8.34]	5.96 [4.53,7.92]	6.71 [5.12,8.74]	8.48 [6.6,11.1]	9.1 [6.91,12.01]	8.82 [6.82,11.7]	8.82 [6.82,11.7]	8.48 [6.6,11.1]	9.1 [6.91,12.01]
Lymphocytes – absolute in $*10^9$/l	1.07 [0.72,1.57]	1.3 [0.82,1.77]	0.98 [0.69,1.35]	1.58 [0.92,2.14]	1.42 [0.9,2.02]	1.47 [0.9,2.08]	1.47 [0.9,2.08]	1.58 [0.92,2.14]	1.42 [0.9,2.02]
Lymphocytes in %	19.2 [11.9,26.9]	23.5 [14.8,30.6]	17.1 [11.4,22.6]	18.9 [10,28.7]	16.2 [9.6,25.5]	17.2 [9.8,26.6]	17.2 [9.8,26.6]	18.9 [10,28.7]	16.2 [9.6,25.5]
CRP in mg/l	28.9 [2.6,73.4]	12.1 [1.5,49.1]	36.2 [7.8,106.6]	5.9 [1,40.6]	10.4 [1.3,53.7]	7.6 [1.2,47.6]	7.6 [1.2,47.6]	5.9 [1,40.6]	10.4 [1.3,53.7]
Procalcitonin in µg/l	0.09 [0.059,0.182]	0.065 [0.059,0.146]	0.102 [0.059,0.237]	0.072 [0.059,0.287]	0.103 [0.059,0.332]	0.093 [0.059,0.332]	0.093 [0.059,0.332]	0.072 [0.059,0.287]	0.103 [0.059,0.332]
D-dimer in µg/l	0.58 [0.35,1.19]	0.6 [0.37,1.22]	0.57 [0.34,1.18]	0.56 [0.29,1.12]	0.59 [0.29,1.27]	0.58 [0.29,1.19]	0.58 [0.29,1.19]	0.56 [0.29,1.12]	0.59 [0.29,1.27]
Ferritin in ng/ml	387 [164,823]	193 [84,395]	578 [308,1194]	121 [62,224]	206.5 [116,410]	163 [85,329]	163 [85,329]	121 [62,224]	206.5 [116,410]
Creatinine in µmol/l	76 [62,95]	62 [54,75]	85 [74,100]	62 [55,77]	83 [71,99]	75 [61,93]	75 [61,93]	62 [55,77]	83 [71,99]
hs-troponin T in ng/l	7 [4,14]	5 [3,13]	8.5 [5,15]	5 [3,16.5]	12 [6,26]	9 [4,22]	9 [4,22]	5 [3,16.5]	12 [6,26]
NT-proBNP in pg/ml	77 [49,242]	66 [49,208]	82.5 [49,250]	110 [49,370]	117 [49,569]	114.5 [49,462]	114.5 [49,461.5]	110 [49,370]	117 [49,569]

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; IQR: interquartile range; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; TIA: transient ischaemic attack; SaO2: arterial oxygen saturation; BMI: body mass index; CRP: C-reactive protein; hs-troponin T: high-sensitivity troponin T; NT-proBNP: N-terminal pro brain natriuretic peptide

the primary factors accounting for the sex differences observed in COVID-19, as a numerical advantage for women was observed across most risk categories. The innate and adaptive immune response to infections is generally stronger in women than in men [18, 19]. Moreover, some sex-related immunological aspects change according to age, which leads to men being potentially more susceptible to infections and therefore having worse outcomes [15]. Thus, sex differences in immune composition and response may be another reason for the observed sex differences in SARS-CoV-2 infection outcome. The key finding of this study is that the observed sex disparities in COVID-19

Table 2:
Outcomes.

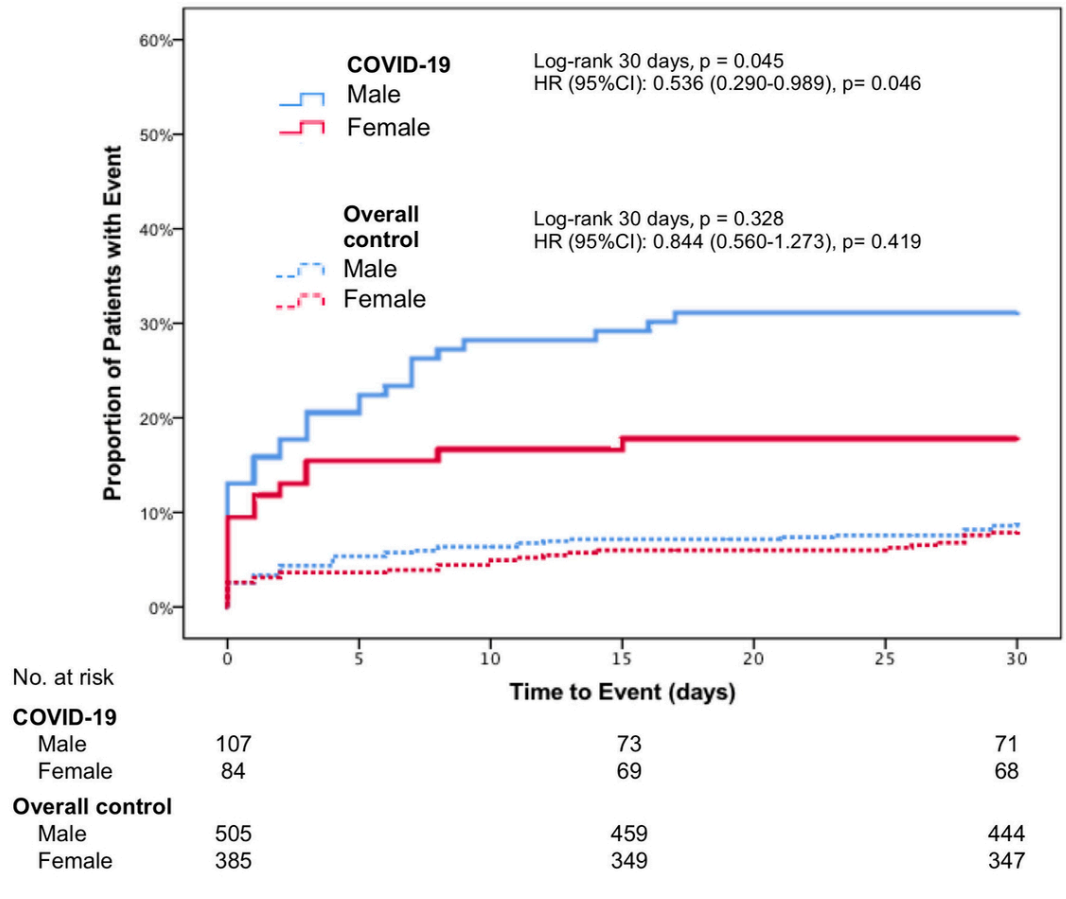
	SARS-CoV-2 positive (Cases)				**SARS-CoV-2 negative** (Overall control group)				**SARS-CoV-2 negative with respiratory infection** (Respiratory control group)			
	All (n = 191)	**Female (n = 84)**	**Male (n = 107)**	**p-value**	**All (n = 890)**	**Female (n = 385)**	**Male (n = 505)**	**p-value**	**All (n = 323)**	**Female (n = 142)**	**Male (n = 181)**	**p-value**
Case management												
– Outpatient	77 (40%)	41 (49%)	36 (34%)	0.034*	451 (50%)	209 (54%)	242 (48%)	0.069*	186 (57%)	87 (61%)	99 (54%)	0.215*
– Inpatient	114 (60%)	43 (51%)	71 (66%)		444 (50%)	179 (46%)	265 (52%)		138 (43%)	55 (39%)	83 (46%)	
Length of stay in days – median [IQR]	3 [0,8]	0 [0,6]	5 [0,11]	0.003*	0 [0,6]	0 [0,5]	0 [0,6]	0.022*	0 [0,6]	0 [0,5]	0 [0,6]	0.045*
Composite endpoint**	48 (25%)	15 (18%)	33 (31%)	0.045	96 (11%)	37 (10%)	59 (12%)	0.323	33 (10%)	13 (9%)	20 (11%)	0.328
– ICU admission	40 (21%)	13 (16%)	27 (25%)		63 (7%)	25 (6%)	38 (8%)		23 (7%)	10 (7%)	13 (7%)	
– All-cause death within 30 days	16 (8%)	5 (6%)	11 (10%)		61 (7%)	21 (6%)	40 (8%)		23 (7%)	8 (6%)	15 (8%)	
– Rehospitalization for respiratory complications	4 (2%)	1 (1%)	3 (3%)		24 (3%)	8 (2%)	16 (3%)		10 (3%)	4 (3%)	6 (3%)	
Intubation	30 (16%)	8 (10%)	22 (21%)		23 (3%)	11 (3%)	12 (2%)		15 (5%)	7 (5%)	8 (4%)	
Haemodynamic support	28 (15%)	7 (8%)	21 (20%)		26 (3%)	10 (3%)	16 (3%)		14 (4%)	6 (4%)	8 (4%)	
ARDS	26 (14%)	7 (8%)	19 (18%)		6 (1%)	2 (1%)	4 (1%)		4 (1%)	2 (1%)	2 (1%)	

* Analyses and p-values are exploratory

** Admission to ICU, rehospitalization for respiratory complication and all-cause death within 30 days

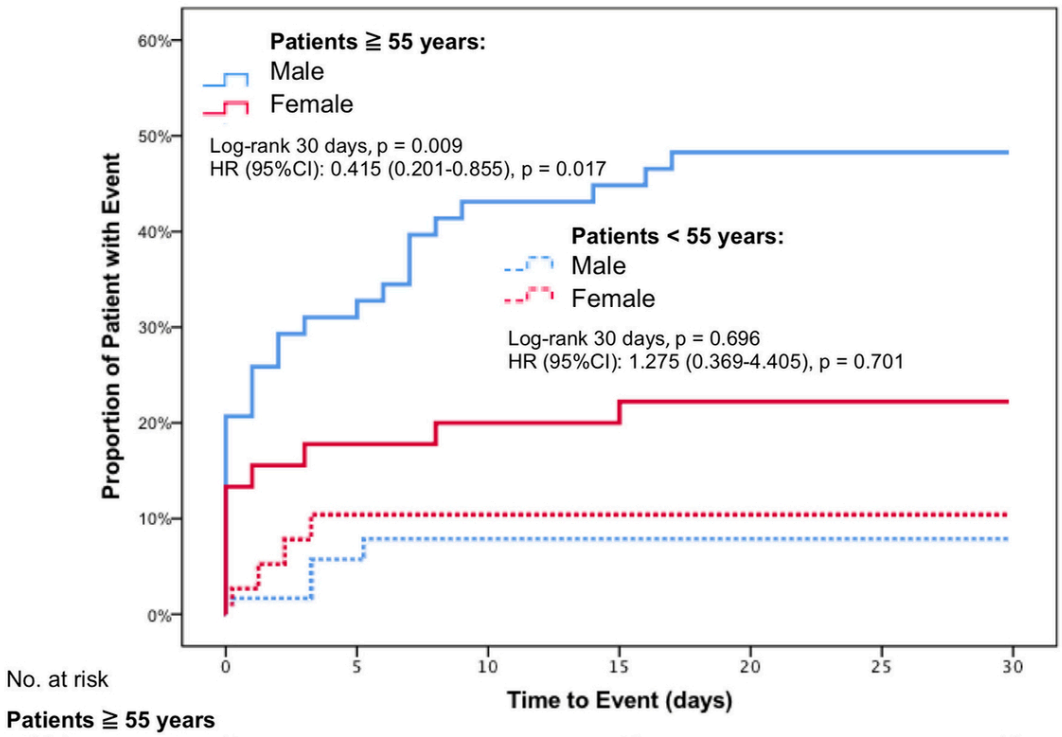
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; IQR: interquartile range; ICU: intensive care unit; ARDS: acute respiratory distress syndrome

Figure 1: Composite outcome of admission to ICU, rehospitalization for respiratory complication and death within 30 days in COVID-19 cases and overall control; depicted hazard ratios (HR) are age-corrected.



could not be seen in either the control group of unselected patients presenting with symptoms suggestive of COVID-19 but testing negative for SARS-CoV-2 or in a subgroup of patients with other upper respiratory infections and pneumonia. Accordingly, the sex disparities seem not to be generalizable to all patients presenting to the ER

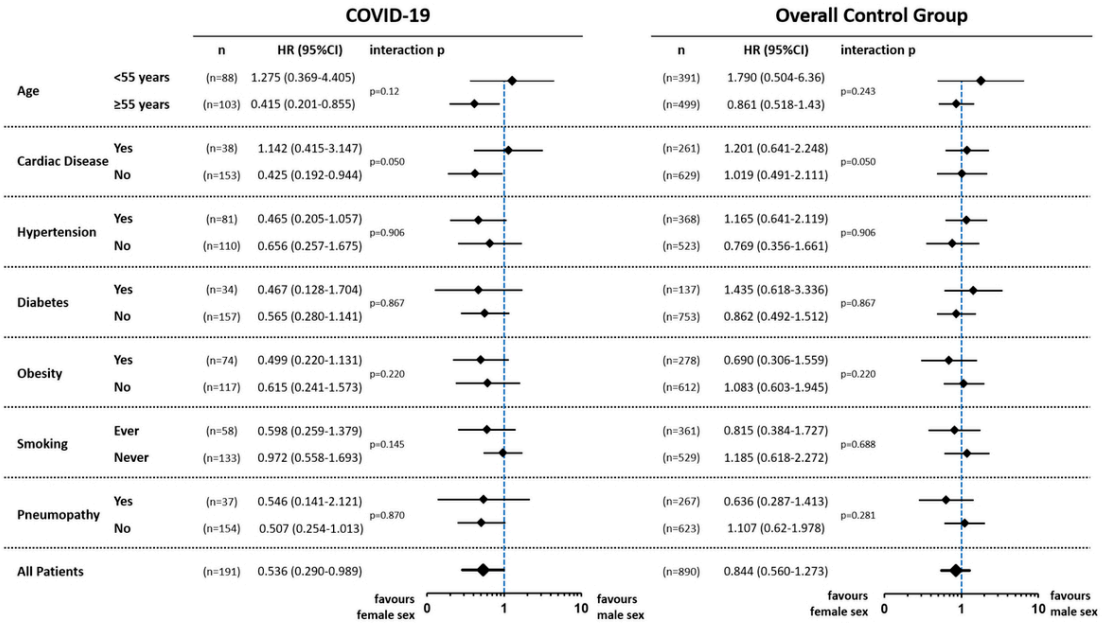
Figure 2: Composite outcome of admission to ICU, rehospitalization for respiratory complication and death within 30 days in SARS-CoV-2 positive patients under and over the age of 55 years.



No. at risk

Patients ≧ 55 years			
Male	49	42	40
Female	39	34	33
Patients < 55 years			
Male	58	31	29
Female	45	35	34

Figure 3: Forest plot showing age-adjusted hazard ratios (HR) and their corresponding 95% confidence intervals to quantify the impact of sex on the composite primary outcome in predefined subgroups within the COVID-19 cases (first column) and the controls (second column).



with symptoms suggestive of COVID-19, but may be related to disease-specific mechanisms involved in COVID-19.

Limitations

The main limitation of our study is its single centre design, with all data coming from one Swiss tertiary centre. However, during the current COVID-19 pandemic the number of affected patients, disease severity and the overloading of limited health care resources have differed widely between regions and health care systems. While most of the data reported are from severely affected regions, our data represent a typical Central European setting with a health care system that was not overloaded. Accordingly, event rates observed in this analysis are lower than the ones reported from North America or China [20, 21]. Second, the study may be insufficiently powered for multivariable analysis due to the limited number of SARS-CoV-2 positive patients, and also, only adjusting for age could have led to substantial residual confounding. Accordingly, no direct causalities can be extrapolated from our findings, as our data only allow us to explore associations. Nevertheless, given the design of this study (i.e. consecutive inclusion of unselected control patients presenting with comparable symptoms in the same time period), the observed results still add valuable information to the literature. In particular, they allow us to put findings observed in COVID-19 patients into perspective when compared with other acute conditions, including respiratory infections from other causes. Our findings need to be validated in larger future studies, as residual confounding could be substantial. Third, the patients for this analysis were recruited if they had symptoms suggesting COVID-19, leading to their triage to the ER during the first wave of the pandemic. Therefore, our findings cannot be extrapolated to the general population or to asymptomatic patients with SARS-CoV-2 infection.

Conclusion

Despite similar prevalences of SARS-CoV-2 infection in women and men, female sex is associated with better outcome in symptomatic COVID-19 patients presenting to the ER, particularly in patients aged years. Sex disparities seem to be specific to COVID-19, as they were not observed in comparable controls. Further studies are needed in order to explain the underlying mechanisms.

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Potential competing interests

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Authors not named here have disclosed no conflicts of interest.

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Appendix

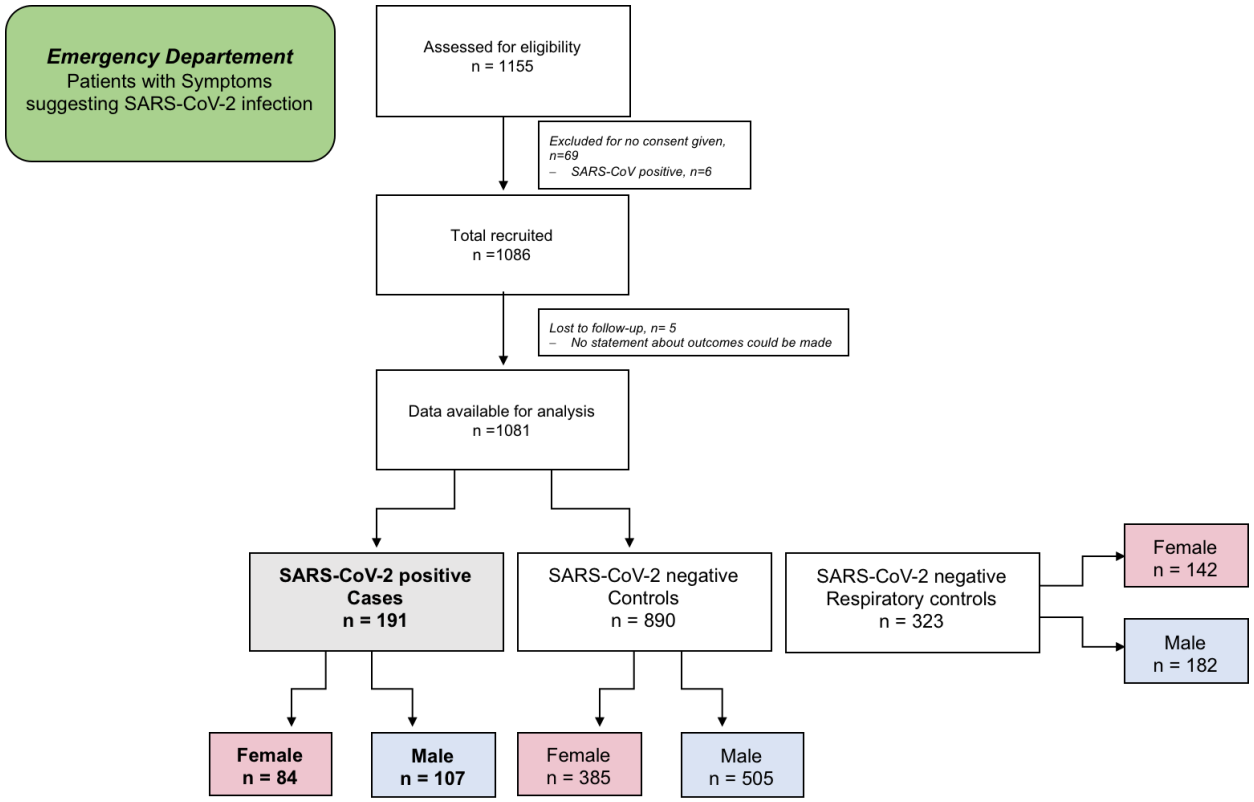

Figure S1: Flow diagram for patient inclusion

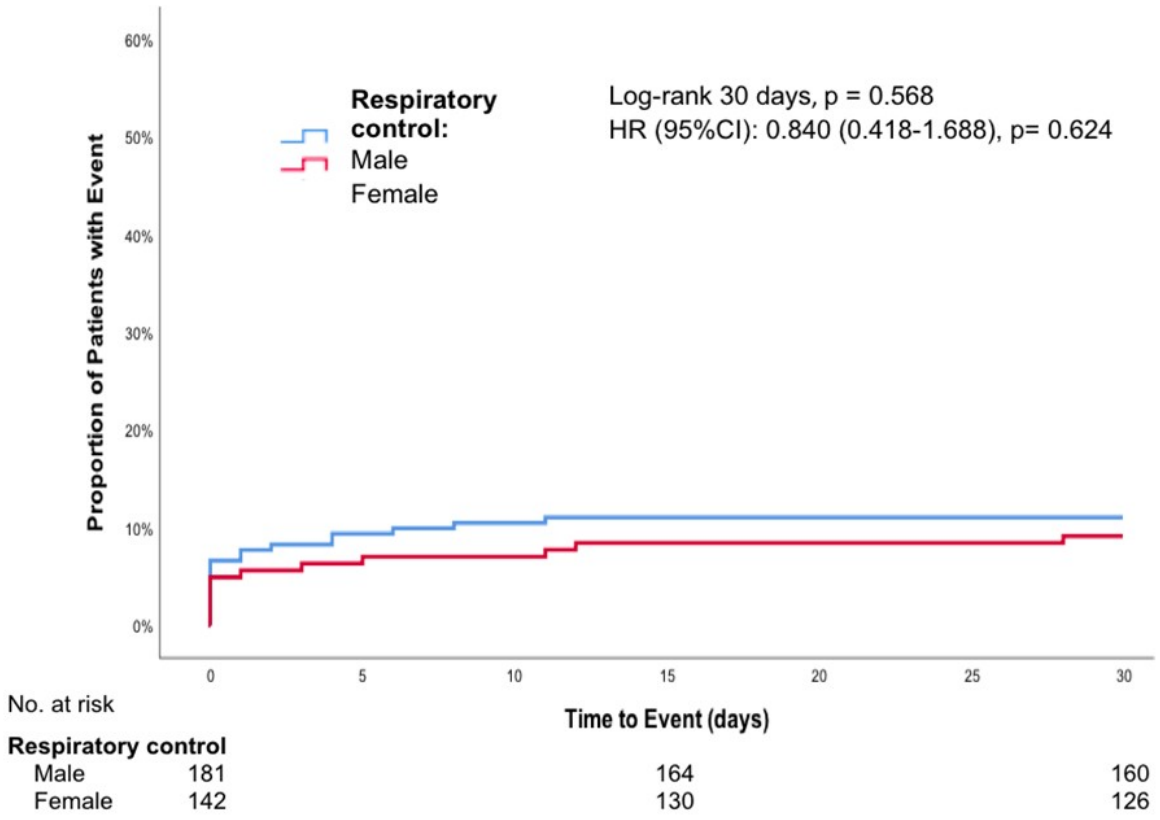

Figure S2: Composite Outcome of admission to ICU, rehospitalization for respiratory complication, death in 30 days in SARS-CoV-2 **negative** patients with **respiratory infection (respiratory control group)**

Table S1: STROBE Statement—Checklist of items that should be included in reports of case-control studies (1)

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5-8
		(*b*) For matched studies, give matching criteria and the number of controls per case	5-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	5-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8

		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how matching of cases and controls was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	9-10
		(c) Consider use of a flow diagram	9/Supplement Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	9-10
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	9-10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls.

Table S2: Final diagnosis in controls. Patients can be adjudicated to more than one diagnosis.

Final diagnosis	All (n=890)	Female (n=385)	Male (n=505)
Post-COVID-19	18	5	13
Infection	506	216	290
- Viral respiratory infection	227	105	122
- Bacterial pneumonia	96	37	59
- Non-respiratory infection	183	74	109
Pneumopathy	84	33	51
Cardiovascular	131	48	83
- ACS	17	4	13
- Hypertensive crisis	16	9	7
- Atrial fibrillation	6	1	5
- Syncope	4	3	1
- Cardiac decompensation	68	19	49
- Other	20	12	8
Neurological	30	14	16
Psychological	56	28	28
Pain/Trauma	77	34	43
Other	76	37	39

Post-COVID-19: Post-COVID-19 Syndrome in which symptoms continue past 12 weeks(2); ACS: acute coronary syndrome

Table S3: Clinical characteristics of the unselected study population				
	All **n = 1081**	**Female** **n = 469**	**Male** **n = 612**	**p-value**
Age – years [IQR]	59 [42,73]	57 [39,74]	60 [44,73]	0.093
Risk factors and History				
Comorbidity burden - median [IQR]	2 [0,3]	1 [0,3]	2 [1,4]	<0.001
Cardiac disease	299 (28%)	96 (21%)	203 (33%)	<0.001
CAD	152 (14%)	28 (6%)	124 (20%)	<0.001
Hypertension	448 (41%)	179 (38%)	269 (44%)	0.056
Smoking	429 (39%)	126 (27%)	293 (48%)	<0.001
COPD	119 (11%)	37 (8%)	82 (13%)	0.004
Diabetes	171 (16%)	53 (11%)	118 (19%)	<0.001
Obesity	352 (33%)	130 (28%)	222 (63%)	0.003
Renal insufficiency	171 (16%)	62 (13%)	109 (18%)	0.04
Stroke/TIA	80 (7%)	28 (6%)	52 (9%)	0.116
Symptoms				
Begin of symptoms in days - median [IQR]	4 [2,9]	4 [2,10]	4 [2,9]	0.419
Fever	457 (42%)	197 (42%)	260 (43%)	0.874
Chills	196 (18%)	95 (20%)	101 (17%)	0.112
Cough	591 (55%)	259 (55%)	332 (54%)	0.749
Dyspnoe	519 (48%)	230 (49%)	289 (47%)	0.553
Clinical parameters – median [IQR]				
Temperature* in °C	37 [36.5,37.7]	37 [36.6,37.7]	37 [36.5,37.5]	0.359
Respiratory rate*	19 [16,23]	19 [16,23]	18 [16,23]	0.774
SaO2* in %	97 [95,98]	97 [96,99]	97 [95,98]	<0.001
Heart rate*	88 [75,103]	89 [75,102]	87 [75,103]	0.727
Blood pressure - systolic* in mmHg	136 [121,154]	135 [119,155]	137 [123,154]	0.076

Blood pressure - diastolic* in mmHg	81 [72,90]	80 [70,86]	82 [74,91]	<0.001
BMI in kg/m²	26 [23,30]	26 [23,31]	26 [24,30]	0.619
Laboratory parameters - median [IQR]				
Leucocytes in*10 9/l	8.34 [6.34,11.09]	8.06 [6.06,10.8]	8.56 [6.58,11.57]	0.011
Lymphocytes – absolute in *10 9/l	1.38 [0.87,2.01]	1.48 [0.91,2.07]	1.33 [0.84,1.98]	0.036
Lymphocytes - in %	17.7 [10.1,26.6]	20.1 [11,28.8]	16.2 [9.9,25]	0.001
CRP in mg/l	9.9 [1.3,52.7]	6.3 [1,42.9]	12.3 [1.5,61.8]	0.001
Procalcitonin in µg/l	0.091 [0.059,0.263]	0.071 [0.059,0.202]	0.103 [0.059,0.278]	0.031
D-Dimer in µg/l	0.58 [0.29,1.19]	0.58 [0.30,1.14]	0.59 [0.29,1.23]	0.903
Ferritin in ng/ml	184 [91,389]	125.5 [66,261]	242 [129,504]	<0.001
Creatinine in µmol/l	75 [61,93]	62 [55,77]	83 [71,99]	<0.001
hs-Troponin T in ng/l	8 [4,21]	5 [3,16]	11 [5,24]	<0.001
NT-proBNP in pg/ml	105.5 [49,430.5]	99 [49,349]	108 [49.512]	0.480

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; IQR: interquartile range; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack; SaO2: arterial oxygen saturation; BMI: body mass index; CRP: C-Reactive Protein; hs-Troponin T: high-sensitivity troponin T; NT-proBNP: N-terminal pro brain natriuretic peptide

Table S4: Clinical characteristics in COVID-19 (cases group)								
	Age ≥ 55 years				Age < 55 years			
	All n = 103	Female n = 45	Male n = 58	p-value	All n = 88	Female n = 39	Male n = 49	p-value
Age – years [IQR]	67 [60,77]	65 [59,81]	68 [61,75]	0.995	43 [35,49]	40 [33,47]	46 [37,50]	0.023
Risk factors and History								
Comorbidity burden - median [IQR]	2 [1,4]	2 [1,3]	3 [1,5]	0.029	1 [0,1]	1 [0,1]	1 [0,1]	0.654
Cardiac disease	36 (35%)	11 (24%)	25 (43%)	0.049	2 (2%)	0 (0)	2 (4%)	0.202
CAD	20 (19%)	2 (4%)	18 (31%)	0.001	1 (1%)	0 (0)	1 (2%)	0.37
Hypertension	65 (63%)	27 (60%)	38 (66%)	0.565	16 (18%)	6 (15%)	10 (20%)	0.544
Smoking	40 (39%)	12 (27%)	28 (48%)	0.026	18 (21%)	7 (18%)	11 (22%)	0.603
COPD	0 (0)	0 (0)	0 (0)	NA	9 (9%)	2 (4%)	7 (12%)	0.174
Diabetes	27 (26%)	10 (22%)	17 (29%)	0.417	7 (8%)	2 (5%)	5 (10%)	0.382
Obesity	47 (46%)	16 (36%)	31 (53%)	0.071	27 (31%)	14 (36%)	13 (27%)	0.344
Renal insufficiency	23 (22%)	10 (22%)	13 (22%)	0.982	3 (3%)	0 (0)	3 (6%)	0.116
Stroke/TIA	9 (9%)	3 (7%)	6 (10%)	0.512	1 (1%)	0 (0)	1 (2%)	0.37
Symptoms								
Begin of symptoms in days -	7 [3,12]	4 [2,12]	8 [3,13]	0.147	7 [3,10]	7 [3,11]	7 [3,10]	0.631

median [IQR]								
Fever	50 (49%)	18 (40%)	32 (55%)	0.126	54 (61%)	24 (61%)	30 (61%)	0.976
Chills	15 (15%)	5 (11%)	10 (17%)	0.382	16 (18%)	6 (15%)	10 (20%)	0.544
Cough	66 (64%)	25 (56%)	41 (71%)	0.112	60 (68%)	27 (69%)	33 (67%)	0.851
Dyspnoe	37 (36%)	14 (31%)	23 (40%)	0.37	44 (50%)	24 (62%)	20 (41%)	0.053
Clinical parameters – median [IQR]								
Temperature* in °C	37.2 [36.8,38.2]	37.1 [36.8,38.1]	37.3 [36.8,38.3]	0.793	37.1 [36.7,37.8]	37.1 [36.6,37.8]	37 [36.8,37.8]	0.751
Respiratory rate*	20 [16,24]	18 [15,23]	21 [16,25]	0.075	20 [16,24]	20 [16,24]	19 [16,24]	0.892
SaO2* in %	95 [94,97]	97 [95,98]	95 [93,96]	<0.001	98 [96,98]	98 [97,99]	98 [96,98]	0.257
Heart rate*	86 [75,101]	84 [71,100]	87 [77,103]	0.222	93 [84,104]	91 [81,104]	95 [85,103]	0.327
Blood pressure - systolic* in mmHg	133 [115,148]	126 [111,159]	134 [119,144]	0.584	135 [125,149]	130 [124,142]	137 [133,152]	0.016
Blood pressure - diastolic* in mmHg	78 [68,88]	74 [69,83]	79 [66,90]	0.624	85 [80,91]	84 [72,90]	86 [80,94]	0.17
BMI in kg/m²	29 [25,32]	29 [24,33]	29 [26,32]	0.667	28 [25,31]	29 [28,35]	27 [24,31]	0.041a
Laboratory parameters - median [IQR]								

Leucocytes in*10 9/l	6.57 [5.42,8.87]	6.14 [4.72,8.61]	6.74 [5.72,8.89]	0.241	5.84 [4.64,7.76]	5.67 [4.53,7.2]	5.87 [4.74,8.34]	0.414
Lymphocytes – absolute in *10 9/l	0.95 [0.61,1.31]	0.97 [0.62,1.4]	0.85 [0.58,1.16]	0.166	1.33 [0.96,1.99]	1.5 [1.15,1.99]	1.08 [0.84,1.79]	0.031
Lymphocytes - in %	14.6 [9.1,21.6]	16.8 [7.9,26.9]	12.8 [9.9,19]	0.053	24.7 [18.1,30.5]	26.8 [23,31.8]	21.2 [14.2,27.9]	0.003
CRP in mg/l	36.3 [11.5,110.5]	17.8 [3.1,69.2]	52.3 [28.9,151.4]	<0.001	10 [1.2,52.1]	3.2 [1,39.1]	16.8 [1.5,58.6]	0.201
Procalcitonin in µg/l	0.112 [0.059,0.257]	0.071 [0.059,0.15]	0.146 [0.077,0.281]	0.028	0.061 [0.059,0.127]	0.059 [0.059,0.118]	0.063 [0.059,0.127]	0.597a
D-Dimer in µg/l	0.85 [0.47,1.72]	0.85 [0.52,1.59]	0.8 [0.45,2.34]	0.805	0.41 [0.29,0.65]	0.44 [0.3,0.65]	0.38 [0.29,0.66]	0.596
Ferritin in ng/ml	500 [236,1158]	237.5 [132,533]	815 [476.5,1328]	<0.001	243 [118.5,565]	121 [57,278]	405 [223,833]	<0.001
Creatinine in µmol/l	84 [64,112]	67 [54,104]	89 [76,126]	<0.001	72 [61,84]	61 [56,69]	81 [70,95]	<0.001
hs-Troponin T in ng/l	13 [7,22.5]	8 [5,23]	14 [10,22]	0.083	4 [3,6]	3 [2.9,5]	5 [4,7]	0.002
NT-proBNP in pg/ml	202 [67,692]	141 [52,560]	208.5 [82.5,871]	0.411	49 [49,79]	49 [49,83]	49 [49,67.5]	0.662

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; IQR: interquartile range; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack; SaO2: arterial oxygen saturation; BMI: body mass index; CRP: C-Reactive Protein; hs-Troponin T: high-sensitivity troponin T; NT-proBNP: N-terminal pro brain natriuretic peptide

References

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