Association Between Male Sex and Outcomes of Coronavirus Disease 2019 (COVID-19)—A Danish Nationwide, Register-based Study

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Background and Objectives. Male sex has been associated with severe coronavirus disease 2019 (COVID-19) infection. We examined the association between male sex and severe COVID-19 infection and if an increased risk remains after adjustment for age and comorbidities.

Methods. Nationwide register-based follow-up study of COVID-19 patients in Denmark until 16 May 2020. Average risk ratio comparing 30-day composite outcome of all-cause death, severe COVID-19 diagnosis or intensive care unit (ICU) admission for men versus women standardized to the age and comorbidity distribution of all patients were derived from multivariable Cox re-

Results. Of 4842 COVID-19 patients, 2281 (47.1%) were men. Median age was 57 [25%–75% 43–73] for men versus 52 [38–71] for women (P < .001); however, octogenarians had equal sex distribution. Alcohol diagnosis, diabetes, hypertension, sleep apnea, prior MI and IHD (all P < .001) as well as AF, stroke, and HF (all P = .01) were more often seen in men, and so was CKD (P = .03). Obesity diagnosis (P < .001) were more often seen in women. Other comorbidity differences were insignificant (P > .05). The fully adjusted average risk ratio was 1.63 [95% CI, 1.44–1.84].

Conclusions. Men with COVID-19 infection have >50% higher risk of all-cause death, severe COVID-19 infection, or ICU admission than women. The excess risk was not explained by age and comorbidities.

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Several risk factors for severe outcomes of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been suggested, including advanced age and frailty, cardiovascular comorbidities (hypertension, heart failure and ischemic heart disease), diabetes, obesity, and chronic obstructive pulmonary disease [1–3]. More recent, yet limited, data have also linked male sex to more severe and fatal trajectories of coronavirus disease 2019 (COVID-19) infection [3–6]. A number of underlying mechanisms for the sex differences in outcomes have been proposed, including (1) smoking differences, with higher prevalence of smoking among men and smoking has been related to higher expression of angiotensin converting enzyme 2 (ACE2; the entry point for SARS-CoV-2 in humans) [7]; (2) higher ACE2 expression in Asian men, with higher risks of COVID-19 disease contraction and disease severity [8]; (3) differences in immunological response, where women are hypothesized to be less susceptible to viral infections and disease severity based on a different innate immunity, steroid/sex hormones, and factors related to sex chromosomes [9]; (4) differences in alcohol intake, with men generally having higher alcohol intake [10]; (5) obesity differences, where obesity in men has been linked with worse outcomes, although women in general are more likely to be obese [11, 12]; and (6) co-

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nationwide administrative registries, we conducted a study of COVID-19 infection in Denmark with a focus on the differential risk of severe COVID-19 infection in men versus women, with adjustment for age and selected comorbidities.

METHODS

Study Setting and Population

In Denmark, all Danish residents are assigned a unique civil personal registration number at birth or upon immigration [15]. This unique identifier is recorded in national administrative registries for economic, social, and healthcare purposes. All Danish residents were available for study inclusion and those with COVID-19 diagnoses (International Classification of Diseases, 10th revision [ICD-10], codes B342, B342A, B972, and B972A) registered in the Danish National Patient Registry [16] were included from the end of February 2020 until 16 May 2020. Nasopharyngeal swabs and real-time reverse transcription–polymerase chain reaction (RT-PCR) tests were used to diagnose COVID-19. Viral transport medium, Universal Transport Medium (UTM), or liquid Amies media (a medium found in ESwab, COPAN Diagnostics Inc.) were used.

Data Sources and Study Variables

Data were linked between national administrative registries using the civil personal registration number registered in the Danish Civil Registration System [15], from which we also obtained data on age and sex. From the Danish National Patient Registry, diagnoses related to obesity and alcohol use as well as diagnosis of sleep apnea, diabetes, chronic obstructive pulmonary disease (as a marker of smoking as well as a risk factor of its own), previous myocardial infarction (MI), ischemic heart disease (IHD), heart failure (HF), atrial fibrillation (AF), stroke, peripheral artery disease, cancer, and liver, rheumatic, and chronic kidney disease (CKD) were included. From the Danish Prescription Registry [17], we defined hypertension when at least 2 antihypertensive drug prescriptions were filled in 2 consecutive 100-day periods prior to the COVID-19 diagnosis, in accordance with previously published studies [18, 19]. In a previously described randomly selected cohort from the Danish population 16 years of age or older, the use of 2 antihypertensive medications to define hypertension had a positive-predictive value of 80% and a specificity of 94.7% [20]. The Danish registries are validated and of high quality, as previously described [21, 22].

Outcome

The primary outcome was a 30-day composite of all-cause death, severe COVID-19 diagnosis (ICD-10 code B972A: COVID-19 infection with severe acute respiratory syndrome), or intensive care unit (ICU) admission. Secondary outcomes were individual outcomes of 30-day all-cause death and ICU admission, with death as a competing risk, as well as a 30-day composite of all-cause death or ICU admission.

Statistical analysis

Median and 25th–75th percentiles were reported for continuous variables and counts and percentages for categorical variables. Accordingly, Wilcoxon and chi-square tests were performed to test for sex differences in patient characteristics. Absolute risks and average risk ratios for outcomes for men versus women standardized to the age and comorbidity distribution of all patients were derived from multivariable Cox regression [23]. The models included the following covariates: age (in groups of <60, 60 to <70, 70 to <80, and ≥80 years), hypertension, and diagnoses indicating obesity and alcohol use, sleep apnea, diabetes, chronic obstructive pulmonary disease, previous MI, IHD, HF, AF, stroke, peripheral artery disease, cancer, liver disease, rheumatic disease, and CKD. Data management was conducted using SAS, version 9.4 (SAS Institute, Cary, NC) and analyses using R, version 3.6.1 (R Foundation for Statistical Computing). A 2-sided P value less than .05 was regarded as significant.

Ethics

In Denmark, registry-based studies do not require ethical committee approval or patient consent. Approval to use the data sources for research purposes was granted by the Science Center for Data Approvals under the Capital Region of Denmark (approval number P-2019–191) in accordance with the General Data Protection Regulation. Data are accessed on secure servers under Statistics Denmark and cannot be shared according to Danish legislation.

RESULTS

Patients and Characteristics

Of a total of 4860 patients with COVID-19, 18 with missing information on sex were excluded, leaving 4842 patients to form the study population. Of these, 2281 (47.1%) were men and 2561 (52.9%) were women. Baseline characteristics for men versus women are shown in Table 1. Median age for men was significantly higher than for women, although the sex distribution was similar for octogenarians. Alcohol intake, diabetes, hypertension, sleep apnea, prior MI, and IHD (all P < .001) as well as AF, stroke, and HF (all P < .01) were more often seen in men, as was CKD (P = .03). Obesity diagnosis (P < .001) were more often seen in women. Other differences in comorbidities were nonsignificant (see Table 1).

Absolute Risks

In total, 500 men (21.9%) versus 303 women (11.8%) experienced the 30-day composite outcome. The corresponding absolute risks for the 30-day composite outcome for men versus women standardized to the age and comorbidity distribution in Table 1 were 20.2% versus 12.4% (see Figure 1). Absolute risks...
with 95% confidence intervals standardized to the age and co-morbidity distribution in Table 1 for the primary and secondary outcomes are shown in Table 2.

Table 1. Baseline Characteristics of Patients With COVID-19 by Sex

| Variable                        | Male (n = 2281) | Female (n = 2561) | P  |
|---------------------------------|-----------------|-------------------|----|
| Age, median [25%, 75%], years   | 57 [43, 73]     | 52 [38, 71]       | < .001 |
| Age <60 years, n (%)            | 1214 (53.2)     | 1620 (63.3)       |    |
| Age 60 to <70 years, n (%)      | 370 (16.2)      | 280 (10.9)        |    |
| Age 70 to <80 years, n (%)      | 387 (17.0)      | 279 (10.9)        |    |
| Age ≥80 years, n (%)            | 310 (13.6)      | 382 (14.9)        | < .001 |
| Diagnosis including alcohol use, n (%) | 65 (2.8)   | 37 (1.4)          | < .001 |
| Obesity diagnosis, n (%)        | 86 (3.8)        | 304 (11.9)        | < .001 |
| Sleep apnea, n (%)              | 92 (4.0)        | 32 (1.2)          | < .001 |
| Hypertension, n (%)             | 233 (10.2)      | 166 (6.5)         | < .001 |
| Diabetes, n (%)                 | 87 (3.8)        | 108 (4.2)         | .52 |
| COPD, n (%)                     | 101 (4.4)       | 39 (1.5)          | < .001 |
| Chronic IHD, n (%)              | 260 (11.4)      | 155 (6.1)         | < .001 |
| Heart failure, n (%)            | 85 (3.7)        | 63 (2.5)          | .01 |
| AF, n (%)                       | 158 (6.9)       | 132 (5.2)         | .01 |
| Stroke, n (%)                   | 104 (4.6)       | 78 (3.0)          | .01 |
| PAD, n (%)                      | 42 (1.8)        | 30 (1.2)          | .07 |
| Liver disease, n (%)            | 49 (2.1)        | 55 (2.1)          | 1.00 |
| Rheumatic disease, n (%)        | 82 (3.6)        | 115 (4.5)         | .13 |
| Chronic kidney disease, n (%)   | 117 (5.1)       | 98 (3.8)          | .03 |

Abbreviations: AF, atrial fibrillation or flutter; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IHD, ischemic heart disease; MI, myocardial infarction; PAD, peripheral artery disease.

Table 2. COVID-19 Outcomes by Sex

| Outcomes            | Male Sex (n = 2281) | Female Sex (n = 2561) | Standardized Average Risk Ratio [95% CI] |
|---------------------|---------------------|-----------------------|----------------------------------------|
| Composite endpoint  | 500 (20.2; 18.8–21.6) | 303 (12.4; 11.2–13.6) | 1.64 [1.44–1.84]                        |
| All-cause death     | 274 (11.2; 10.1–12.2) | 178 (7.4; 6.5–8.2)    | 1.53 [1.30–1.80]                        |
| ICU admission       | 187 (7.5; 6.4–8.5)   | 78 (3.4; 2.7–4.2)     | 2.22 [1.70–2.91]                        |

The numbers of events with standardized absolute risks and average risk ratios are shown. Data are presented as n (%; 95% CI) unless otherwise indicated. The composite endpoint includes severe COVID-19 diagnosis, ICU admission, or fatal trajectory. Cox regression models included age groups (<60, 60 to <70, 70 to <80, ≥80 years), alcohol, obesity, hypertension, diabetes, chronic obstructive pulmonary disease, sleep apnea, prior myocardial infarction, chronic ischemic heart disease, heart failure, atrial fibrillation or flutter, stroke, peripheral artery disease, liver disease, rheumatic disease, chronic kidney disease, and cancer.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Average Risk Ratio
The average risk ratio standardized to the age and comorbidity distribution of all patients for the 30-day composite endpoint of all-cause death, severe COVID-19 diagnosis, or ICU admission was 1.64 (95% confidence interval [CI], 1.44–1.84) (see Table 2). Men were also significantly associated with all-cause death within 30 days after COVID-19 diagnosis as well as ICU admission, and these corresponding risk ratios are also shown in Table 2. The average risk ratio standardized to the age and comorbidity distribution of all patients for the 30-day composite of all-cause death or ICU admission was 1.62 (95% CI, 1.40–1.85).

Figure 1. Standardized absolute risks for the 30-day composite endpoint for male versus female sex. The composite endpoint includes severe coronavirus disease 2019 (COVID-19) diagnosis, intensive care unit admission, or fatal trajectory. Standardized absolute risks for male versus female sex are obtained from adjusted Cox regression models. The adjusted model included age groups (<60, 60 to <70, 70 to <80, ≥80 years), alcohol, obesity, hypertension, diabetes, chronic obstructive pulmonary disease, sleep apnea, prior myocardial infarction, chronic ischemic heart disease, heart failure, atrial fibrillation or flutter, stroke, peripheral artery disease, liver disease, rheumatic disease, chronic kidney disease, and cancer.
DISCUSSION

In this nationwide register-based follow-up study of 4842 patients with COVID-19, the male to female ratio in those diagnosed with COVID-19 was almost equal. However, male sex was associated with an increased risk of worse outcomes in COVID-19 relative to women, including all-cause death, ICU admission, and a composite of these 2 outcomes, and severe COVID-19 diagnosis. The risk was more than 50% higher for all of these 30-day outcomes with COVID-19 in men relative to women.

The first results indicating a substantial difference in COVID-19 severity between men and women were from a single-center study from Wuhan, where 99 cases with COVID-19–related pneumonia were included between 1 and 20 January 2020 and two-thirds were men [1]. In particular, older men had an associated high risk of severe COVID-19 infection, and additional mortality data from the Wuhan area have shown that 70% of those who died were men [3]. Similar figures have been reported from the United Kingdom [24] and Italy [2], as well as in a study of 5700 patients hospitalized with COVID-19 from New York City hospitals, where approximately 60% were men [5]. While the ratio of men to women contracting COVID-19 in society appears to be equal [8], significantly more men than women are hospitalized [2, 5, 24]. This pattern also applied to our study, and this finding is in line with many other countries including Spain and Italy [2, 8]. While it has been suggested that more men than women contract COVID-19 in Asia, the current picture from Asia is mixed. While the male to female ratios are high in Singapore and Japan, the ratio is 40% men versus 60% women in South Korea. In China, COVID-19 contraction in women has also increased in more recent times, with a current male to female ratio being almost equal [8]. In society, women traditionally work in caregiver/healthcare jobs and women continue to fulfill this role despite societal strategies, including lockdown. This may explain why women might be more at risk of contracting COVID-19, and different testing strategies between countries are also likely to affect the male to female ratio of positive tests, in particular if testing is not performed widely in the general public and used more widely among healthcare personnel, where women constitute a majority. In Denmark, the male to female ratio was initially around 60%, but more recently, more women have been diagnosed with COVID-19, and currently the male to female ratio is almost equal.

In line with the Chinese, South Korean, and UK-based reports, we report a significantly increased risk for more severe COVID-19 infection in men relative to women. A number of mechanisms have been proposed to explain the sex-differential risk in COVID-19 severity, including differences in immunological response to SARS-CoV-2 and higher levels of antibodies in women relative to men, and sex-related differences in lifestyle factors (alcohol, smoking, and obesity) and comorbidities are also likely to play a role [7, 9]. In the New York City study of 5700 hospitalized patients with COVID-19, just under 70% of those treated in the ICU were men and mortality rates were higher for men versus women for every 10-year age interval from 20 years and upwards [5]. Interestingly, male sex remained significantly associated with severe COVID-19 infection when we adjusted for age, hypertension, obesity, and alcohol-use–related diagnoses; sleep apnea; diabetes; chronic obstructive pulmonary disease; previous MI, IHD, HF, AF, stroke, peripheral artery disease, cancer, liver disease, rheumatic disease, and CKD. Thus, we cannot find evidence to support that the sex-related differences in COVID-19 severity is related to patient age, lifestyle, or comorbidity factors. Male sex was similarly an independent risk factor in another study from the New York City area and as well as in other studies [25–27]. As such, it may be that the findings we provide underline actual differences between women and men related to immunological differences. In addition, current evidence remains inconclusive with regard to smoking as a risk factor in men or other subgroups in COVID-19 [7]. Given that our results represent actual differences between men and women, the hypothesis of immunological differences between sexes may actually play a significant role in the sex-related differences in COVID-19 severity [9].

A better understanding of the sex differences in COVID-19 could potentially prevent disease severity and help save lives. Sex-related differences in immunological response have been linked to X chromosomes, making women less susceptible to severe viral infections but, on the other hand, more susceptible to autoimmune diseases, including rheumatoid arthritis and Crohn disease. Specifically, a protein gene named TLR7 involved in the detection of single-strand RNA viruses including the SARS-CoV-2 virus is located on the X chromosome, and even though 1 of 2 X chromosomes in women normally is inactivated, it has been put forward that the TLR7 gene is activated in both X chromosomes in women, making the immune response in COVID-19 disease in women stronger [9]. Hormonal differences between men and women have also been suggested to play a role, by extension of prior research on mice and severe acute respiratory syndrome (SARS) coronavirus, where male mice were more susceptible to SARS, and when estrogen receptor antagonists were administered in female mice, significantly higher SARS susceptibility was seen [28]. In humans, more men than women also died during the SARS coronavirus outbreak in 2003 [29]. Estrogen has been linked to suppression of cytokines that play a crucial role in the escalation of the immune response, with lung tissue damage and pulmonary vessel leakage seen in acute respiratory distress syndrome related to COVID-19 severity [30, 31]. Women produce higher levels of antibodies that remain active in the circulation for a longer time and produce less inflammatory interleukin (IL)-6 after infection than men, which is associated with shorter disease duration and longevity [9].
Identifying the underlying mechanisms that lead to women being less susceptible to severe COVID-19 could aid laboratory scientists in creating drugs that strengthen men’s immune response to the SARS-CoV-2 virus. There are current and future-planned trials on certain drug therapies against COVID-19 severity, including CoV-19 receptor blockers, hydroxychloroquine, different anti-inflammatory biological drugs used in rheumatic disease, monoclonal antibodies, anti–IL-1 and –IL-6, remdesivir which was effective against Ebola virus, and vaccines [9]. The sex-differentiated data we report are important to inform researchers that men and women may react differently to potential vaccines and treatments. Thus, our data have implications for drug safety and efficacy in ongoing and future clinical trials, and it is vital that sex is taken into account when treatment and vaccine trials are designed and analyzed [9].

Given the observational nature of our study, the associations found may not be causal. Although we were able to adjust for multiple confounding factors, we cannot rule out unmeasured or residual confounding. In our study, lifestyle factors, including obesity, alcohol use, and smoking status, were defined using diagnoses from hospitalizations or outpatient contacts, and smoking status was only indirectly assessed through diagnosis of chronic obstructive pulmonary disease. Furthermore, we were not able to assess severity of the comorbid conditions. Although we did not have laboratory data to confirm that each case had a positive swab test, coding of tested persons both with tentative diagnosis codes and eventually those with positive swabs with definite diagnosis codes has been and is systematically performed. Potential misclassification of COVID-19 may be related to false-negative tests, as well as the fact that we do not fully capture all patients with COVID-19 in Denmark through ICD-10 diagnosis codes. However, in a recently published study by our group, the University Hospital of Copenhagen undertook a quality assessment of COVID-19 ICD-10 codes: of 98 patient records with an ICD-10 code for COVID-19, 97 of these had a laboratory-confirmed real-time RT-PCR test for SARS-CoV-2 (extrapolated positive-predictive value, 98%) [32]. Follow-up data on outcome were limited to 16 May 2020, which may limit the registration of severe COVID-19 infection for patients diagnosed with COVID-19 at the end of the study period. Data on presumed causes of death as well as autopsy-confirmed deaths were not available. Although the majority of cases were from more densely populated areas in Denmark, the complete nationwide sample of consecutively included patients with COVID-19 minimizes selection bias based on geographical differences.

Conclusions
In this nationwide study of 4842 patients with COVID-19 from Denmark, the male to female ratio of COVID-19 diagnosis was equal. However, men were significantly associated with higher risks of a 30-day composite endpoint of all-cause death, severe COVID-19 diagnosis, or ICU admission as well as individual components of all-cause death and ICU admission. For all of these outcomes, the risk was, on average, more than 50% higher for men relative to women. Since the significantly higher risk in men was not explained by differences in age and comorbidities between men and women, future investigations underpinning sex-related disease mechanisms in COVID-19 infection are warranted. There may be important differences in the immunological response to COVID-19 infection between the 2 sexes, with implications for the design and analysis of studies of drug and vaccine efficacy in COVID-19 infectious disease.

Notes
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