Association between male sex and outcomes of

Coronavirus Disease 2019 (Covid-19) – a Danish nationwide, register-based study

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Summary: Men with Covid-19 infection have a more than 50% higher risk of a 30-day composite outcome of all-cause death, severe Covid-19 infection, or ICU admission than women. This excess risk was not explained by age or underlying comorbid conditions.

Abstract:

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 May 16, 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 regression. Included covariates were age, hypertension, diagnoses including obesity, alcohol, sleep apnea, diabetes, chronic obstructive pulmonary disease, previous myocardial infarction (MI), ischemic heart disease (IHD), heart failure (HF), atrial fibrillation (AF), stroke, peripheral artery disease, cancer, liver-, rheumatic-, and chronic kidney disease (CKD).

Results: Of 4,842 Covid-19 patients, 2,281 (47.1%) were men. Median age was 57 [25%-75% 43-73] for men versus 52 [38-71] for women (P<0.001); however, octogenarians had equal sex distribution. Alcohol diagnosis, diabetes, hypertension, sleep apnea, prior MI and IHD (all P<0.001) as well as AF, stroke and HF (all P=0.01) were more often seen in men, and so was CKD (P=0.03). Obesity diagnosis (P<0.001) were more often seen in women. Other comorbidity differences were insignificant (P>0.05). 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.

Keywords: Sex; Covid-19; severity; outcomes.

Introduction

Several risk factors for severe outcomes of novel 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 ACE2 (angiotensin converting enzyme 2, the entry point for severe acute respiratory syndrome virus 2 [SARS-CoV-2] in human)[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 have been linked with worse outcomes, although women in general are more likely to be obese[11,12]; and 6) comorbidity differences, with men in general having higher prevalence of cardiovascular risk factors as well as higher prevalence and incident risk of cardiovascular disease.[13,14] Thus, many of the listed underlying mechanisms are related to confounding factors and it remains unclear whether the increased risk for severe and fatal Covid-19 infection in men remains after adjustment for patient age, lifestyle differences, and comorbidities. Therefore, by use of nationwide administrative registries, we conducted a study of Covid-19 infection in Denmark with 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 (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 May 16, 2020. Nasopharyngeal swabs and real-time reverse transcription-polymerase chain reaction (PCR) tests were used to diagnose Covid-19. Viral transport medium, Universal Transport Medium (UTM®) or liquid Amies media (a medium found in ESwab™) 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, ischemic heart disease, heart failure, atrial fibrillation, stroke, peripheral artery disease, cancer, liver, rheumatic, and chronic kidney disease were included. From The Danish Prescription Registry[17], we defined hypertension when at least two antihypertensive drug prescriptions were filled in two 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, the use of two 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

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 competing risk, as well as a 30-day composite of all-cause death or ICU admission.

Statistics

Median and 25-75 percentiles were reported for continuous variables and counts and percentages for categorical variables. Accordingly, Wilcoxon and Chi Squared tests were performed to test for sex differences of 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 <60, 60-<70, 70-<80 and ≥80 years), hypertension, and diagnoses indicating obesity and alcohol use, sleep apnea, diabetes, chronic obstructive pulmonary disease, previous myocardial infarction, ischemic heart disease, heart failure, atrial fibrillation, stroke, peripheral artery disease, cancer, liver disease, rheumatic disease, and chronic kidney disease. Data management was conducted using SAS, version 9.4 (Cary, NC, USA) and analyses using R, version 3.6.1. A two-sided P-value <0.05 was regarded as significant.

Ethics

In Denmark, register-based studies do not require ethical committee approval or patient consent. Approval to use the data sources for research purposes was granted by the data responsible institute in the Capital Region of Denmark (approval number P-2019-191) in accordance with the General Data Protection

Regulation (GDPR). 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 4,860 patients with Covid-19, 18 with missing information on sex were excluded, leaving 4,842 patients to form the study population. Of these, 2,281 (47.1%) were men and 2561 (52.9%) 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 diagnosis, diabetes, hypertension, sleep apnea, prior MI and IHD (all P<0.001) as well as AF, stroke and HF (all P=0.01) were more often seen in men, and so was CKD (P=0.03). Obesity diagnosis (P<0.001) were more often seen in women. Other differences in comorbidities were insignificant; 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 comorbidity distribution in Table 1 for the primary and secondary outcomes are shown in Table 2.

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% 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).

Discussion

In this nationwide register-based follow-up study of 4,842 Covid-19 patients, the male to female ratio in Covid-19 diagnosed patients 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 two outcomes and severe Covid-19 diagnosis. The risk was more than 50% higher for all of these 30-day outcomes after 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 January 1 and 20, 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 has shown that 70% of those who died were men.[3] Similar figures have been reported from the UK[24] and Italy[2] as well as a study of 5,700 Covid-19 hospitalized patients 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 are traditionally working in caregiver /

healthcare jobs and women continue to fulfill this role despite of societal strategies including lockdown. This may explain why women might be more at risk of contracting Covid-19 as well as different test 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 were 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 affection 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 related to sex chromosomes and higher levels of antibodies in women relative to men as well as 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 5,700 hospitalized Covid-19 patients, just under 70% of those treated in the intensive care unit 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 myocardial infarction, ischemic heart disease, heart failure, atrial fibrillation, stroke, peripheral artery disease, cancer, liver disease, rheumatic disease, and chronic kidney disease. 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 diasease.[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 has 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's disease. Specifically, a protein gene named TLR7 involved in detection of single-stranded RNA viruses including the SARS-CoV-2 virus is located on the X chromosome, and even though one of two X chromosomes in women normally is inactivated, it has been put forward that 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 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. 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 as well as women produce less inflammatory 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 –IL6, remdesevir that was effective against ebola disease, 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 has 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. Despite we did not have laboratory data to confirm that each case had a positive swab test, coding of both tested persons with tentative diagnosis codes and eventually those with positive swabs with definite diagnosis codes have been and are systematically performed. Potential misclassification of Covid-19 may be related to false negative tests, as well as we do not fully capture all Covid-19 patients 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 reverse transcription–polymerase chain reaction test for SARS-CoV-2 (extrapolated positive predictive value, 98%).[32] Follow-up data on outcome was limited to May 16, 2020, which may limit the registration of severe Covid-19 infection for patients diagnosed with Covid-19 in 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 Covid-19 patients minimizes selection bias based on geographical differences.

Conclusions

In this nationwide study of 4,842 Covid-19 patients 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 two sexes with implications for the design of and analysis of studies of drug and vaccine efficacy in Covid-19 infectious disease.

Conflicts of interest: None of the authors have any conflicts of interest to report.

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Table 1: Baseline characteristics of patients with Covid-19 by sex.

Variable	Male (n=2,281)	Female (n=2,561)	P-value
Age, median [25%, 75%]	57 [43, 73]	52 [38, 71]	<0.001
Age <60 years, n (%)	1,214 (53.2)	1,620 (63.3)	
Age 60-<70 years, n (%)	370 (16.2)	280 (10.9)	
Age 70-<80years, n (%)	387 (17.0)	279 (10.9)	
Age ≥80 years, n (%)	310 (13.6)	382 (14.9)	<0.001
Diagnosis including alcohol use, n (%)	65 (2.8)	37 (1.4)	<0.001
Obesity diagnosis, n (%)	86 (3.8)	304 (11.9)	<0.001
Sleep apnea, n (%)	92 (4.0)	32 (1.2)	<0.001
Hypertension, n (%)	574 (25.2)	497 (19.4)	<0.001
Diabetes, n (%)	233 (10.2)	166 (6.5)	<0.001
COPD, n (%)	87 (3.8)	108 (4.2)	0.52
Prior MI, n (%)	101 (4.4)	39 (1.5)	<0.001
Chronic IHD, n (%)	260 (11.4)	155 (6.1)	<0.001
Heart failure, n (%)	85 (3.7)	63 (2.5)	0.01
AF, n (%)	158 (6.9)	132 (5.2)	0.01
Stroke, n (%)	104 (4.6)	78 (3.0)	0.01
PAD, n (%)	42 (1.8)	30 (1.2)	0.07
Liver disease, n (%)	49 (2.1)	55 (2.1)	1.00
Rheumatic disease, n (%)	82 (3.6)	115 (4.5)	0.13
Chronic kidney disease, n (%)	117 (5.1)	98 (3.8)	0.03

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

Table 2. Covid-19 outcomes by sex: n of events with standardized absolute risks and average risk ratios

Outcomes	Male sex N=2,281	Female Sex N=2,561	Standardized average risk ratio [95% CI]
Composite endpoint, n (%; 95% CI)	500 (20.2; 18.8-21.6)	303 (12.4; 11.2-13.6)	1.64 [1.44-1.84]
All-cause death, n (%; 95% CI)	274 (11.2; 10.1-12.2)	178 (7.4; 6.5-8.2)	1.53 [1.30-1.80]
ICU admission, n (%; 95% CI)	187 (7.5; 6.4-8.5)	78 (3.4; 2.7-4.2)	2.22 [1.70-2.91]

Abbreviations: Covid-19, coronavirus disease 2019; n, number; 95% CI, 95% confidence interval; ICU, intensive care unit.

The composite endpoint includes severe Covid-19 diagnosis, intensive care unit admission or fatal trajectory.

Cox regression models included age groups (<60 [reference], 60-<70, 70-<80, and ≥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.

Figure 1. Standardized absolute risks for the 30-day composite endpoint for male versus female sex.

The composite endpoint includes severe 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 [reference], 60-<70, 70-<80, and ≥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.