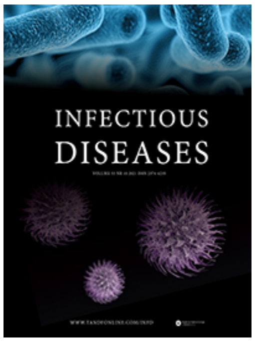

Infectious Diseases

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/infd20

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To cite this article: Erik Forsblom, Suvi Silén, Elisa Kortela, Maarit Ahava, Hanna-Riikka Kreivi, Ville Holmberg, Asko Järvinen, Johanna Hästbacka, Sanna-Maria Kivivuori & Atte Meretoja (2021) Male predominance in disease severity and mortality in a low Covid-19 epidemic and low case-fatality area – a population-based registry study, Infectious Diseases, 53:10, 789-799, DOI: 10.1080/23744235.2021.1936157

To link to this article: https://doi.org/10.1080/23744235.2021.1936157

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INFECTIOUS DISEASES,
2021; VOL. 53,
NO. 10, 789–799
https://doi.org/10.1080/23744235.2021.1936157

ORIGINAL ARTICLE

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Male predominance in disease severity and mortality in a low Covid-19 epidemic and low case-fatality area – a population-based registry study

Erik Forsblom[a*], Suvi Silén[b*], Elisa Kortela[a], Maarit Ahava[c], Hanna-Riikka Kreivi[d], Ville Holmberg[a,e], Asko Järvinen[a], Johanna Hästbacka[f], Sanna-Maria Kivivuori[g] and Atte Meretoja[h]

[a]Division of Infectious Diseases, Inflammation Center, Helsinki University Hospital, Helsinki, Finland; [b]Department of Otorhinolaryngology-Head and Neck Center, Helsinki University Hospital, Helsinki, Finland; [c]Diagnostic Center, Clinical Microbiology, HUSLAB, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [d]Division of Respiratory Diseases, Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland; [e]Department of Medicine, Clinicum, University of Helsinki, Helsinki, Finland; [f]Department of Anesthesiology, Intensive Care and Pain Medicine, Division of Intensive Care Medicine, Helsinki University Hospital, Helsinki, Finland; [g]Helsinki University Hospital and University of Helsinki, Helsinki, Finland; [h]General Administration, Helsinki University Hospital, Helsinki, Finland

ABSTRACT

Background: Men reportedly suffer from a more severe disease and higher mortality during the global SARS-CoV-2 (Covid-19) pandemic. We analysed sex differences in a low epidemic area with low overall mortality in Covid-19 in a population based setting with patients treated in specialized healthcare.

Methods: We entered all hospitalized laboratory-confirmed Covid-19 cases of all specialized healthcare hospitals of the Capital Province of Finland, into a population-based quality registry and described demographics, severity and case-fatality by sex of the first Covid-19 wave February–June 2020.

Results: Altogether 5471 patients (49% male) were identified. Patients hospitalized in the specialist healthcare ($N = 585$, 54% male, OR 1.25; 95% CI 1.05–1.48) were of the same age. Men had less asthma and thyroid insufficiency and more coronary artery disease compared to women. Mean time from symptom onset to diagnosis was at least one day longer for men ($p = .005$). Men required intensive care unit (ICU) more often (27% vs. 17%) with longer lengths-of-stays at ICU. Male sex associated with significantly higher case-fatality at 90-days (15% vs. 8%) and all excess male deaths occurring after three weeks from onset. Men with fatal outcomes had delays in both Covid-19 testing and hospital admission after a positive test. The delays in patients with the most severe and fatal outcomes differed markedly by sex. In multivariable analysis, male sex associated independently with case-fatality (OR 2.37; 95% CI 1.22–4.59).

Conclusions: Male sex associated with higher disease severity and case-fatality. Late presentation of male fatal cases could represent different treatment-seeking behaviour or disease progression by sex.

KEYWORDS
Covid-19
mortality
male sex

ARTICLE HISTORY
Received 11 February 2021
Revised 27 April 2021
Accepted 23 May 2021

CONTACT
Erik Forsblom
erik.forsblom@hus.fi
Division of Infectious Diseases, Inflammation Center, Helsinki University Hospital, Meilahti Triangle Hospital, P.O. Box 372, Haartmaninkatu 4, FIN-00029 HUS, Helsinki, Finland

*Both authors contributed equally to this work.

Supplemental data for this article can be accessed here.

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Introduction

Covid-19 is a new respiratory infection caused by coronavirus SARS-CoV-2 and first reported in Wuhan, China in December 2019 [1,2]. The Covid-19 rapidly spread worldwide forcing World Health Organization to declare a state of pandemic on 11 March 2020 [3]. The clinical characteristics of Covid-19 vary from subclinical symptoms to high fever, cough, myalgia, shortness of breath and acute respiratory distress syndrome with fatal outcome [4,5].

From the very beginning of the Covid-19 pandemic initial reports stated that male sex, higher age and comorbidities were associated with a more severe Covid-19 disease and higher case-fatality [6,7]. A recent meta-analysis [8] and a systematic review [9] concluded a higher case-fatality risk in males compared to females. Further reports have suggested that the sex-related morbidity and case-fatality are most likely a multifactorial phenomenon including both biological sex variations, e.g. chromosomal and sex steroid variations as well as sex-specific risk behaviour [10]. Poorer male survival has been suggested to be caused by poor health habits such as smoking and alcohol abuse [10–12] and higher degree of age-adjusted co-morbidities such as cardiovascular disease [13]. The impact of co-morbidities on case-fatality in Covid-19 is greater for male patients even after age adjustment [7]. However, many previous reports on sex differences in severity and case-fatality in Covid-19 are either hospital based or from areas with difficult Covid-19 epidemic situations [8–10] and to the best of our knowledge population-based studies on sex-related differences for hospitalized Covid-19 patients have not been performed.

The severity of the Covid-19 epidemic has differed between countries and even within different areas in a country. Many reports come from areas with high epidemic burden and heavily reorganized healthcare which may have a contributed to sex differences. The epi-centrum of Covid-19 infection in Finland has been in the southern part of the country with highest population number and density. Yet, the epidemic in this area has been among the mildest in Europe with only 5471 laboratory confirmed cases during the first wave until 21 June 2020.

The aim of the study was to quantify sex difference and identify potential underlying mechanisms for such differences by using a population-based quality registry of all hospitalized patients treated in specialized healthcare in the Capital Province of Finland during the first ware of Covid-19.

Methods

This is a retrospective observational population-based quality registry study of all Covid-19 inpatients in the specialized healthcare (including altogether 22 hospitals of specialized healthcare) of the Capital Province (southern Province of Helsinki and Uusimaa) of Finland.

Study population

The present study is the first report from the COVID-19 quality registry of the specialized healthcare of the Capital Province of Finland (including Helsinki University Hospital). The registry covers all specialized healthcare across the Province of Helsinki and Uusimaa, the capital region of Finland. The population of the province is 1.7 million with total population of Finland being 5.6 million inhabitants. This province is the largest hospital district in Finland and one of the largest healthcare organizations in Europe. The hospital district of the Capital Province of Finland (HUS Helsinki University Hospital) is a full-coverage specialized healthcare organization with up to 2.7 million annual patient visits and 27,000 healthcare employees. Finland has a tax-funded universal healthcare system, with the health district being the sole provider of specialist inpatient care for previously independent COVID-19 patients. Previously institutionalized and/or assistance dependent patients, such as nursing home patients, may be treated in primary-care hospitals run by the municipalities. All Covid-19 diagnoses in Finland are registered in the *National Registry of Communicable Diseases* enabling a reliable quality registry. We included in the quality registry all patients with at least one positive real-time reverse transcription polymerase chain reaction (real-time RT-PCR) test for Covid-19 who either died or received a minimum of 6 h of treatment at either emergency room, hospital ward or intensive care unit (ICU) in the specialized healthcare of the Capital Province of Finland during the first wave of the Covid-19 pandemic spring 2020 until 21 June 2020. Patients managed at home, institution or treated in primary-care hospitals were not included in the registry and their data were not available.

We collected clinical data from local and national electronic patient records and referral letters, radiology and pathology information systems, and the prescription database. Data documentation included sex, age, living arrangements, employment status, retirement and dependency status, pre-existing conditions and comorbidities, risk behaviour, body mass index (BMI), symptoms, onset date of symptoms, laboratory results, radiological examinations and findings of electrocardiogram and echocardiogram, medicines used in the hospital, illness severity, need for ICU, occurrence of complications, hospital length-of-stay (LOS) and all-cause case-fatality.

Definitions

The first wave of the Covid-19 epidemic in spring 2020 was defined as the onset of the epidemic from the first diagnosed patient case, i.e. 27 February 2020 until 21 June 2020 when the epidemic clearly declined. Everyday dependence or independence status was defined by use of the ECOG scale and 0–2 points defined as independent [14].

Outcome

The primary outcome measure was all-cause case-fatality up to 90 days (calculated from hospital admission). Secondary outcomes were ICU treatment, ICU and hospital LOS and complications.

Statistical analyses

All continuous variables were tested for normal distribution using the Shapiro–Wilk test, and reported as mean with standard deviation or median with interquartile range, as appropriate. Univariate analyses were performed using the Mann–Whitney *U*-test, Pearson's chi-square test or Fisher's exact test, as appropriate. Univariate factors with $p<.1$ for which no missing data were available were included in multivariable logistic regression analysis for estimation of parameters associated with outcome. The Kaplan–Meier method and log-rank test were applied for survival estimates. Tests were two-tailed and $p< .05$ was considered significant. Analyses were done with SPSS 25.0.0 IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY).

Institutional review and patient consent

The quality registry was institutionally approved as a quality registry without requirement for patient consent (approvals HUS/1049/2020/§4 and HUS/157/2020/§94). Consent for registration was not sought, allowing all consecutive patients to be included.

Results

Altogether 5471 inhabitants were diagnosed with Covid-19 in the Capital Province of Finland (including also private healthcare providers) during the first wave of Covid-19 (Figure 1). Among the Covid-19 cases 4952 (91%) were positive in RT-PCR testing and in 213 (4%) cases the diagnosis was based on antibody testing only and for 306 (6%) of cases, the diagnostic method was not registered in the *National Registry of Communicable Diseases*. These latter cases represent mainly the very early cases when the laboratory test was not included in the registry and have almost exclusively been diagnosed with RT-PCR which was the only method used in the laboratories in the beginning. Altogether, 49% (2683) of the Covid-19 positive inhabitants were male, corresponding to the 49% of males in the overall 1.7 million population. The majority, 4426 (81%) of the cases, did not require hospitalization whereas 1045 (19%) required hospital treatment which was provided in 460 (44%) cases at primary-care hospitals and in 585 (56%) cases at specialized healthcare hospitals of the Capital Province of Finland (Figure 1). All-cause case-fatality was 3% for non-hospitalized patients, 22% for patients treated in primary-care hospitals and 12% in specialized healthcare hospitals.

Patient characteristics

Of the 585 patients treated at specialized healthcare hospitals of the Capital Province of Finland 269 (46%) were female and 316 (54%) male (OR 1.25; 95% CI 1.05–1.48 for hospitalization for men). Differences according to sex were not observed in age, retirement, functionality or age adjusted living status among hospitalized patients (Table 1). History of smoking (28% vs. 15%) and alcohol use (4% vs. <0.5%) were more common in males than in females whereas no differences were observed in injection drug use. Mean BMI was higher in women who also had more often BMI over 30 than men ($p<.001$) (Table 1). Coronary artery disease was more common in men than in women (9% vs. 4%) whereas asthma (9% vs. 25%) and thyroid insufficiency (5% vs. 16%) were more frequent in women (Table 1).

Covid-19 diagnosis

Data on dates for symptom onset, diagnosis and hospital admission were retrieved for 315 male and 268 female patients. The total time from symptom onset to hospitalization did not differ according to sex (Table 2,

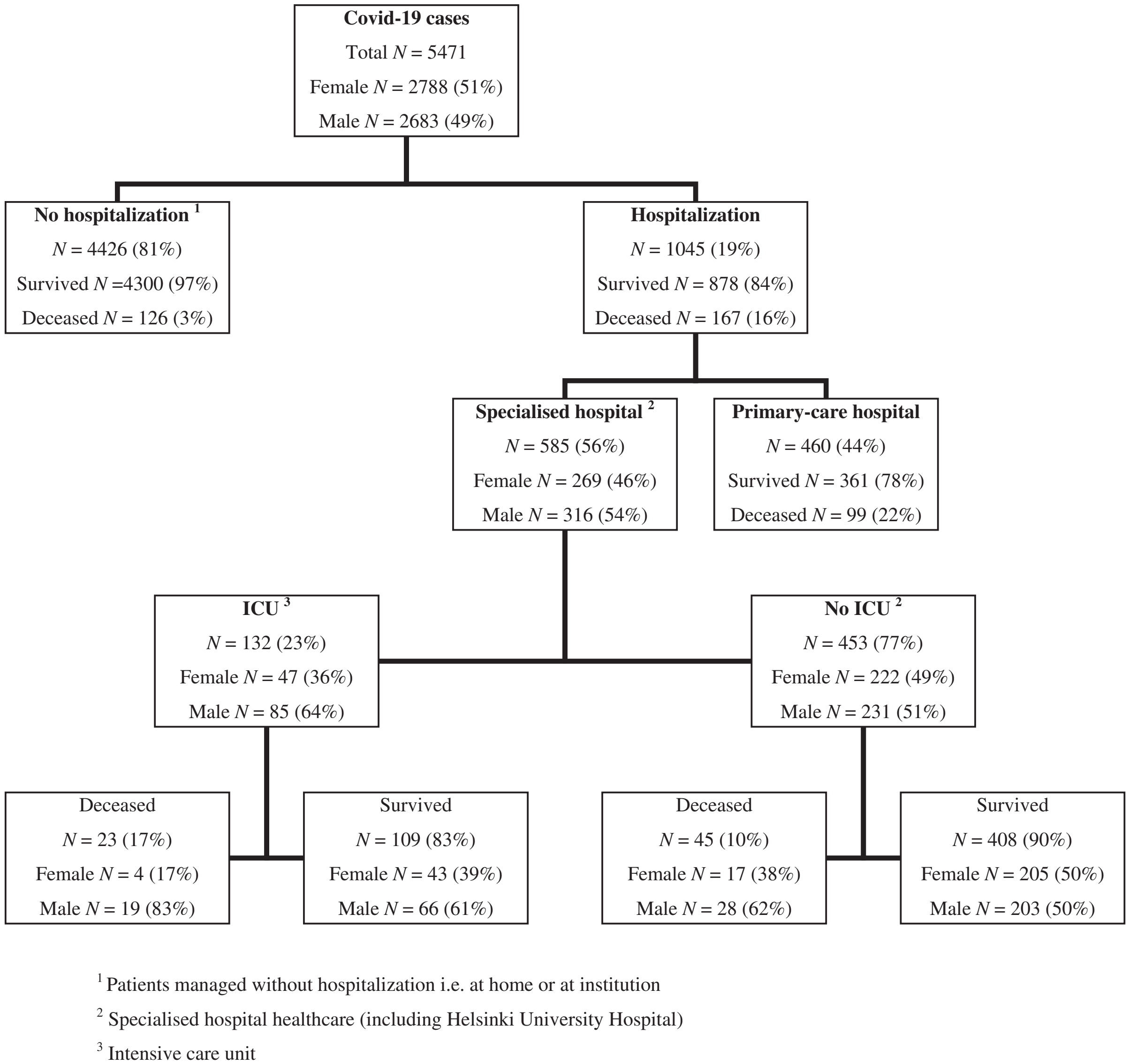

Figure 1. Flowchart for the first wave of Covid-19 patients in the Capital Province of Finland January to 21 June 2020. [1]Patients managed without hospitalization, i.e. at home or at institution. [2]Specialized hospital healthcare (including Helsinki University Hospital). [3]Intensive care unit.

Figure 2). The mean duration from the onset of symptoms to the diagnosis and from the diagnosis to hospitalization was 5.6 ± 5 days and 2.5 ± 6 days, respectively (Table 2, Supplementary Figures S1 and S2). The mean time from symptom onset to diagnosis was significantly longer (p=.005) whereas the mean time from diagnosis to hospitalization was significantly shorter (p=.008) for men compared to women (Table 2). However, the delays in patients with the most severe and fatal outcomes differed markedly by sex. While all women who had a fatal outcome presented within a week of their symptom onset, half of the men who succumbed had at least seven days symptoms prior to hospital admission (Figure 2). Men with fatal outcome had delays in both seeking to a PCR test and in hospital admission after a positive test (Supplementary Figures S1 and S2).

ICU treatment

Altogether 132 (23%) patients were admitted to ICU treatment with a mean ICU LOS of 13.8 (±11, SD) days. Male patients required more often pre-evaluation of ICU need (p=.030), received more often ICU treatment (p=.007), had longer ICU LOS (p<.001) and required more often ICU treatment interventions such as mechanical ventilation (p<.001) or dialysis (p=.001) than females (Table 2).

Complications

The most common complications were inflammatory changes in radiological imaging of the lungs in 463 (79%), acute pulmonary embolus in 19 (3%), dialysis treatment in 16 (3%) and sepsis in 13 (2%) of the 585

Table 1. Patient demographics, risk behaviour and underlying conditions of 585 patients with laboratory confirmed *Covid-19* and treated in specialized healthcare hospital stratified according to sex.

Characteristics	*N*, number Available data	Parameter *N* (%)	Male sex *N* = 316 (54)	Female sex *N* = 269 (46)	Univariate OR (95% CI)	Univariate *p* Value
Demographics						
Age, years (median, IQR)	585/585	57.0 (46.0–70.0)	58.5 (48.0–70.0)	57.0 (45.0–71.0)	–	.432
Age ≥65 years	585/585	197 (34)	112 (35)	85 (32)	1.19 (0.84–1.68)	.327
Retired from work	585/585	224 (38)	124 (39)	100 (37)	1.09 (0.78–1.53)	.608
Normal functionality[a]	585/585	489 (84)	264 (84)	225 (84)	1.01 (0.65–1.57)	.974
Age ≥65 + independent[b]	585/585	174 (30)	104 (33)	70 (26)	1.40 (0.97–2.00)	.069
Age ≥65 + not independent[b]	585/585	23 (4)	8 (3)	15 (6)	0.44 (0.18–1.05)	.059
Age <65 + independent[b]	585/585	384 (66)	202 (64)	182 (68)	0.85 (0.60–1.19)	.343
Age <65 + not independent[b]	585/585	4 (1)	2 (1)	2 (1)	0.85 (0.12–6.06)	.869
Body mass index >30	585/408	136 (33)	58 (43)	78 (58)	0.44 (0.29–0.67)	<.001
Body mass index (median, IQR)	585/408	28.0 (24.7–32.0)	27.5 (24.4–30.2)	29.8 (25.0–35.0)	–	<.001
Risk behaviour						
Current smoker	585/419	31 (5)	18 (6)	13 (5)	1.09 (0.52–2.28)	.822
History of smoking	585/419	127 (22)	88 (28)	39 (15)	2.29 (1.47–3.56)	<.001
Excess alcohol use	585/570	15 (3)	14 (4)	1 (<0.5)	12.5 (1.64–95.8)	.002
Injection drug abuse	585/570	2 (<0.5)	1 (<0.5)	1 (<0.5)	0.87 (0.05–14.0)	.923
Background conditions						
Cardiovascular						
Hypertension	585/585	223 (38)	117 (37)	106 (39)	0.90 (0.65–1.26)	.555
Diabetes mellitus	585/585	128 (22)	77 (24)	51 (19)	1.38 (0.93–2.06)	.115
Coronary artery disease	585/585	37 (6)	27 (9)	10 (4)	2.41 (1.15–5.08)	.017
Peripheral atherosclerosis	585/585	7 (1)	6 (2)	1 (<0.5)	5.20 (0.62–43.5)	.090
Neurological						
Previous stroke or TIA	585/585	18 (3)	10 (2)	8 (1)	1.07 (0.42–2.74)	.894
Dementia diagnosis	585/585	31 (5)	16 (5)	15 (6)	0.91 (0.44–1.87)	.783
Pulmonary						
Obstructive sleep apnoea	585/585	37 (6)	22 (7)	15 (6)	1.27 (0.65–2.50)	.493
Pulmonary fibrosis	585/585	1 (<0.5)	0	1 (<0.5)	–	–
Asthma bronchiale	585/585	95 (16)	29 (9)	66 (25)	0.31 (0.19–0.50)	<.001
Chronic obstructive pulmonary disease	585/585	15 (3)	8 (3)	7 (3)	0.98 (0.35–2.74)	.957
Other conditions						
Malignancy	585/585	48 (8)	29 (9)	19 (7)	1.33 (0.73–2.44)	.353
HIV infection	585/585	3 (1)	1 (<0.5)	2 (1)	0.43 (0.04–4.72)	.471
Thyroid insufficiency	585/585	57 (10)	15 (5)	42 (16)	0.27 (0.15–0.50)	<.001
Chronic liver or kidney failure	585/585	26 (4)	18 (6)	8 (3)	1.98 (0.85–4.62)	.111
End-stage renal disease	585/585	9 (2)	6 (2)	3 (1)	1.72 (0.43–6.95)	.443
Systemic connective tissue disease	585/585	2 (<0.5)	0	2 (1)	–	–
Immunodeficiency disease/state	585/585	41 (7)	21 (7)	20 (7)	0.89 (0.47–1.68)	.709
Coagulopathy	585/585	39 (7)	22 (7)	17 (6)	1.12 (0.58–2.16)	.756

Data are patients (%) and odds ratios (OR) (95% confidence intervals).
[a]According to ECOG 0–4 scale [14].
[b]Independent, i.e. living at home, non-independent, i.e. living at institution.

patients. All complications occurred more often in men than in women (Table 2).

Outcome

The overall case fatality of patients in specialized healthcare at 7-, 28- and 90-days were 4%, 11% and 12%, respectively. Male patients, compared to females, had a higher case fatality at 28 days (p=.043) and 90 days (p=.008) whereas no sex difference was observed in case fatality rates at 3 or 7 days (Table 2, Figure 3). The mean hospital LOS was 10.0 days (±11, SD) days and male patients had significantly longer hospital LOS than women (p<.001) (Table 2). The mean duration from symptom onset to fatal outcome was 18.4 days (±13, SD) and significantly longer for males compared to female patients (Table 2). Male patients who deceased were younger (p=.015), had less often retired from work (p=.015) and had more often a diagnosis of diabetes mellitus (p=.023) or malignancy (p=.049) and less often a diagnosis of dementia (p=.004) than their female counterparts (Table 3). In univariate analysis male sex, hypertension, diabetes mellitus, coronary artery disease, dementia, malignancy and immunodeficiency associated with increased case-fatality whereas lack of underlying diseases improved outcome (Table 4(a)). In multivariable analysis parameters connecting independently to 90-days case-fatality were male sex, age, dementia and malignancy (Table 4(a)). However, when analysing ICU patients separately in multivariable analysis only age impacted outcome (Table 4).

Discussion

The main observation of the present study was that both sexes were equally infected by SARS-CoV2.

Table 2. Clinical management, complications and outcome of 585 patients with laboratory confirmed *Covid-19* in specialized healthcare hospital and stratified according to sex.

Characteristics	*N*, number Available data	Parameter *N* (%)	Male sex *N* = 316 (54)	Female sex *N* = 269 (46)	Univariate OR (95% CI)	Univariate *p* Value
Hospital length of stay						
Days, mean (±SD)	585/585	10.0 ± 11	11.7 ± 13	8.0 ± 8	–	<.001
Days, median (quartiles)	585/585	7.0 (3.0–12.0)	7.0 (3.0–14.0)	6.0 (3.0–10.0)	–	<.001
ICU length of stay						
Days, mean (±SD)	585/585	13.8 ± 11	16.8 ± 11	8.4 ± 6	–	<.001
Days, median (quartiles)	585/585	12.5 (5.0–18)	15.0 (8.0–23.5)	7.0 (3.0–13.0)	–	<.001
Time intervals						
Symptoms to diagnosis, days, mean (±SD)	585/583	5.6 ± 5	6.1 ± 5	5.0 ± 5	–	.005
Diagnosis to hospital admission, days, mean (±SD)	585/585	2.5 ± 6	1.9 ± 6	3.3 ± 7	–	.008
Symptoms to hospital admission, days mean (±SD)	585/583	8.1 ± 7	8.0 ± 7	8.3 ± 8	–	.603
Symptoms to death, days mean (±SD)	68/68	18.4 ± 13	21.2 ± 15	12.4 ± 6		.001
Intensive care unit						
Pre-evaluation[a]	585/585	151 (26)	93 (29)	58 (22)	1.52 (1.04–2.21)	.030
Admitted to ICU	585/585	132 (23)	85 (27)	47 (17)	1.74 (1.16–2.30)	.007
Mechanical ventilation	585/585	109 (19)	77 (24)	32 (12)	2.39 (1.52–3.74)	<.001
Prone treatment	585/585	72 (12)	50 (16)	22 (8)	2.11 (1.24–3.59)	.005
ECMO treatment[b]	585/585	0	0	0	–	–
Complications						
Sepsis	585/585	13 (2)	11 (4)	2 (1)	4.82 (1.06–21.9)	.025
Inflammatory lung changes[c]	585/585	463 (79)	261 (83)	202 (75)	1.57 (1.05–2.35)	.026
Acute pulmonary embolus	585/585	19 (3)	16 (5)	3 (1)	4.73 (1.36–16.4)	.007
Acute cardiac insufficiency	585/585	10 (2)	7 (2)	3 (1)	2.01 (0.51–7.85)	.306
Dialysis treatment	585/585	16 (3)	15 (5)	1 (<0.5%)	13.4 (1.75–102)	.001
Cerebrovascular event	585/585	3 (1)	2 (1)	1 (<0.5%)	1.71 (0.15–18.9)	.659
Case-fatality						
3 days	585/585	7 (1)	4 (1)	3 (1)	1.14 (0.25–5.12)	.867
7 days	585/585	25 (4)	18 (6)	7 (3)	2.26 (0.93–5.49)	.065
28 days	585/585	62 (11)	41 (13)	21 (8)	1.76 (1.01–3.06)	.043
90 days	585/585	68 (12)	47 (15)	21 (8)	2.06 (1.20–3.55)	.008

Data are patients (%) and odds ratios (OR) (95% confidence intervals).
[a]Transfer from ward to ICU evaluated.
[b]Extracorporeal membrane oxygenation.
[c]Inflammatory changes in radiological imaging of the lungs.

However, male patients had an increased risk for specialized healthcare hospital admission, with longer hospital LOS, more ICU admissions and higher case-fatality during the first wave of Covid-19. Male patients had more coronary artery disease and excess alcohol use but less obesity and less asthma. Male sex was a risk factor for a severe Covid-19 disease irrespective of any underlying conditions. The delays from symptom onset to diagnosis and hospital admission were longer for men with fatal outcome than female. Accounting for all prognostic parameters in multivariable analysis, men had twice the odds of dying compare to women even in a country with a low level epidemic.

Comparison of case-fatality rates from earlier studies is challenging due to differences in study setups, age-sex adjustments and reported follow-up times. In-hospital Covid-19 case-fatality seems to fall into a certain range. Previous studies report overall hospital case-fatality rates of 12–27% [15–19] including ICU patients with case-fatality ranges of 24–62% [17,19,20]. In the present study, the overall 90 day fatality was 12% among patients in specialized healthcare and 17% for ICU patients. The case-fatality rates of the present study are lower than those presented earlier. There are several plausible explanations available. First, the first wave of Covid-19 reached Finland at a late stage as compared to other countries in Europe. Hence, Finland and the specialized healthcare hospitals of the Capital Province had a unique position as we had the possibility to incorporate and develop treatment strategies from other countries before Covid-19 reached Finland. Second, throughout the Covid-19 wave in spring 2020, the ICU capacity of the specialized healthcare hospitals of the Capital Province was not overstretched. Hence, no patients requiring ICU treatment had to be excluded due to lack of ICU capacity.

It is estimated that up to 15% of Covid-19 patients need hospital care and of hospitalized patients who qualify for ICU treatment those up to 30% become critically ill and require advanced care and ICU treatment [21]. The observations of the present study are in line with this although our cohort study had slightly more hospitalized patients (19%) and less ICU admissions (23%). Since the outbreak of Covid-19 in 2020 studies indicate a general global pattern: Covid-19 infects men and women equally [22,23], but disease severity and case-fatality are higher among men [24,25]. Reports propose that Covid-19 infection rates are primary due to

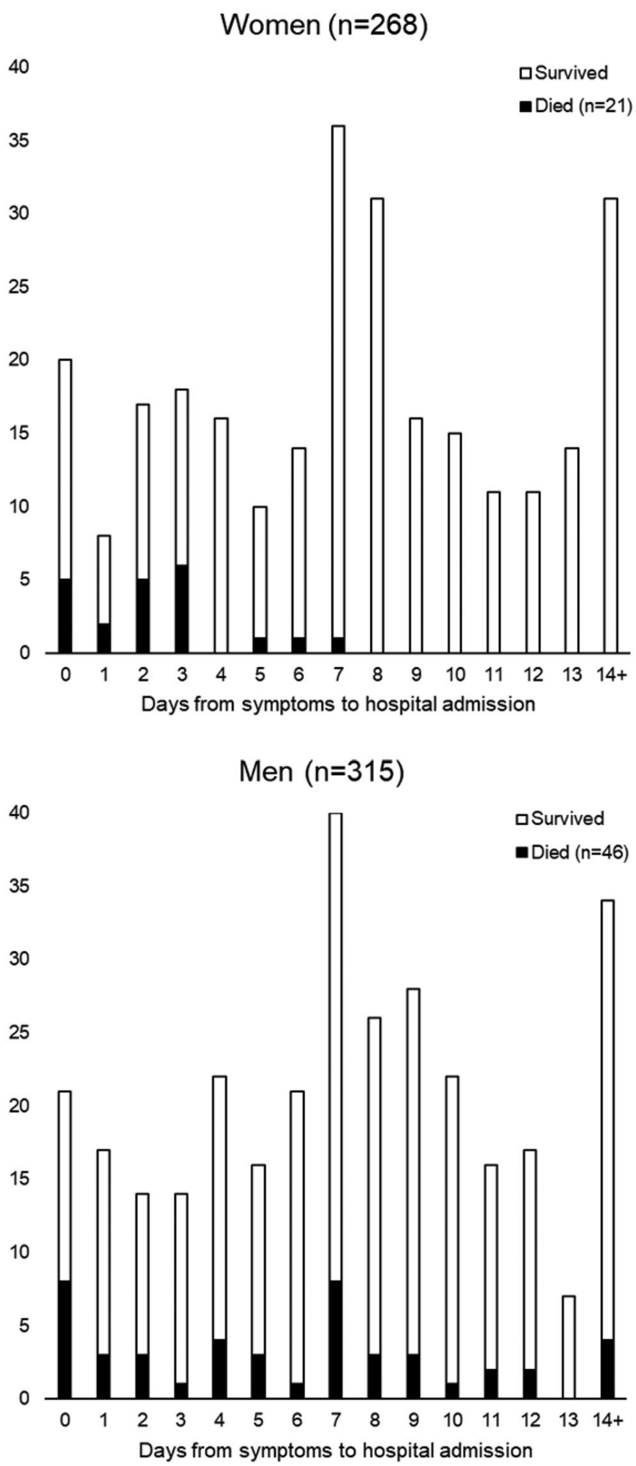

Figure 2. Time period (days) from symptom onset to hospital admission in women ($N = 268$) and men ($N = 315$) with laboratory confirmed Covid-19 treated in specialized healthcare hospitals.

social factors, health seeking behaviour and health status and not sex dependent [26]. Poorer outcome of men is suggested to be a multifactorial phenomenon with biological sex variations and sex specific behavioural risk factors such as smoking and alcohol use [10]. Many observations in the present study are in line with these previous reports.

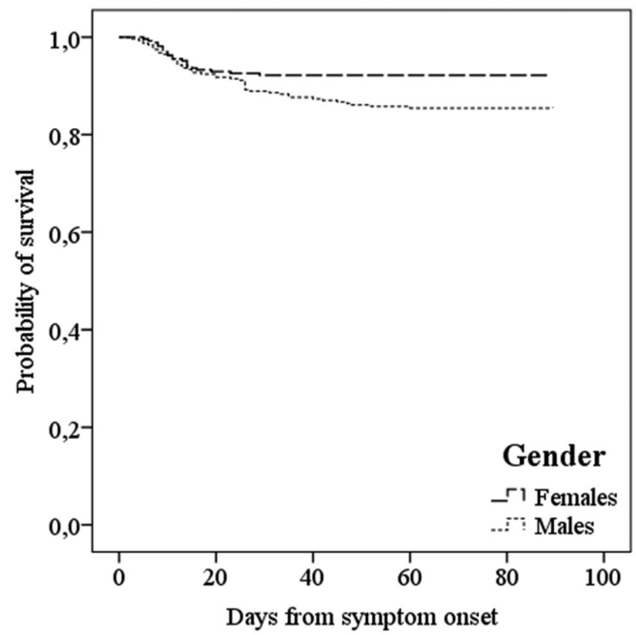

Figure 3. The Kaplan–Meier interpretation of 90-days survival in 585 patients with laboratory confirmed Covid-19 and treated in specialized healthcare hospitals and categorized according to sex. Log-rank 0.010.

The present study observed no sex differences in diagnoses of Covid-19. We observed, however, trends reflecting health-seeking behaviour which relates to the very different diagnostic and admission delays in men and women having the most severe disease leading to death. The duration from the onset of symptoms to the diagnosis was significantly longer for males compared to females. Furthermore, while all women with fatal outcome had short diagnostic delay and were admitted to the hospital soon after the covid-19 diagnosis, this was not the case at all with men, who had both longer diagnostic and admission delays. Some previous data of longer duration from symptom onset to testing among males compared to females exist [27]. A recent report concluded that men pursue Covid-19 testing less frequently than women [28] and studies have shown that women seek healthcare service more frequently than men [29,30]. However, the time from the onset of symptoms to the hospitalization did not differ between sexes.

Previous reports on Covid-19 have repeatedly connected male sex to higher rates of severe and critical disease [7,17,27,31] and male sex is presented as an independent risk factor for admission to ICU and ICU related complications [9,32]. Furthermore, multivariable analyses have reported male sex as an independent parameter for case-fatality [17,27]. However, when including only ICU patients male sex was not an independent

Table 3. Patient characteristics, management and complications in patients with laboratory confirmed *Covid-19* treated in specialized healthcare hospital who died during 90 days follow-up.

Parameters	*N* (%) 68	Male sex *N* = 47 (69)	Female sex *N* = 21 (31)	Univariate OR (95% CI)	Univariate *p* Value
Demographics					
Age, years (median, IQR)	78.5 (68–84)	77 (65–83)	81 (73–89)	–	.015
Age ≥65 years	55 (81)	36 (77)	19 (90)	0.34 (0.07–1.72)	.179
Retired from work	57 (84)	36 (77)	21 (100)	1.31 (1.12–1.53)	.015
Normal functionality[a]	34 (50)	26 (55)	8 (38)	2.01 (0.70–5.76)	.189
Age ≥65 + independent[b]	44 (65)	33 (70)	11 (52)	2.14 (0.72–6.19)	.155
Age ≥65 + not independent[b]	11 (16)	3 (6)	8 (38)	0.11 (0.03–0.48)	.001
Age <65 + independent[b]	11 (16)	9 (19)	2 (10)	2.25 (0.44–11.5)	.319
Age <65 + not independent[b]	2 (3)	2 (4)	0	–	–
Underlying conditions					
No underlying diseases	6 (9)	6 (13)	0	–	–
Cardiovascular					
Hypertension	37 (54)	23 (49)	14 (67)	0.48 (0.16–1.40)	.175
Diabetes mellitus	23 (34)	20 (43)	3 (14)	4.44 (1.15–17.2)	.023
Coronary artery disease	13 (19)	10 (21)	3 (14)	1.62 (0.40–6.63)	.498
Peripheral atherosclerosis	1 (2)	1 (2)	0	–	–
Neurological					
Previous stroke or TIA	5 (7)	3 (6)	2 (10)	0.65 (0.10–4.19)	.647
Dementia diagnosis	17 (25)	7 (15)	10 (48)	0.19 (0.06–0.62)	.004
Pulmonary					
Obstructive sleep apnoea	2 (3)	2 (4)	0	–	–
Pulmonary fibrosis	0	0	0	–	–
Asthma bronchiale	5 (7)	3 (6)	2 (10)	0.65 (0.10–4.20)	.647
Chronic obstructive pulmonary disease	3 (4)	2 (4)	1 (5)	0.89 (0.08–10.4)	.925
Other conditions					
Malignancy	17 (25)	15 (32)	2 (10)	4.45 (0.92–21.6)	.049
HIV positive	0	0	0	–	–
Thyroid insufficiency	7 (10)	4 (9)	3 (14)	0.56 (0.11–2.75)	.469
Chronic liver/kidney failure	5 (7)	5 (11)	0	–	–
End-stage renal disease (including dialysis)	2 (3)	1 (2)	1 (5)	0.44 (0.03–7.30)	.553
Systemic connective tissue disease	0	0	0	–	–
Immunodeficiency disease/state	10 (15)	7 (15)	3 (14)	1.05 (0.24–4.53)	.948
Coagulopathy	7 (10)	5 (11)	2 (10)	1.13 (0.20–6.36)	.889
Intensive care unit					
Transfer evaluated[c]	30 (44)	22 (47)	8 (38)	1.43 (0.50–4.09)	.504
Admitted ICU	23 (34)	19 (40)	4 (19)	2.88 (0.84–9.92)	.085
Mechanical ventilation	23 (34)	19 (40)	4 (19)	2.88 (0.84–9.92)	.085
Prone treatment	17 (25)	15 (32)	2 (10)	4.45 (0.92–21.6)	.049
ECMO treatment[d]	0	0	0	–	–
Complications					
Sepsis	1 (2)	1 (2)	0	–	–
Inflammatory lung changes[e]	50 (74)	35 (75)	15 (71)	1.17 (0.37–3.69)	.793
Acute pulmonary embolus	4 (6)	3 (6)	1 (5)	1.36 (0.13–13.9)	.703
Acute heart insufficiency	3 (4)	2 (4)	1 (5)	0.89 (0.08–10.4)	.925
Dialysis treatment	2 (3)	2 (4)	0	–	–
Cerebrovascular event	1 (2)	1 (2)	0	–	–

Data are patients (%) (OR, 95% CI).
[a]According to ECOG 0–4 scale [14].
[b]Independent, i.e. living at home, non-independent, i.e. living at institution.
[c]Transfer from ward to ICU evaluated.
[d]Extracorporeal membrane oxygenation.
[e]Inflammatory changes in radiological imaging of the lungs.

factor for case-fatality [33]. The results of the present study are in line with these previous observations with male sex connecting to more ICU admission, longer ICU and hospital LOS as well as more complications.

In the present study, altogether 23% were admitted to ICU. In the ICU, mechanical ventilation was the most frequently provided organ support and given to 94% (19% of all hospitalized Covid-19 patients) whereas no patient was in need of extracorporeal membrane oxygenation (ECMO) support. In addition to inflammatory changes in radiological imaging of the lungs, the two most common complications were acute pulmonary embolus and dialysis treatment in 3% of cases. The occurrence of complications is slightly lower as compared to previous reports on Covid-19 with up to 30% requiring ICU including mechanical ventilation and ECMO in 12–27% and 0.5–11%, respectively, and acute pulmonary embolus in 8% and dialysis in 5–12% of cases [15,17,21,33,34]. Moreover, only 19 patients (3%) in our material had pulmonary embolus which may be due to the fact that already in the middle of March 2020 all hospitalized patients were recommended to be treated with a full thrombosis treatment dose of low molecular weight heparin.

Table 4. Multivariate analysis for parameters impacting 90-days mortality in patients with laboratory confirmed *Covid-19* disease treated in specialized healthcare hospital categorized according to the whole patient cohort ($N=585$) (a) and intensive care unit ($N=132$) (b).

(a)

All patients $N=585$	Univariate analysis: Died $N=68$ (12)	Survived $N=517$ (88)	OR (95% CI)	p Value	Multivariate analysis: OR (95% CI)	p Value
Demographics						
Male sex	47 (69)	269 (52)	2.06 (1.20–3.60)	.008	2.37 (1.22–4.59)	.011
Age[a]	79 (69–84)	56 (45–66)	2.44 (1.96–3.04)	<.001	2.04 (1.56–2.66)	<.001
No underlying diseases	6 (9)	191 (37)	0.17 (0.07–0.39)	<.001	0.47 (0.16–1.41)	.181
Hypertension	37 (54)	186 (36)	2.12 (1.28–3.54)	.003	0.71 (0.35–1.44)	.348
Diabetes mellitus	23 (34)	105 (20)	2.01 (1.16–3.46)	.011	1.07 (0.53–2.15)	.849
Coronary artery disease	13 (19)	24 (5)	4.86 (2.34–10.1)	<.001	1.55 (0.64–3.79)	.335
Dementia diagnosis	17 (25)	14 (3)	11.9 (5.58–25.7)	<.001	3.00 (1.18–7.68)	.022
Malignancy	17 (25)	31 (6)	5.23 (2.71–10.1)	<.001	2.94 (1.31–6.59)	.009
Immunodeficiency	10 (15)	31 (6)	2.70 (1.26–5.79)	.008	1.73 (0.68–4.38)	.251

(b)

Intensive care unit patients $N=132$	Univariate analysis: Died $N=23$ (17)	Survived $N=109$ (83)	OR (95% CI)	p Value	Multivariate analysis: OR (95% CI)	p Value
Demographics						
Male sex	19 (83)	66 (61)	3.09 (0.99–9.72)	.045	2.28 (0.65–8.01)	.200
Age[a]	70 (57–78)	58 (49–66)	1.94 (1.26–3.00)	.003	1.64 (1.01–2.67)	.045
Malignancy	6 (26)	5 (5)	7.34 (2.02–26.7)	.001	3.32 (0.79–13.9)	.101
Mechanical ventilation	22 (96)	81 (74)	7.61 (0.98–59.0)	.025	4.46 (0.53–37.3)	.168
Dialysis treatment	2 (10)	11 (11)	0.85 (0.18–4.11)	.838	0.72 (0.13–3.98)	.707

Data are patients (%), median (interquartile range) and odds ratios (OR) (95% confidence intervals). OR for age reported per 10 year increase.
[a]OR for age reported per 10 year increase.

The present study observed only few differences in underlying conditions and risk behaviour between the sexes. However, these results should be compared to national data on underlying conditions for Finnish citizens in order to fully evaluate the profile of patients with Covid-19. Previous reports have concluded that obesity is a risk factor for more severe Covid-19 infection [33,35]. Among hospital patients in our study 43% of men and 58% of women had BMI more than 30 as compared to the overall Finnish population where 26% of men and 28% of women are obese [36]. Thus, among patients requiring treatment in hospital, females were more often obese than men and in this patient cohort overall obesity was more frequent than in the Finnish general population. Smoking, however, was less prevalent in hospital treated Covid-19 patients than in population on average. Altogether 5% of hospitalized Covid-19 patients were current smokers while smoking prevalence in 20–64 year old Finns is 14% [37]. No differences in current smoking habits were observed by sex whereas males had more often a history of smoking. Coronary artery disease was more frequent among men (9%) compared to women (4%). These figures are lower than among the general population where 14% of males over 50 years of age and 7% of all women suffer from coronary artery disease [36]. Both asthma and thyroid insufficiency were more prevalent among hospitalized Covid-19 patients as compared to the general population. In the present study, the occurrence of asthma among men and women were 9% and 25% whereas that of thyroid insufficiency was 5% and 16%. The corresponding figures for the general population are 10% for over 30 year old males and 14% for women for asthma [36] and 1% for men and 6% for women for thyroid insufficiency [38].

The present study includes strengths, as well as weaknesses, that have to be taken into account when interpreting results. Strengths; first, due to the unique national personal identification code given to all Finnish residents, combined with electronic patient records, laboratory records, and we could identify and record all laboratory confirmed Covid-19 patients across different sections of the specialized healthcare hospitals of the Capital Province into the quality registry. Second, the *National causes of death* registry enabled us to follow-up all-cause case-fatality for all deceased patients. Third, the fully centralized specialized hospital service and universal healthcare coverage allowed for identification of all consecutive patients and ensured that no laboratory positive hospitalized Covid-19 patients have been lost.

Weaknesses of the study include; first, this was a retrospective registry report with all the caveats that go with a retrospective observational setting. Thus, the observations are solid, but the multivariable analyses must be considered hypothesis generating. Second, the report is from a country where the primary prevention of COVID-19 has been quite successful. The patient numbers are therefore small. Still, the specialized healthcare hospitals of the Capital Province area cover about 30% of the national population and our area took care of 75% (5471/7277) [39] of all Covid-19 cases in the country during the first wave. Third, although patients have not been systematically followed up for possible disability after discharge, in our opinion, the all-cause case-fatality is a robust outcome metric. Fourth, the authors recognize that the current study does not qualify as a fully population-based study due to the fact that medical details of previously institutionalized and/or dependent patients are not included as these patients have been treated in the primary-care hospitals of the municipalities. However, on the other hand, the coverage of previously independent patients is comprehensive.

In conclusion, during the first wave of Covid-19 at the specialized healthcare hospitals of the Capital Province of Finland, the frequency of laboratory confirmed cases did not differ according to sex. However, male sex was associated with a more severe disease and higher case-fatality. Men with fatal outcome had more often delayed diagnosis and delayed admission. Our findings could represent different treatment-seeking behaviour by sex, different disease progression by sex or a combination of these. These findings could have implications for both patient monitoring for severe disease and for communication to the general public regarding testing. Understanding the potential differences underlying this phenomenon warrants further research.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

EF and AJ have received a grant from Wilhelm and Else Stockmann Foundation. VH has received a grant from Finska Läkaresällskapet.

ORCID

Maarit Ahava http://orcid.org/0000-0001-6653-3238
Ville Holmberg http://orcid.org/0000-0002-5866-9634

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