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ORIGINAL ARTICLE

Sex differences in COVID-19 symptoms and outcomes in people with kidney failure treated with dialysis: a prospective cohort study

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Abstract

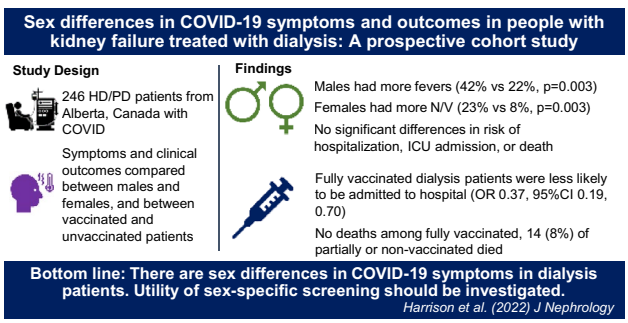
Background People with kidney failure treated with dialysis are at increased risk of SARS-CoV-2 infection, and severe COVID-19 outcomes such as hospitalization and death. Though there are well-defined sex differences in outcomes for the general population with COVID-19, we do not know whether this translates into kidney failure populations. We aimed to estimate the differences in COVID-19 symptoms and clinical outcomes between males and females treated with maintenance dialysis.

Methods In this prospective observational cohort study, we included adults treated with maintenance dialysis in Southern Alberta, Canada that tested positive for COVID-19 between March 2020 and February 2022. We examined the association between sex (dichotomized as male and female) with COVID-19 symptoms including fever, cough, malaise, shortness of breath, muscle joints/aches, nausea and/or vomiting, loss of appetite, diarrhea, headache, sore throat, and loss of smell/taste using chi-square or Fisher's exact tests. Secondary outcomes included 30-day hospitalization, ICU admission, and death.

Results Of 1,329 cohort participants, 246 (18.5%) tested positive for SARS-CoV-2 and were included in our study, including 95 females (39%). Of 207 participants with symptoms assessed, females had less frequent fever ($p=0.003$), and more nausea or vomiting ($p=0.003$) compared to males, after correction for multiple testing. Males exhibited no symptoms 25% of the time, compared with 10% of females ($p=0.01$, not significant when corrected for multiple testing). We did not identify statistically significant differences in clinical outcomes between the sexes, though vaccinated patients had lower odds of hospitalization.

Conclusions Sex differences in COVID-19 symptoms were identified in a cohort of patients treated with maintenance dialysis, which may inform sex-specific screening strategies in dialysis units. Further work is necessary to examine mechanisms for identified sex differences.

Graphical abstract



Keywords Kidney failure · Dialysis · COVID-19 · SARS-CoV-2 · Sex

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Introduction

People with kidney failure treated with dialysis are a vulnerable population with high comorbidity burden and baseline mortality risk [1, 2]. Many are elderly, have underlying cardiovascular disease, are immunocompromised, and have frequent exposure to health-care settings for acute and chronic disease management [2, 3]. These factors, among others in the general population, have been found to be associated with increased risk of morbidity and mortality as a result of infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus responsible for the ongoing coronavirus disease 2019 (COVID-19) pandemic [4–7]. Given the increased burden of these risk factors in people with kidney failure, they have an increased risk of both infection with SARS-CoV-2 and severe complications of COVID-19, including mortality [8–12]. Identification of cases based on symptoms and other factors is crucial to allow for targeted COVID-19 care in this high-risk population. Further, as the majority of people with kidney failure receiving dialysis have frequent health-care encounters for dialysis treatments or medical visits, there is potential risk of viral transmission to other vulnerable patients, health-care providers, and institutions.

There is consistent evidence in the general population that biological sex plays a role in COVID-19 pathophysiology and epidemiology; males experience COVID-19 differently [13] and have worse outcomes, such as higher mortality, when compared to females [14–17]. These differences are not clearly delineated in people with kidney failure, where rates of infection and COVID-19 severe outcomes are higher overall but may not be meaningfully different between males and females [8, 9, 12]. Outside of disparate outcomes, literature investigating sex- and gender-related differences in COVID-19 symptoms upon presentation have reported conflicting findings [13, 18–21], and to our knowledge, it is not clear whether there are sex differences in COVID-19 symptoms for people with kidney failure. As this group is at risk of severe outcomes, determining which symptoms are more or less likely to be present based on sex has important dialysis screening and unit planning implications.

Therefore, we aimed to estimate the differences in COVID-19 symptoms between males and females with kidney failure treated with dialysis in a prospective cohort study based in Southern Alberta, Canada. Our secondary objectives were to examine differences in COVID-19 severe outcomes including hospitalization, Intensive Care Unit (ICU) admission, and death between males and females.

Methods

Study design and setting

This study was a prospective observational cohort study of people with kidney failure receiving dialysis in Southern Alberta, Canada that tested positive for COVID-19 between March 15, 2020 and February 28, 2022. Alberta is a province of approximately 4.4 million people, and due to universal public health insurance, dialysis care is organized and covered by the provincial health authority [22, 23]. Hence, we have complete capture of the total dialysis population for Southern Alberta within the Alberta Kidney Care-South (AKC-S) organization. At the start of our study, there were a total of 1329 individuals receiving dialysis, with 931 receiving in-center conventional hemodialysis (HD) and 398 receiving home dialysis (296 Peritoneal dialysis [PD] and 102 home HD [HHD]). In March 2020, AKC-S began implementing non-pharmaceutical interventions (NPIs) including continuous masking, and applied standardized nurse-led screening for COVID-19 exposure risk and symptoms for patients receiving dialysis as they entered outpatient clinics and HD units. Any person with a positive screen underwent testing for SARS-CoV-2 using a validated real-time reverse-transcriptase polymerase chain reaction (rtRT-PCR) assay [24]. A positive screen was defined as any COVID-19 symptoms (outlined below), recent travel outside of the country, exposure history, living in an outbreak facility, or receiving dialysis care at a site with two or more COVID-19 cases. All COVID-19 testing results were automatically uploaded from provincial laboratory systems into our AKC-S patient-based renal information system (PARIS). The reasons for COVID-19 testing and the patient-reported symptoms were recorded for every AKC-S dialysis patient that tested positive for COVID-19. All patients that tested positive for SARS-CoV-2, were included in our cohort and followed for 30 days to ascertain outcomes using electronic medical record data. For context, by the end of February 2022, 11.9% of the Albertan population had tested positive for COVID-19 [25]. COVID-19 vaccinations were broadly approved for administration in the dialysis population in April 2021 (unless the patient was a frontline health-care worker or received their vaccine abroad). We conducted this study and reported our findings in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [26]. We were granted ethics approval with waiver of informed consent by the University of Calgary Conjoint Health Research Ethics Board (REB20-0651).

Participants

All adults (18 years and older) who were part of the AKC-S dialysis program and received maintenance in-center conventional HD, PD, or HHD and who tested positive for COVID-19 during the study period were included. Duration of dialysis had to be at least 90 days prior to their positive test to be included. Only the first COVID-19 positive event was included per person.

Variables

For all analyses, sex was treated as our independent variable, and was dichotomized as male and female. This information was obtained and linked from our regional electronic health record registration system (Clinibase, Alberta Health Services), which is dependent on health registry sex data, into our PARIS database.

We examined several symptoms as primary outcomes and analyzed them independently. Fever was defined as objectively measured temperature greater than 37.3° Celsius (99.1° Fahrenheit); the rest of the symptoms were patient-reported and included cough, malaise, shortness of breath, muscle joints/aches, nausea and/or vomiting, loss of appetite, diarrhea, headache, sore throat, and loss of smell/taste. The rationale for the temperature threshold for identifying fever was based on initial AKC-S COVID-19 planning and literature suggestions [27]. Where symptom screens were not completely recorded, it was categorized as missing and not included in our primary analyses. Our secondary outcomes included hospitalization, admission to ICU, and death, all within 30 days of their positive test.

Age (in years) was extracted and determined at the time of COVID test positivity. Comorbidity data were extracted, and included hypertension, diabetes, congestive heart failure, smoking history, peripheral artery disease, malignancy history, coronary artery disease, cerebrovascular disease, and chronic obstructive lung disease. These were entered into PARIS by members of the dialysis health care team. We collected the reason for kidney failure, categorized into diabetes, hypertension, glomerulonephritis, obstructive nephropathy or acute kidney injury, and other. Dialysis modality was also obtained, and ascertained at the time of COVID-19 positivity. The reason for COVID-19 testing was also collected. Vaccines became available to our patient population in early 2021, and in our province we defined receipt of a full vaccine series in dialysis patients as 3 doses, partial vaccination as 1–2 doses, and not vaccinated as 0 doses prior to each participant testing positive for COVID-19.

Statistical methods

We summarized baseline characteristics for the overall cohort and stratified by sex. Counts and percentages for categorical or dichotomous variables were calculated, and age was summarized using median and interquartile range (IQR). Sample size calculations were not performed for our primary outcome analyses, as we included all COVID-19 positive individuals within AKC-S dialysis programs. Differences in the number of males and females on dialysis with each primary COVID-19 symptom were explored using either chi-square analysis or Fisher's exact test. We considered the risk of error introduced with multiple testing (11 symptom comparisons), and to account for the family-wise error rate of 0.43, the p-value for significance for each symptom comparison was 0.00454. For our secondary outcomes, we used univariate logistic regression to estimate odds ratios (and accompanying 95% confidence intervals) for an association between sex and the odds of death, hospitalization, or ICU admission. As an exploratory and descriptive analysis, we report the symptom proportions by sex for cohort participants that experienced a composite of our secondary clinical outcomes. We also explored descriptively whether receiving a full vaccine series modified the sex differences in symptoms, and whether there were clinical outcome differences in this population depending on vaccine status. All statistical analyses were completed using Stata Software v16.0 (StataCorp) [28].

Results

There were 1,329 people with kidney failure in the AKC-S dialysis program during the study period frame, and 246 patients tested positive for COVID-19, which represents an estimated 18.5% of our AKC-S dialysis population. Of the COVID-19 positive individuals, 180 received in-center conventional HD, 57 received PD, and 9 HHD, with a median dialysis vintage of 2.6 years (IQR 1.2, 4.6) (Table 1). Our cohort included 95 females (39%), and the median age of the cohort was 62 years (IQR 50, 71). Hypertension (90%), diabetes (65%), and coronary artery disease (31%) were the most common comorbidities, with diabetes also being the most common etiology of kidney failure (44%). Reasons for COVID-19 testing were due to symptoms (57%), COVID-19 exposure (16%), outbreak (11%), for routine testing done at the time of hospital admission (3%), or for travel (1%). An estimated 42% of our cohort were unvaccinated, 27% received a partial vaccine series, and 30% were fully vaccinated at the time of their positive COVID-19 test.

The most frequent COVID-19 symptoms overall were cough (49%), fever (34%), and malaise (28%) (Table 2;

Table 1 Baseline characteristics of cohort

Characteristic	Overall ($n=246$)	Female ($n=95$)	Male ($n=151$)
Age, median years (IQR)	62 (50, 71)	64 (50, 73)	61 (50, 71)
Female sex, *n* (%)	95 (39)	–	–
Dialysis modality			
In-centre hemodialysis, *n* (%)	180 (73)	68 (72)	112 (74)
Peritoneal dialysis, *n* (%)	57 (23)	24 (25)	33 (22)
Home hemodialysis, *n* (%)	9 (4)	3 (3)	6 (4)
Dialysis Vintage, median years (IQR)	2.6 (1.2, 4.6)	2.6 (1.1, 5.0)	2.6 (1.3, 4.4)
Comorbidities			
Hypertension, *n* (%)	221 (90)	83 (87)	138 (91)
Diabetes, *n* (%)	158 (65)	64 (67)	94 (62)
Coronary artery disease, *n* (%)	77 (31)	28 (29)	49 (32)
Congestive heart failure, *n* (%)	57 (23)	19 (20)	38 (25)
Malignancy, *n* (%)	33 (13)	12 (13)	21 (14)
Peripheral artery disease, *n* (%)	26 (11)	10 (11)	16 (11)
Current smokers, *n* (%)	30 (12)	10 (11)	20 (13)
Chronic obstructive lung disease, *n* (%)	43 (17)	18 (19)	25 (17)
Cerebrovascular disease, *n* (%)	26 (11)	12 (13)	14 (9)
Etiology of kidney failure, n (%)			
Diabetes	109 (44)	45 (47)	64 (42)
Hypertension	37 (15)	15 (16)	22 (15)
Glomerulonephritis	49 (20)	17 (18)	32 (21)
Obstruction or AKI	21 (9)	8 (8)	13 (9)
Other (ischemic, PKD)	30 (12)	10 (11)	20 (13)
Indication for testing, n (%)			
Symptoms	139 (57)	53 (56)	86 (57)
Exposure	39 (16)	17 (18)	22 (15)
Outbreak	21 (11)	6 (6)	15 (10)
Routine testing at time of hospital admission	7 (3)	3 (3)	4 (3)
Travel	1 (0.5)	1 (1)	0 (0)
Unknown	39 (16)	15 (16)	24 (16)
Vaccine status			
Unvaccinated	104 (42)	39 (41)	65 (43)
Partially vaccinated	67 (27)	28 (29)	39 (26)
Fully vaccinated	70 (30)	28 (29)	47 (31)

Fig. 1). Anosmia and headache were the most infrequent symptoms, occurring in 8% and 7% of the cohort, respectively. After correction for family-wise error rate, we found that males were more likely to present with fevers compared with females (42% versus 22%, $p=0.003$). Females reported more nausea or vomiting, with 23% compared to 8% of males ($p=0.003$). Though the rest of the symptom comparisons did not reach statistical significance criteria, the point estimates of nearly all symptoms were more common in females. There were 10% of females in our cohort that had no reported symptoms, compared with 25% of males ($p=0.01$, not significant when corrected for multiple testing). In our exploratory analysis of symptom differences for people that experienced a clinical outcome, proportions of all symptoms in this group appeared similar to the overall group though there may be more fever, dyspnea, and nausea or vomiting (Supplementary Table 2). Differences between females and males appeared similar across vaccination status, though overall the symptom burden was similar between these groups (Supplementary Table 3).

In terms of our secondary outcomes, 80 (33%) people in our cohort were admitted to hospital due to COVID-19, 14 (6%) experienced an ICU admission, and 14 (6%) died, all within 30 days of a positive test (Table 3). We did not identify statistically significant evidence of an association of male sex with odds of hospitalization (OR 0.62 [95% CI 0.36, 1.07]), ICU admission (OR 0.83 [95% CI 0.28, 2.47]), or death (OR 1.61 [95% CI 0.49, 5.30]). Fully vaccinated cohort participants were significantly less likely to be admitted to hospital (OR 0.37 [95% CI 0.19, 0.70])

Table 2 COVID-19 Symptoms for cohort of people receiving dialysis in Southern Alberta, Canada

COVID symptoms	Overall cohort ($n=207$)	Female ($n=77$)	Male ($n=130$)	p-values
Cough, *n* (%)	102 (49)	41 (53)	61 (47)	0.4
Fever, *n* (%)	72 (34)	17 (22)	55 (42)	0.003*
Malaise, n (%)	57 (28)	25 (32)	32 (25)	0.2
Sore throat, *n* (%)	39 (19)	19 (25)	20 (15)	0.1
Dyspnea, *n* (%)	38 (18)	15 (19)	23 (18)	0.7
Nausea or vomiting, *n* (%)	29 (14)	18 (23)	11 (8)	0.003*
Loss of appetite, *n* (%)	26 (13)	9 (12)	17 (13)	0.8
Diarrhea, *n* (%)	24 (12)	14 (18)	10 (8)	0.02
Myalgia or arthralgia, *n* (%)	20 (10)	8 (10)	12 (9)	0.8
Anosmia, *n* (%)	16 (8)	7 (9)	9 (7)	0.6
Headache, *n* (%)	15 (7)	9 (12)	6 (5)	0.06
No symptoms	40 (19)	8 (10)	32 (25)	0.01

Symptom frequency compared between females and males with a chi-square test or Fisher's exact test. Significance defined as $p<0.00454$ after adjustment for multiple testing. *P*-values are rounded to nearest one non-zero digit

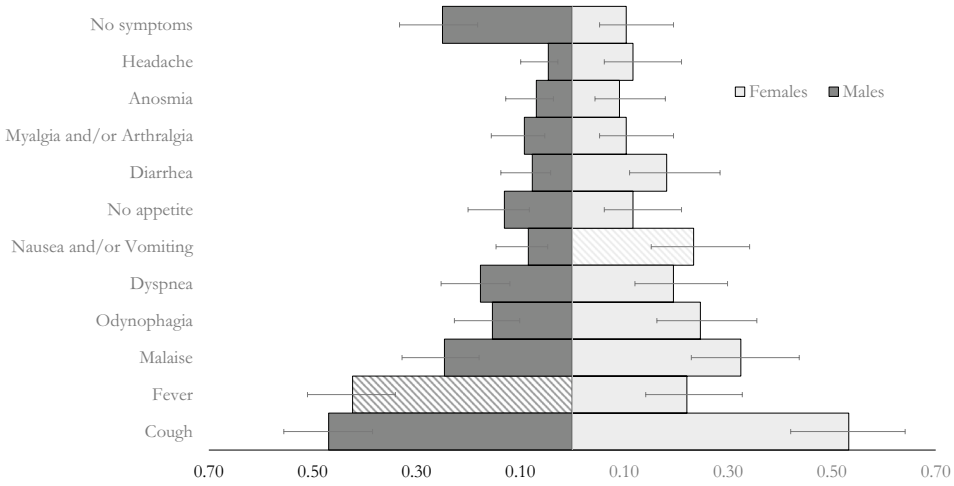

Fig. 1 Sex-stratified COVID-19 Symptom Proportions for People with Kidney Failure. The estimated proportion of males and females with each COVID-19 symptom is included, along with 95% confidence intervals. Bars that are cross-hatched indicate that this symptom was statistically higher in the respective sex when tested

Table 3 Clinical COVID-19 Outcomes

Outcomes	Overall cohort ($n=246$)	Female ($n=95$)	Male ($n=151$)	Odds ratio, male vs female (95%CI)
Hospitalized, *n* (%)	80 (33)	37 (39)	43 (28)	0.62 (0.36, 1.07)
ICU, *n* (%)	14 (6)	6 (6)	8 (5)	0.83 (0.28, 2.47)
Death, *n* (%)	14 (6)	4 (4)	10 (7)	1.61 (0.49, 5.30)

CI confidence interval, *ICU* intensive care unit

(Supplementary Table 4). There were no deaths among fully vaccinated dialysis patients, and 14 (8%) of partially or non-vaccinated participants died.

Discussion

In this prospective cohort study of people with kidney failure receiving dialysis, we identified 246 individuals that tested positive for COVID-19 between March 2020 and February 2022, representing nearly one fifth of the dialysis population in Southern Alberta, Canada. We found

that males had statistically more fevers as part of their COVID-19 presentation compared to females, and females had statistically more nausea or vomiting. There were no statistically significant differences between sexes for the odds of hospitalization, ICU admission, or death, though a large proportion experienced these outcomes overall, particularly in patients that had not received a full vaccine series.

The risk of COVID-19 among our dialysis population was sizable, though it must be interpreted in light of risk among the general population in Alberta and other similar cohorts of people receiving dialysis. By the end of February 2022, an estimated 12% of the Albertan population had tested positive for COVID-19, which is likely an underestimate of the overall COVID-19 burden with reduced regional testing capacity at later stages of the pandemic [25]. Further, of these positive cases, 4.7% were hospitalized, 0.7% went to ICU, and 0.8% died in Alberta. These metrics suggest that dialysis patients in our program were more likely to become infected with SARS-CoV-2 and have worse clinical outcomes, or alternatively that they were more likely to be tested. In the province of Ontario, Canada, over a period of March 2020 to November 2020, 239 of 13,512 (1.8%) people receiving dialysis tested positive for COVID-19 [29]. They reported a much higher rate of hospitalization, at 86%, and of the composite of mortality and/or ICU admission at 21%. Though this represents the most similar cohort of dialysis recipients to our own, direct comparison becomes difficult given the differences in the study period, potential differences in screening strategies, and dialysis population demographics. Further, the timing and significance of COVID-19 waves varied between these two jurisdictions [30]. If we directly compared these groups, the prevalence of COVID-19 in our program overall appears to be higher, though with less frequent severe outcomes. This may reflect more sensitive screening practices that identified patients with milder symptoms and COVID-19 illness in our program, differences in the pandemic course between provinces, and capture of different variant waves in each respective study.

There are many suggested reasons for sex and gender differences in people with COVID-19. Biological variables such as differences in innate immune cytokines (IL-8 and IL-18), induction of non-classical monocytes, and T-cell activation have been suggested to play a role in sex-specific differential susceptibility to SARS-CoV-2 infection, COVID-19 outcomes, and symptoms [31]. SARS-CoV-2 requires binding to the membrane-bound protein angiotensin converting enzyme 2 (ACE2) for cellular uptake, and sex-based mechanisms for down-regulation of this enzyme in females have been extensively described [17]. Further, the distributions of many chronic diseases associated with poor COVID-19 outcomes are different between males and females [32]. On top of these sex-based biological variables, there are important social context mechanisms for COVID-19 that are influenced by gender factors [33]. For example, health behaviors such as smoking traditionally occur more frequently in masculine gender roles, which can influence COVID-19 outcomes by contributing to worse respiratory illness but also contribute to higher burden of cardiovascular disease which also portends a worse COVID-19 prognosis [14, 34]. Additionally, gender factors such as differences in occupation (with more women participating in health and service sectors), adherence to NPIs such as hand-washing and mask-wearing, social and family obligations, all play a role in contributing to variable exposure to SARS-CoV-2 infection [14, 17, 33]. These variables are not fixed for men and women, and are modified by country of origin, age, and ethnicity [14, 35].

When we examine individual symptoms from our study, the underlying reasons for the differences in fever occurrence are not completely clear, although possible explanations include sex differences in immune system (e.g. differences in T-cell and monocyte activation and cytokine levels) [31] and hormonal regulation. In several animal studies, females had lower capacity to develop fever without co-administration of testosterone, which then equalized fever generation [36], with older age found to exacerbate sex differences in fever capacity [37]. In humans, circulating estrogens promote lower body temperature and dissipation of heat, and progesterone is associated with higher body temperature (at baseline) with peripheral vasoconstriction [38]. Considering the mechanisms outlined above, Sha et al. examined a cohort of Chinese COVID-19 cases from three hospitals [21]. When they stratified clinical outcomes and symptoms by both sex and age dichotomized at 55 years (to approximate menopause for females), females under the age of 55 had significantly less fever compared to males, whereas females above 55 years had no significant difference in fever compared with similar aged males. Given our cohort median age of 60 years, which was comparable between the sexes, the influence of menopause and hormonal factors such as estrogen deficiency on the occurrence of fever is likely important. To our knowledge, examination of the differences in fever by sex with assessment of age as a modifying variable has not been explored. In addition to biological sex-related factors for differences in fever, it is possible that gender factors are at play. Women may be more aware of their symptoms, leading to administration of anti-pyretic medication such as acetaminophen, thus masking fever [39, 40]. Nausea and vomiting was more common in our cohort in females; this has been also found in other COVID-19 literature. In the same Chinese cohort listed above, only females over 55 years had more gastrointestinal symptoms than age-matched males [21]. In a US-based cohort study by Mathad et al., females were also more likely to experience gastrointestinal symptoms [20]. In both studies, no

postulated mechanisms were suggested. Gastrointestinal symptoms are more common for females in many disease processes, including irritable bowel syndrome [41] and acute coronary syndrome [42]. Somatic symptoms are more often reported by women in many clinical situations [43]; as most symptoms relied on patient self-report in our study, this suggests that we might observe possible gender differences by this mechanism in COVID-19 symptoms as well. Overall, although we could not find other kidney disease-specific literature comparing female and male COVID-19 symptoms, our findings are consistent with other COVID-19 literature in the general population, and with fundamental scientific principles that underlie the development of the symptoms themselves.

There are several limitations to consider when interpreting our study results. First, although we have examined differences in symptoms based on sex as recorded in our EMR, it is difficult to ascertain whether identified differences were based on biological sex or socio-cultural gender factors. Though we captured all COVID-19-positive dialysis recipients for half of a large Canadian province, assessment of clinical outcomes was limited by sample size. More simply, our study was likely underpowered to detect small differences in clinical symptoms and outcomes between the sexes. Further, considering the number of events we identified, we did not feel that it was methodologically appropriate to adjust our outcome estimates for important covariates and confounding variables, nor test for important interactions with age. Additionally, examination of the sex differences in symptoms would have been complemented with subgroup analyses with stratification by age. This may allow for greater exploration and hypothesis generation into the hormonal contribution to sex differences in COVID-19 symptoms. Though we based our rationale for a lower fever threshold on relevant literature [27], the impact of biological sex variables on baseline temperatures (i.e. with females having lower temperature) may have led to this symptom criterion being more sensitive in males and overestimating this symptom prevalence in a differential way. However, as our results are consistent with the rest of the COVID-19 literature, we do not think this has significant implications on our study validity. Finally, patients receiving home dialysis modalities may not be seen in a health-care setting as often as people receiving conventional in-center HD, they would be screened less often and perhaps less often in person, leading to lower sensitivity in identifying their positive COVID-19 symptoms.

Our study, coupled with the overall COVID-19 literature on sex differences, has several potential implications. The most obvious impact of these results is to raise awareness for clinicians treating dialysis patients, so that these sex-based differences are incorporated into the decisions surrounding testing for COVID-19. On a system or dialysis program basis, our findings may inform screening practices for people with kidney failure. Considering people receiving dialysis have a high burden of diverse symptoms at baseline [44], it may be more difficult to recognize new symptoms [45]; thus the prevalences of symptoms in our study were often lower than studies in the general population. Since we found differences in COVID-19 symptoms by sex, our results may provide impetus for the development of sex-specific COVID-19 symptom screening questionnaire development. For example, as females had nearly three times more nausea or vomiting compared to males, and males were more than two times more likely to present with no symptoms, these are factors that could be incorporated into sex-specific screening strategies. Perhaps it is likely that females with gastrointestinal symptoms are more likely to be missed with conventional screening that includes only febrile and respiratory manifestations. The United States Preventive Services Task Force (USPSTF) has now supported a mandate to incorporate sex and gender into future clinical preventive recommendations [46], thus design of dialysis program COVID-19 screening programs that account for sex differences aligns with this goal. Further, the impact of sex-stratified COVID-19 screening should be tested prospectively to see if there is truly an impact on disease identification. This approach could provide benefit not only to people with kidney failure but the general population as well. Finally, if we could gather a sufficient sample of people receiving dialysis that were tested for SARS-CoV-2, we could evaluate COVID-19 symptoms and their collective predictive ability for a positive test in a multivariable risk prediction model. This has been assessed in a large UK cohort study [47], but without incorporation of sex as a variable, and not specifically for people with kidney failure. Overall, given the equipoise in the literature about sex differences in COVID-19 symptoms, larger confirmatory studies among dialysis populations are needed.

Conclusions

In this prospective cohort of 246 COVID-19 positive dialysis patients in Alberta, Canada, we explored the differences in symptoms and outcomes between males and females. To our knowledge, this was the first study to report on these sex differences in a dialysis population. We found that males had more fevers than females, and females had more nausea or vomiting. Though not statistically significant once corrected for multiple testing, we observed that males exhibited no symptoms more often than females. This may represent sex-based differences in symptom manifestation or gender-based differences in symptom reporting. Our results are generalizable to other healthcare jurisdictions with publicly-funded dialysis provision, and in settings with similar COVID-19 epidemiology. Further work is necessary

to explore the mechanisms of symptom differences, and to determine whether a sex-specific screening strategy translates to improved infection control.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40620-022-01448-0.

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Authors' contributions Research idea and study design: JMM, JP; statistical analysis: TGH, TT, JMM; data analysis and interpretation: All; Drafting of manuscript: All. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Declarations

Conflict of interest All the authors declared no competing interests.

Ethics approval and consent to participate We were granted ethics approval with waiver of informed consent by the University of Calgary Conjoint Health Research Ethics Board (REB20-0651).

Consent for publication All authors have reviewed this manuscript in its current form and consent to its publication.

Data sharing statement This study is based in part on data provided by Alberta Health and Alberta Health Services. We are not able to make our dataset available due to restrictions on sharing confidential patient-level data in the setting of waived consent of participants, and patients could be identifiable with our sample size.

References

1. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol. 1998;9:12 Suppl:S16–23; https://www.ncbi.nlm.nih.gov/pubmed/11443763.
2. Fraser SD, Taal MW (2016) Multimorbidity in people with chronic kidney disease: implications for outcomes and treatment. Curr Opin Nephrol Hypertens 25(6):465–472. https://doi.org/10.1097/mnh.0000000000000270
3. Kent S, Schlackow I, Lozano-Kühne J, Reith C, Emberson J, Haynes R et al (2015) What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? BMC Nephrol 16:1. https://doi.org/10.1186/s12882-015-0054-0
4. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X et al (2020) Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382(18):1708–1720. https://doi.org/10.1056/nejmoa2002032
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223):497–506. https://doi.org/10.1016/s0140-6736(20)30183-5
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054–1062. https://doi.org/10.1016/s0140-6736(20)30566-3
7. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J et al (2020) Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect 81(2):e16–e25. https://doi.org/10.1016/j.jinf.2020.04.021
8. Taji L, Thomas D, Oliver MJ, Ip J, Tang Y, Yeung A et al (2021) COVID-19 in patients undergoing long-term dialysis in Ontario. Can Med Assoc J 193(8):E278–E284. https://doi.org/10.1503/cmaj.202601
9. Lano G, Braconnier A, Bataille S, Cavaille G, Moussi-Frances J, Gondouin B et al (2020) Risk factors for severity of COVID-19 in chronic dialysis patients from a multicentre French cohort. Clin Kidney J 13(5):878–888. https://doi.org/10.1093/ckj/sfaa199
10. Goicoechea M, Sánchez Cámara LA, Macías N, Muñoz De Morales A, Rojas ÁG, Bascuñana A et al (2020) COVID-19: clinical course and outcomes of 36 hemodialysis patients in Spain. Kidney Int 98:27–34. https://doi.org/10.1016/j.kint.2020.04.031
11. Tortonese S, Scriabine I, Anjou L, Loens C, Michon A, Benabdelhak M et al (2020) COVID-19 in patients on maintenance dialysis in the paris region. Kidney Int. Rep. 5(9):1535–1544. https://doi.org/10.1016/j.ekir.2020.07.016
12. Valeri AM, Robbins-Juarez SY, Stevens JS, Ahn W, Rao MK, Radhakrishnan J et al (2020) Presentation and Outcomes of Patients with ESKD and COVID-19. J Am Soc Nephrol 31(7):1409–1415. https://doi.org/10.1681/asn.2020040470
13. Ancochea JIJ (2021) Evidence of gender differences in the diagnosis and management of coronavirus disease 2019 patients: an analysis of electronic health records using natural language processing and machine learning. J Womens Health 30(3):393–404. https://doi.org/10.1089/jwh.2020.8721
14. Islam N, Khunti K, Dambha-Miller H, Kawachi I, Marmot M (2020) COVID-19 mortality: a complex interplay of sex, gender and ethnicity. Eur J Pub Health 30(5):847–848. https://doi.org/10.1093/eurpub/ckaa150
15. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L et al (2020) Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. https://doi.org/10.1136/bmj.m1985
16. Jun T, Nirenberg S, Weinberger T, Sharma N, Pujadas E, Cordon-Cardo C et al (2021) Analysis of sex-specific risk factors and clinical outcomes in COVID-19. Commun Med. 1:1. https://doi.org/10.1038/s43856-021-00006-2
17. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL (2020) Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ 11:1. https://doi.org/10.1186/s13293-020-00304-9
18. Meng Y, Wu P, Lu W, Liu K, Ma K, Huang L et al (2020) Sex-specific clinical characteristics and prognosis of coronavirus

disease-19 infection in Wuhan, China: A retrospective study of 168 severe patients. PLOS Pathog. 16:e1008520. https://doi.org/10.1371/journal.ppat.1008520
19. Su YJ, Kuo KC, Wang TW, Chang CW (2021) Gender-based differences in COVID-19. New Microbes New Infect. 42:100905. https://doi.org/10.1016/j.nmni.2021.100905
20. Mathad JS, Lee MH, Chalem A, Frey MK, Chapman-Davis E, Kopparam RV et al (2021) Sex-related differences in clinical presentation and risk factors for mortality in patients hospitalized with coronavirus disease 2019 in New York city. Open Forum Infect Dis 8:8. https://doi.org/10.1093/ofid/ofab370
21. Sha J, Qie G, Yao Q, Sun W, Wang C, Zhang Z et al (2021) Sex differences on clinical characteristics, severity, and mortality in adult patients with COVID-19: a multicentre retrospective study. Front Med 8:123. https://doi.org/10.3389/fmed.2021.607059
22. Hemmelgarn BR, Clement F, Manns BJ, Klarenbach S, James MT, Ravani P et al (2009) Overview of the Alberta kidney disease network. BMC Nephrol 10:30. https://doi.org/10.1186/1471-2369-10-30
23. Government of Alberta Office of Statistics and Information. Quarterly Population Report. Accessed July 30, 2019.
24. Pabbaraju K, Wong AA, Douesnard M, Ma R, Gill K, Dieu P et al (2021) Development and validation of RT-PCR assays for testing for SARS-CoV-2. Off J Assoc Med Microbiol Infect Dis Canada 6(1):16–22. https://doi.org/10.3138/jammi-2020-0026
25. Taeau Health Analytics Portal. 2021. https://tableau.albertahealthservices.ca (contact author for questions as password protected). https://tableau.albertahealthservices.ca (contact author for questions as password protected).
26. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP et al (2008) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 61(4):344–349. https://doi.org/10.1016/j.jclinepi.2007.11.008
27. Li J, Xu G (2020) Lessons from the experience in wuhan to reduce risk of COVID-19 infection in patients undergoing long-term hemodialysis. Clin J Am Soc Nephrol 15(5):717–719. https://doi.org/10.2215/cjn.03420320
28. Stata Statistical Software: Version 16. StataCorp; 2019.
29. Perl J, Thomas D, Tang Y, Yeung A, Ip J, Oliver MJ et al (2021) COVID-19 among adults receiving home versus in-center dialysis. Clin J Am Soc Nephrol. https://doi.org/10.2215/cjn.04170321
30. Detsky AS, Bogoch II (2020) COVID-19 in Canada: experience and response. JAMA 324(8):743–744. https://doi.org/10.1001/jama.2020.14033
31. Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, Klein J et al (2020) Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature 588(7837):315–320. https://doi.org/10.1038/s41586-020-2700-3
32. Gomez JMD, Du-Fay-De-Lavallaz JM, Fugar S, Sarau A, Simmons JA, Clark B et al (2021) Sex differences in coronavirus disease 2019 (COVID-19) hospitalization and mortality. J Womens Health 30(5):646–653. https://doi.org/10.1089/jwh.2020.8948
33. Shattuck-Heidorn H, Danielsen AC, Gompers A, Bruch JD, Zhao H, Boulicault M et al (2021) A finding of sex similarities rather than differences in COVID-19 outcomes. Nature 597(7877):E7–E9. https://doi.org/10.1038/s41586-021-03644-7
34. Burström B, Tao W (2020) Social determinants of health and inequalities in COVID-19. Eur J Pub Health 30(4):617–618. https://doi.org/10.1093/eurpub/ckaa095
35. Dehingia N, Raj A (2021) Sex differences in COVID-19 case fatality: do we know enough? Lancet Glob Health 9(1):e14–e15. https://doi.org/10.1016/s2214-109x(20)30464-2
36. Murakami N, Ono T (1987) Sex-related differences in fever development of rats. Am J Physiol 252(2 Pt 2):R284–R289. https://doi.org/10.1152/ajpregu.1987.252.2.R284
37. Refinetti R, Ma H, Satinoff E (1990) Body temperature rhythms, cold tolerance, and fever in young and old rats of both genders. Exp Gerontol 25(6):533–543. https://doi.org/10.1016/0531-5565(90)90019-X
38. Charkoudian N, Stachenfeld N (2016) Sex hormone effects on autonomic mechanisms of thermoregulation in humans. Auton Neurosci 196:75–80. https://doi.org/10.1016/j.autneu.2015.11.004
39. Richardson J, Holdcroft A (2009) Gender differences and pain medication. Womens Health 5(1):79–88. https://doi.org/10.2217/17455057.5.1.79
40. Paulose-Ram R, Hirsch R, Dillon C, Losonczy K, Cooper M, Ostchega Y (2003) Prescription and non-prescription analgesic use among the US adult population: results from the third National Health and Nutrition Examination Survey (NHANES III). Pharmacoepidemiol Drug Saf 12(4):315–326. https://doi.org/10.1002/pds.755
41. Cain KC, Jarrett ME, Burr RL, Rosen S, Hertig VL, Heitkemper MM (2009) Gender differences in gastrointestinal, psychological, and somatic symptoms in irritable bowel syndrome. Dig Dis Sci 54(7):1542–1549. https://doi.org/10.1007/s10620-008-0516-3
42. Patel H, Rosengren A, Ekman I (2004) Symptoms in acute coronary syndromes: does sex make a difference? Am Heart J 148(1):27–33. https://doi.org/10.1016/j.ahj.2004.03.005
43. Barsky AJ, Peekna HM, Borus JF (2001) Somatic symptom reporting in women and men. J Gen Intern Med 16(4):266–275. https://doi.org/10.1046/j.1525-1497.2001.016004266.x
44. Murtagh FE, Addington-Hall J, Higginson IJ (2007) The prevalence of symptoms in end-stage renal disease: a systematic review. Adv Chronic Kidney Dis 14(1):82–99. https://doi.org/10.1053/j.ackd.2006.10.001
45. Sniekers DC, Jung JKH, Blake PG, Cooper R, Leis JA, Muller MP et al (2021) Province-wide prevalence testing for SARS-CoV-2 of in-center hemodialysis patients and staff in Ontario, Canada: a cross-sectional study. Can J Kidney Health Dis 8:20543581211036212. https://doi.org/10.1177/20543581211036213
46. Caughey AB, Krist AH, Wolff TA, Barry MJ, Henderson JT, Owens DK et al (2021) USPSTF approach to addressing sex and gender when making recommendations for clinical preventive services. JAMA. https://doi.org/10.1001/jama.2021.15731
47. Elliott J, Whitaker M, Bodinier B, Eales O, Riley S, Ward H et al (2021) Predictive symptoms for COVID-19 in the community: REACT-1 study of over 1 million people. PLOS Med 18:e1003777. https://doi.org/10.1371/journal.pmed.1003777

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