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Socioeconomic deprivation is associated with COVID-19 severity among patients on haemodialysis: a multi-centre cross-sectional study

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Abstract

Objectives: To assess the applicability of risk factors for severe COVID-19 defined in the general population for patients on haemodialysis.

Setting: A retrospective cross-sectional study performed across thirty four haemodialysis units in midlands of the United Kingdom.

Participants: All 274 patients on maintenance haemodialysis who tested positive for SARS-CoV-2 on polymerase chain reaction testing between March and August 2020, in participating haemodialysis centres.

Exposure: The utility of obesity, diabetes status, ethnicity, Charlson comorbidity index (CCI), and socioeconomic deprivation scores were investigated as risk factors for severe COVID-19.

Main outcomes and measures: Severe COVID-19, defined as requiring supplemental oxygen or respiratory support, or a C-reactive protein of ≥75mg/dL (RECOVERY trial definitions), and its association with obesity, diabetes status, ethnicity, Charlson comorbidity index (CCI), and socioeconomic deprivation.

Results: 63.5% (174 patients) developed severe disease. Socioeconomic deprivation associated with severity, being most pronounced between the most and least deprived quartiles (OR 2.81, 95% CI 1.22 – 6.47, P = 0.015), after adjusting for age, sex and ethnicity. There was no association between obesity, diabetes status, ethnicity or CCI with COVID-19 severity.

Conclusion: The incidence of severe COVID-19 is high among patients on haemodialysis; this cohort should be considered high risk. There was strong evidence of an association between socioeconomic deprivation and COVID-19 severity. Other risk factors that apply to the general population may not apply to this cohort.

Strengths and Limitations:

- A multicentre centre study of thirty four haemodialysis units representative of urban and rural units
- Largest study to date looking at risk factors for COVID-19 severity among patients on haemodialysis
- Data collection was retrospective
- Sample size was limited by the number of COVID-19 cases in the given time frame

Key words: Haemodialysis, COVID-19, SARS-CoV-2, Risk, Socioeconomic deprivation

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Introduction

Coronavirus disease 2019 (COVID-19) continues to exert a significant strain on healthcare systems worldwide, despite promising developments in treatment and prevention [1,2]. It presents as a clinical spectrum, with severe disease often manifesting as respiratory compromise leading to significant morbidity and mortality [3-5]. The impact of severe COVID-19 goes beyond direct effects on patients and families; prolonged hospital admissions have compromised care of non-COVID related diseases both in elective and emergency settings [6-8].

Identifying those at risk of severe COVID-19 is crucial. Factors influencing severity have been rigorously interrogated in the general population and include age, ethnicity, cardiovascular disease, diabetes status, chronic lung disease, obesity, immunosuppression, and chronic kidney disease [9-20]. The elucidation of these factors has directly informed public health guidance, not only by defining at-risk groups who have been advised to strictly social distance but also to guide the rationing of newly approved vaccinations [21,22].

Patients on haemodialysis are high risk, but it is clear that not all develop severe disease [23-30]. Identifying risk factors associated with severe COVID-19 within this cohort is particularly important: traditional public health measures do not always apply to this population, due to their obligation to attend their dialysis units for regular treatment and interact with health care professionals. Defining at risk dialysis patients may highlight those in need of added protective measures when global 'lockdowns' ease and facilitate prioritisation of vaccinations for those at highest risk. Reducing the incidence of severe COVID-19 in people on dialysis could ultimately improve morbidity and mortality amongst this cohort and ease the burden currently faced by in-patient nephrology units.

In this study, we report the incidence of severe COVID-19 in patients on haemodialysis from thirty four dialysis units, managed by 5 tertiary centres in the United Kingdom, and investigate the applicability of accepted risk factors for severe COVID-19 in the general population for patients on maintenance haemodialysis.

Methods

Study design and participants

Data were collected retrospectively from thirty four haemodialysis units across the United Kingdom, from 1st March 2020 until 1st August 2020. Participants included adults (≥ 18 years) with end-stage kidney disease (ESKD) of any aetiology receiving maintenance haemodialysis at the time of data collection, with the SARS-CoV-2 virus confirmed on polymerase chain reaction (PCR) swab testing. The swabs were taken either in hospital, at dialysis units or from community testing, and for indications, including: development of symptoms suggestive of COVID-19; exposure to an individual with COVID-19; hospital admission screening (emergency and elective), or: routine clinical testing during inpatient hospital stay.

Following a recent directive from the UK Government Department of Health and Social Care on the Control of Patient Information (COPI) in response to COVID-19 [31], patient consent was not required. However, principles of the declaration of Helsinki, and the International Conference on Harmonisation Good Clinical Practice Guideline (ICH-GCP) were followed. The lead centre for this work was University Hospitals of Leicester NHS Trust (UHL) (registered project number 10802). Collection and sharing of anonymised patient data were approved with each participating renal network (appendix 1). Subject data were de-identified within their local centres and data anonymity was maintained throughout.

Patient and Public Involvement

No formal patient and public involvement was under taken for this study.

Outcomes of interest

The primary outcome of interest was the development of severe COVID-19 infection, defined as new oxygen requirement and/or a C-reactive protein level ≥ 75 mg/L [1]. Admission to hospital during time of a positive SARS-CoV-2 PCR test, and 30-day mortality from date of a positive SARS-CoV-2 PCR test were also collected.

The primary exposures of interest were diabetes status (inclusive of all subtypes), body mass index (BMI), ethnicity, Charlson Co-morbidity Index (CCI) and socioeconomic deprivation. Socioeconomic deprivation was

identified through the UK government 'English indices of deprivation 2019' tool and was collected as deprivation ranks [23].

Secondary exposures of interest included: blood pressure, haemoglobin, history of renal transplantation, immunosuppressant use, medical blockade of the renin-angiotensin aldosterone system (RAAS) and vitamin D supplementation. Additional characteristics collected included: age, sex, date of progression to ESKD, dialysis vintage, dialysis access and location of dialysis.

Data collection

All data were collected from electronic hospital clinical records (laboratory results and observation charts). Medical records were requested to clarify any events that were uncertain from electronic documentation. Patient identifiers were removed from the data collection tool prior to transfer to UHL NHS Trust for analysis.

Statistical analysis

Data were locked prior to analysis using SPSS v26 for Windows IBM Corp. as per the pre-specified statistical analysis plan (appendix 2). Categorical data are presented as frequencies with percentages. Ethnicity was classified as Caucasian (includes British, Irish, Northern Irish, English, Scottish, Welsh, Cornish, white European, and any other white background) and non-Caucasian (all other ethnicity groups) for analysis. The CCI and socioeconomic deprivation rank were divided into quartiles. For socioeconomic deprivation rank, the first quartile represents the most deprived and the fourth quartile represents the least deprived. Distribution of continuous data were assessed visually using Shaprio-Wilk tests and Q-Q plots, and are presented as either mean with standard deviation, or median with interquartile range (IQR), as appropriate. Univariate analyses comparing categorical risk factors by COVID-19 severity were completed using Chi-square tests. Continuous risk factors were compared using independent T-tests or Mann-Whitney tests dependent upon data distribution. Unadjusted odds ratios were calculated for risk factors associated with severe COVID-19 infection. For social deprivation ranks, the odds ratios were calculated by comparing non-severe and severe COVID-19 infection for the first to third quartiles, to the fourth quartile. Logistic regression analysis with adjustments for age, sex, and ethnicity (Caucasian and non-Caucasian) were planned for any primary exposure found to have statistically significant relationship with COVID-19 severity. Data are rounded to 3 significant figures where appropriate. Patients with missing data were omitted from the analysis of that variable.

Results

Five dialysis networks contributed to data collection, gathered from thirty four haemodialysis units, as outlined in Table 1. The total prevalent haemodialysis population was 2,899 patients; 274 had a positive SARS-CoV-2 viral PCR swab result during the 5-month data collection period, representing an overall incidence of infection of 9.45%. The 30-day mortality for the 274 patients with positive SARS-CoV-2 viral PCR was 73 patients (26.6%).

Patients were categorised into groups of 'non-severe' (n = 77, 28.1%) or 'severe' (n = 174, 63.5%) COVID-19 infection. Incomplete severity data were recorded for 23 patients who were excluded from further analysis. From the 251 patients included in the analysis, 67 (26.7%) died within 30-days of their positive SARS-CoV-2 swab result.

Baseline characteristics

Table 2 demonstrates the key demographic features. The outcome groups (non-severe COVID-19 and severe COVID-19) were well-matched with regard to age, sex, length of time with ESKD, dialysis vintage, dialysis access and location of routine haemodialysis. There were significant differences between the outcome groups for admission to hospital [$X^2(1, N = 251) = 86.8$, $P < 0.001$] and 30-day mortality [$X^2(1, N = 244) = 18.2$, $P < 0.001$] (Table 2).

Primary exposures of interest

On univariate analysis, there was no evidence of an association between diabetes status, ethnicity (Caucasian vs non-Caucasian), BMI or CCI with severe COVID-19. These exposures were well matched between the two outcome groups (table 3).

There was strong evidence of an association between socioeconomic deprivation and severe COVID-19. More patients living in the most deprived areas developed severe COVID-19 compared to those living in the least deprived areas. On unadjusted analysis by logistic regression, there was a greater risk of severe COVID-19 among the first quartile (OR 2.37, 95% CI 1.12 – 5.03, $P = 0.025$), second quartile (OR 2.42, 95% CI 1.14 –

5.13, $P = 0.021$) and third quartile (OR 2.57, 95% CI 1.18 – 5.57, $P = 0.017$) of socioeconomic deprivation, compared to the fourth quartile (the least deprived). On adjusted analysis (Figure 1), the evidence for an association persisted: first quartile (OR 2.81, 95% CI 1.22 – 6.47, $P = 0.015$), second quartile (OR 2.63, 95% CI 1.19 – 5.79, $P = 0.017$) and the third quartile (OR 2.74, 95% CI 1.24 – 6.05, $P = 0.012$).

Secondary exposures of interest

Most secondary exposures of interest were not significantly different between the outcome groups: previous renal transplantation, immunosuppressant therapy, RAAS blockade, and systolic blood pressure (Table 3). There was strong evidence of an association between vitamin D supplementation for mineral bone disease treatment (OR 2.43, 95% CI 1.35 – 4.38, P = 0.03) and severe COVID-19. There was also strong evidence of an association between haemoglobin level and severe COVID-19 [$t(249) = 2.19$, $P = 0.029$], with a mean haemoglobin level of 108g/L in the non-severe group, and 103g/L in the severe group (OR 0.981, 95% CI 0.964 – 0.998, $P = 0.031$).

Discussion

In this multi-centre, retrospective, cross-sectional study, we investigated risk factors that associate with severe COVID-19 among haemodialysis patients. This study produced three key findings. We found strong evidence that socioeconomic deprivation associates with severe COVID-19 (defined as new oxygen requirement and/or a C-reactive protein level ≥ 75 mg/L) after adjusting for age, sex and ethnicity, while other risk factors reported in the general population may not apply to haemodialysis patients. This study also highlights the high incidence of severe COVID-19 and subsequent 30-day mortality amongst patients on haemodialysis.

The incidence of severe COVID-19 in our cohort was 63.5%, considerably higher than in the general population, where it is estimated to be closer to 20% [33, 34]. This finding corroborates previously published data arising from smaller cohorts from across the world [23-29], and adds credence to the notion that all haemodialysis patients should be managed as being at risk for severe disease. Pragmatic steps to this effect should be encouraged and could include prioritising this cohort for vaccinations as they become available, further reinforcing social distancing, isolated dialysis when appropriate and rigorous infection prevention measures at all dialysis units.

The high incidence observed is likely to be multifactorial. The generalised immunosuppressed state of haemodialysis patients has been well documented and is further evidenced by their increased susceptibility to infections and muted responses to immunisations [35,36]. Dialysis patients are also obliged to spend prolonged periods of time in enclosed, populated spaces to receive their treatment; this may increase their exposure to SARS-CoV-2 viral particles and subsequent viral load [37], particularly if other asymptomatic patients yet to be tested are dialysing out of isolation within the same unit, as may have occurred early in the pandemic [38-40]. Indeed, this has been observed in the context of other communicable diseases which propagate through droplet transmission [41-43]. As viral load correlates with disease severity [44], these factors together may predispose the entire haemodialysis cohort to severe COVID-19.

Despite the high rate of severe COVID-19 among haemodialysis patients, a proportion do not develop severe disease [23-29]. We subsequently interrogated our data to determine if risk factors that associate with severe COVID-19 in the general population could be applicable to our cohort. Our key finding was strong evidence of an association between socioeconomic deprivation and COVID-19 severity among patients on haemodialysis. Socioeconomic deprivation has long been established as a predictor of poor health outcomes, and this has been demonstrated in the context of COVID-19 [30, 45-49]. We used the English Index of Multiple Deprivation (IMD) as a marker of social deprivation. The IMD is a weighted composite of seven domains (income, employment, education, health, crime, barriers to housing, and living environments) which assigns a rank to 32,844 areas in England, with a rank of one considered the most deprived on the index [32]. We strong evidence that the IMD associated with a greater risk of severe COVID-19, being most pronounced between the least and most deprived quartiles. This finding persisted after adjusting for age, sex and ethnicity (OR 2.81, 95% CI 1.22 – 6.47, $P = 0.015$). The Scottish Renal Registry recently demonstrated patients living in more deprived areas were more susceptible to contracting COVID-19 [50], but to the best of our knowledge, this is the first study demonstrating a link between socioeconomic deprivation and COVID-19 severity in the haemodialysis population.

Determining the precise factors that account for the relationship between the IMD and COVID-19 severity among haemodialysis patients is beyond the scope of this study, however there are a number of potential contributors that could warrant further investigation. Household overcrowding is incorporated into the IMD as a

contributing factor of social deprivation [32]. As with dialysis units, it is possible that this contributes to a greater exposure to viral load, should another member of the household be COVID-19 positive [44-46]. Additionally, we were unable to collect data on patient smoking status, which may confound this association. Indeed, smoking is a possible a risk factor for severe COVID-19, and smoking habits are four times as more likely in areas ranked as most deprived by the IMD [51,52]. Other factors that may explain this association are likely to be less COVID-19 specific; dialysis patients living in areas considered to be deprived have poorer survival rates [53,54], and this may be reflective of the physiological stressors associated with socioeconomic deprivation. Exposure to noise pollution, crowding, threat of crime, poor nutrition, and other life pressures, including job and housing insecurity, can contribute to a state of chronic stress [55]. This exerts negative impacts on immunity [56,57] and can promote pro-inflammatory states which pre-dispose to cardiovascular frailty [58,59], perhaps accounting for the poor outcomes noted in this population.

Obesity, ethnicity and diabetes status predict severity in the general population [10,12,14-20], however, we found no evidence these factors associating with COVID-19 severity in haemodialysis patients. This finding is in keeping with results of smaller French (122 patients) and Chinese (154) studies [60,61]. We also investigated the Charlson Comorbidity index, a weighted index that predicts ten-year survival in patients with multiple comorbidities [62], as a risk factor for COVID-19 severity. The CCI has shown value in predicting severe COVID-19 in the general population [63-66], but again, we found no evidence of an association with severe COVID-19 among patients on haemodialysis. This finding contrasts with those reported by Stefan et al, who found a positive correlation between CCI and COVID-19 severity in a cohort of 37 Romanian dialysis patients [23]. However, the definition of severity used was different and a proportion of the patients in this study received treatments that included glucocorticoids, hydroxychloroquine, lopinavir-ritonavir, and tocilizumab, which may have altered disease progression, confounding results. Other risk factors reported to be significant in the general population, including sex, cardiovascular disease and blood pressure were evenly matched in our severe and non-severe COVID-19 groups. These findings further corroborate the results of smaller previously published studies [60,61]. It is possible that the risk conferred by haemodialysis for severe COVID-19 far outweighs that of the established risk factors defined for the general population, minimising their effect sizes in this select cohort of patients.

We also noted strong evidence of an association between prescribed vitamin D supplementation and severe

COVID-19 (OR 2.43, 95% CI 1.35 – 4.38, P = 0.03). Vitamin D prescription in the dialysis population is principally in its activated from, used for the management for chronic kidney disease-related mineral bone disease, and not for routine supplementation [67]. Those supplemented with vitamin D are therefore at higher risk of hyperphosphataemia, secondary hyperparathyroidism and ultimately vascular calcification, all of which associate with poor outcomes [68]. Rather than suggesting these data infer any causal relationship between vitamin D supplementation and development of a severe manifestation of COVID-19, it is more likely that this 'relationship' is driven by residual confounding of the indications for vitamin D supplementations and related co-morbidity. A difference was also noted in the haemoglobin levels between those with severe disease and non-severe disease (103g/L vs 108g/L, $P = 0.029$). Although both groups showed evidence of chronic kidney disease-related anaemia, they also appeared to be adequately treated and within the limits recommended by international guidelines [69]. As with socioeconomic deprivation, establishing if these links are causal are beyond the scope of this study, but are hypothesis generating, nevertheless.

The limitations of our study lie in sample size and cross-sectional design. This work included all haemodialysis patients for whom data was available, who tested positive for the SARS-CoV-2 virus on a PCR test during the first wave of the United Kingdom's COVID-19 pandemic. Although this is the largest study of its kind to date, the relatively small sample size available limited its ability to identify smaller effect sizes that may have been exerted by the investigated exposures. It also prevented us from providing further granularity with regards to both ethnicity and socioeconomic deprivation and their associations with severe COVID-19, prompting a restriction in our analysis to Caucasian vs non-Caucasian and quartiles of socioeconomic deprivation, respectively. Given this was a cross-sectional observational study, causality cannot be inferred, and indeed it is likely that social deprivation associates with other key determinants of COVID-19 severity, that was beyond the scope of this study.

We opted to investigate severity over the commonly reported metrics of total incidence and mortality, as we found it to be more representative of the burden placed on healthcare resources by COVID-19. Mortality is mostly reported as a death occurring within 28 or 30 days of a positive PCR test [70-75] and could therefore include mortalities not strictly attributable to COVID-19. Furthermore, risk factors for mortality may not be COVID-19 specific; this can be challenging to differentiate between and therefore act upon. Incidence is increasingly being accounted for by asymptomatic patients who place little strain on healthcare services beyond

the need to dialyse in isolation [38,39]. We found that COVID-19 severity as defined by the RECOVERY trial, associated with admission rates and mortality ($P < 0.001$), and was therefore an adequate, relevant and generalisable marker for severity with regards to the objectives of this study. We opted to use the RECOVERY trial's definition for COVID-19 severity as it provided a pragmatic and clinically relevant definition. We avoided hospital admission in our definition of severity; early in the pandemic admissions occurred to facilitate the logistics of isolated dialysis for COVID-19 patients who were otherwise well, and therefore an admission *per se* may not be truly reflective of disease severity.

Conclusion

We confirmed a high incidence of severe COVID-19 among patients on haemodialysis and found that risk factors that apply to the general population may not be applicable in the same way for patients on haemodialysis. For patients on haemodialysis socioeconomic deprivation appears to be more closely associated with COVID-19 severity, but further work is needed to establish whether there is because of a causal link, or whether there are confounding factors that account for this finding.

Contributorship Statement

HS, KLH and JOB designed the study. HS, KLH, SFA, SA, MCC, MH, RH, AK, HK, ML, HSL, KM, SN, BO, SS, and MT collected data. HS and KLH coordinated data collection. KLH performed the statistical analysis supervised by LG. HS, KLH and JOB interpreted the data. HS and KH wrote the manuscript supervised by JOB. SFA, MGB, MH, ML, JFM and SN critically revised the manuscript. All authors edited and approved the final manuscript. JOB guarantors this study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

All pseudonymised data collected will be shared in spreadsheet format. The statistical analysis plan has been included as an appendix.

Transparency Declaration

HS, KLH and JOB affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Dialysis network	Included dialysis units, n = 34 (%)	Prevalent dialysis patients, n = 2899 (%)	+ve SARS-CoV-2 swabs, n = 274 (%)	Non-severe COVID-19, n = 97 (%)	Severe COVID-19, n = 174 (%)
Leicester	9 (26.5)	762 (26.3)	74 (27.0)	7 (22.1)	42 (24.4)
Birmingham	1 (2.95)	1031 (35.6)	105 (38.3)	23 (42.9)	67 (38.5)
Nottingham	5 (14.7)	454 (15.7)	31 (11.3)	10 (13.0)	20 (11.5)
Stoke	3 (8.82)	271 (9.35)	22 (8.0)	7 (7.29)	15 (8.62)
Coventry	6 (17.7)	381 (13.1)	42 (15.3)	13 (14.3)	30 (17.2)

Table 1 - demonstrates the number of haemodialysis units for each participating dialysis network, with the proportion of positive SARS-CoV-2 nasopharyngeal swabs, and the proportion of non-severe and severe COVID-19 outcomes

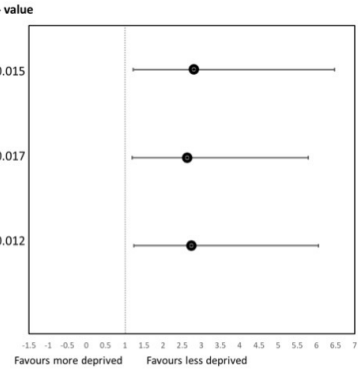
Characteristic	Non-severe COVID-19 (n = 77)	Severe COVID-19 (n = 174)	Missing data, n (%)
Age, years, median (IQR)	70 (57 – 80)	68 (60 – 78)	0
Sex, female, n (%)	34 (44.2)	67 (39.4)	0
Ethnicity:-			
Mixed British, n (%)	43 (55.8)	94 (54.0)	
Any other white background, n (%)	1 (1.30)	3 (1.91)	
Indian or British Indian, n (%)	11 (14.3)	21 (12.1)	
Pakistani or British Pakistani, n (%)	7 (9.10)	18 (10.3)	
Bangladeshi or British Bangladeshi, n (%)	3 (3.90)	3 (1.70)	
Any other Asian background, n (%)	2 (2.60)	6 (3.45)	
Caribbean, n (%)	1 (1.30)	4 (2.30)	0
African, n (%)	0	1 (0.60)	
Mixed Black, n (%)	0	2 (1.10)	
Black British, n (%)	1 (1.30)	1 (0.60)	
Any other Black background, n (%)	5 (6.50)	14 (8.00)	
Chinese, n (%)	0	1 (0.60)	
Any other ethnic group, n (%)	2 (2.60)	0	
Not stated, n (%)	1 (1.30)	6 (3.40)	
Years since developing ESKD, median (IQR)	4 (2 – 7)	4 (2 – 8)	6 (2.39)
Dialysis vintage, years, median (IQR)	3 (2 – 7)	4 (2 – 7)	24 (9.56)
Hospital-based unit, n (%)	20 (26.0)	45 (25.9)	
Satellite unit, n (%)	55 (71.4)	125 (71.8)	1 (0.398)
Home haemodialysis, n (%)	2 (2.60)	3 (1.70)	
Arteriovenous fistula or graft, n (%)	54 (70.1)	135 (77.6)	1 (0.398)
Haemodialysis catheter, n (%)	23 (29.9)	38 (21.8)	
ESKD diagnosis:-			
Diabetes, n (%)	28 (36.4)	66 (37.9)	
Glomerulonephritis, n (%)	12 (15.6)	26 (14.9)	
Hypertension, n (%)	3 (3.90)	11 (6.30)	
Polycystic kidney disease, n (%)	2 (2.60)	9 (5.20)	0
Pyelonephritis, n (%)	1 (1.30)	3 (1.70)	
Renal vascular disease, n (%)	2 (2.60)	6 (3.40)	
Other, n (%)	18 (23.4)	26 (14.9)	
Uncertain aetiology, n (%)	11 (14.3)	27 (15.5)	
Admitted to hospital, n (%)*	25 (32.5)	156 (89.7)	0
Death, n (%)*	6 (7.80)	61 (35.1)	7 (2.79)

*Table 2 - baseline characteristics for the two outcome groups, *p < 0.001**

Characteristic	Non-severe COVID-19 (n = 71)	Severe COVID-19 (n = 170)	*P* - value	Missing data, n (%)
Primary Exposures				
Caucasian, n (%) Non-Caucasian, n (%)	44 (57.1) 33 (42.9)	97 (55.7) 77 (44.3)	0.891	0
Diabetes mellitus, n (%)	44 (57.1)	103 (59.2)	0.788	2 (0.797)
CCI first quartile (1 – 4), n (%) CCI second quartile (5 – 6), n (%) CCI third quartile (7), n (%) CCI fourth quartile (≥ 8), n (%)	11 (14.3) 25 (32.5) 13 (16.9) 28 (36.4)	26 (14.9) 44 (25.3) 40 (23.0) 64 (36.8)	0.388	0
BMI, kg/m^2, median (IQR)	27.7 (23.6 – 31.4)	28.5 (24.2 – 34.5)	0.143	24 (9.56)
Deprivation rank 1st quartile, n (%) Deprivation rank 2nd quartile, n (%) Deprivation rank 3rd quartile, n (%) Deprivation rank 4th quartile, n (%)	17 (22.1) 17 (22.1) 15 (19.5) 28 (36.4)	46 (26.4) 47 (27.0) 44 (25.3) 32 (18.4)	0.03*	5 (1.99)
Secondary Exposures				
Previous renal transplant, n (%)	6 (7.80)	23 (13.2)	0.285	2 (0.797)
Immunosuppressant therapy, n (%)	5 (6.50)	20 (11.5)	0.246	83 (33.1)
Vitamin D supplementation, n (%)	46 (59.7)	134 (77.0)	0.005*	5 (1.99)
RAAS blockade	7 (9.10)	22 (12.6)	0.423	0
Haemoglobin, g/L, mean (SD)	108 (+/- 15)	103 (+/-16)	0.029*	2 (0.797)
Systolic blood pressure, mm/Hg, mean (SD)	142 (+/- 25)	136 (+/-28)	0.174	6 (2.39)

*Table 3 - summary of the results for the primary and secondary exposures of interest. *denotes statistical significance (P < 0.05)*

Exposure vs. control	Exposure (1st – 3rd quartile ranks)	Control (4th quartile rank)	OR (95% CI)	*P* - value
1st vs. 4th quartile of the deprivation rank	46 (27.2%)	32 (18.9%)	2.81 (1.22 – 6.47)	0.015
2nd vs. 4th quartile of the deprivation rank	47 (27.8%)	32 (18.9%)	2.63 (1.19 – 5.79)	0.017
3rd vs. 4th quartile of the deprivation rank	44 (26.0%)	32 (18.9%)	2.74 (1.24 – 6.05)	0.012



Forest plot demonstrating the odds ratios when comparing the risk of developing severe COVID-19 between the most socially deprived (first to third deprivation ranks quartiles) and the least socially deprived areas (fourth deprivation rank quartiles).

107x60mm (300 x 300 DPI)

Project Registration Numbers for Participating Dialysis Networks

Dialysis Network	Project Registration Number
University Hospitals of Leicester NHS Trust	10802
Nottingham University Hospital NHS Trust	21-050C
University Hospitals of Birmingham NHS Trust	CARMS-16409
University Hospitals of North Midlands NHS Trust	CA41620
University Hospitals of Coventry and Warwickshire NHS Trust	10009

Risk Factors for Severe COVID-19 Among In-Centre Haemodialysis Patients.

Statistical Analysis Plan

Study Title: Risk factors for severe COVID-19 among in-centre haemodialysis patients.

Short Title: Severe COVID in ICHD patients.

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1. INTRODUCTION

1.1. STUDY BACKGROUND

Coronavirus disease 2019 (COVID-19) presents on a clinical spectrum, with severe disease requiring supplemental oxygenation, escalating to mechanical ventilation and even extra-corporeal membrane oxygenation (ECMO) in extreme cases. Factors influencing the severity of presentation has been rigorously interrogated in the general population, and include cardiovascular disease, diabetes mellitus, chronic lung disease, obesity, malignancy, immunosuppression and chronic kidney disease. The elucidation of these factors has directly informed public health advice, by defining at-risk patient groups who are advised to strictly social distance or shield, and is likely to guide rationing of the recently approved vaccinations.

Although those who require in-centre haemodialysis (ICHD) fall into the high risk category, not all develop severe disease. Understanding risk factors for severity of COVID19 among ICHD patients is of the utmost priority; traditional public health measures cannot apply to this group due to their obligation to travel to and from their units, and the need to interact with health care professionals at least three times a week. In this study, we report the incidence of COVID19 among HD patients in the midlands, a strongly multi-ethnic region in the United Kingdom, and explore risk factors for severity of infection, defining a cohort for whom added protective measures may need to be considered in the context of global easing of 'lockdowns', and perhaps who should be prioritised for vaccinations when they become available.

1.2. STUDY OBJECTIVES

This study aims to provide insights into unresolved questions regarding risk factors that may predispose to severe COVID19 among in-centre haemodialysis (ICHD) patients.

Hypothesis:

1. Obesity, diabetes, ethnicity are risk factors for severe COVID19 among ICHD patients

2. The Charlson Co-morbidity Score and Socioeconomic Deprivation are risk factors for severe COVID19 among ICHD patients

1.3. STUDY DESIGN

The study design is a multi-centre, retrospective cross-sectional observational study.

1.4. SAMPLE SIZE

Estimated sample size based on UK renal registry data is 350. This is the total number of patients with COVID19 in dialysis units based in the midlands between February 2020 to August 2020, and is therefore all the data available to us at present. Based on our pilot data of 69 patients, this sample should be adequate enough to detect the effect of BMI, Diabetes and Socioeconomic deprivation (as measured by the index of multiple deprivation (IMD)), however it may not be adequate enough to detect the effect of ethnicity or the Charlson Co-morbidity index. Sample size calculations were performed assuming an alpha of 0.5 and a power of 80% (https://clincalc.com/stats/samplesize.aspx):

Severe COVID in BMI >/=25 = 70%
Severe COVID in BMI <25 = 51%
Alpha 0.5, Power 80%
Total n = 206 (103 in each group)

Severe COVID in Diabetes = 76%
Severe COVID in non-diabetics = 45%
Alpha 0.5, Power 80%
Total n = 76 (38 in each group)

Severe COVID in White British = 58%
Severe COVID in other ethnicities = 53%
Alpha 0.5, Power 80%
Total n = 3100 (1550 in each group)

Severe COVID in Charlson Index >/= 5 = 55%
Severe COVID in Charlson Index < 5 = 50%
Alpha 0.5, Power 80%
Total n = 3130 (1565 in each group)

Severe COVID in lowest IMD deciles = 53%
Severe COVID in highest IMD deciles = 23%
Alpha 0.5, Power 80%
Total n = 80 (40 in each group)

1.5. STUDY POPULATIONS

All ICHD patients who tested positive for COVID19, on a hospital based real time reverse transcription quantitative polymerase chain reaction tests, were included in this study.

1.6. STATISTICAL ANALYSIS PLAN (SAP)

1.6.1. SAP OBJECTIVES

The objective of this SAP is to describe the statistical analyses to be carried out for the final analysis of this study.

1.8.2. General Principles

An alpha level of 0.05, and confidence intervals be set at 95% will be used for all statistical tests. Power of 0.8 was assumed when calculating sample sizes.

1.8.3. Software

Analyses will be carried out using SPSS, R, or Prism.

2. Analysis

2.1. Study Populations

All ICHD patients who tested positive for COVID19, on a hospital based real time reverse transcription quantitative polymerase chain reaction tests, will be included in this study.

These patients will be divided into those who had severe COVID19 (defined as respiratory support with supplemental oxygen or more, and/or a CRP of >75) and those who were able to oxygenate effectively on room air (no supplemental oxygen, or further interventions required).

2.2. Outcomes

2.2.1. Primary Outcome

The primary outcome of this study is COVID severity, as defined above in section 2.1. The effect of exposures on this outcome will be assessed in this study and has been detailed in section 2.3

2.3. **EXPOSURES**

2.3.1 Primary Exposures

The primary exposures of interest are:

1) Diabetes status (collected as a yes/no categorical variable), inclusive of all variants.

2) BMI collected as a continuous variable

3) Ethnicity, defined as a categorical variable based on office of national statistics categories.

4) The Charlson Comorbidity index

5) Social deprivation will be collected using the English Index of Multiple Deprivation rank and deciles, as an ordinal variable.

2.3.2 Exploratory Exposures

Exploratory exposures of interest will include association age, sex, dialysis vintage, dialysis access, renin-angiotensin inhibition, transplant status, immunosuppression status, haemoglobin, vitamin D supplementation and blood pressure.

2.4 ANALYSIS PLAN

2.4.1 Baseline data

Incidence of COVID-19 and Severe COVID-19 will be calculated against the total dialysis population belonging to each participating haemodialysis unit, during the time frame of data collection.

Continuous variables will be summarised by mean and standard deviation, minimum and maximum. Categorical variables will be summarised by N (%).

2.4.2 Exposure effect exploration

The incidence of severe COVID between exposed and non exposed groups, as defined in sections 2.3.1 and 2.3.2 will be compared. Continuous variables will be summarised by mean and standard deviation, minimum and maximum. Categorical variables will be summarised by N (%).

2.4.3.Modelling – adjusted and unadjusted

Risk factor effects on primary outcomes (severe COVID19) will be analysed using logistic regression models. Adjustments will be made for sex, age and ethnicity.

3. DOCUMENT HISTORY

This is version 1.3 of the SAP for this study, dated 19th of December 2020, the fourth iteration of this document.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6,21,22
Outcome data	15*	Report numbers of outcome events or summary measures	21,22
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7

		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk Factors associated with COVID-19 severity among patients on maintenance haemodialysis: a retrospective multi-centre cross-sectional study in the United Kingdom

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Risk Factors associated with COVID-19 severity among patients on maintenance haemodialysis: a retrospective multi-centre cross-sectional study in the United Kingdom

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Abstract

Objectives: To assess the applicability of risk factors for severe COVID-19 defined in the general population for patients on haemodialysis.

Setting: A retrospective cross-sectional study performed across thirty four haemodialysis units in midlands of the United Kingdom.

Participants: All 274 patients on maintenance haemodialysis who tested positive for SARS-CoV-2 on polymerase chain reaction testing between March and August 2020, in participating haemodialysis centres.

Exposure: The utility of obesity, diabetes status, ethnicity, Charlson comorbidity index (CCI), and socioeconomic deprivation scores were investigated as risk factors for severe COVID-19.

Main outcomes and measures: Severe COVID-19, defined as requiring supplemental oxygen or respiratory support, or a C-reactive protein of ≥75mg/dL (RECOVERY trial definitions), and its association with obesity, diabetes status, ethnicity, Charlson comorbidity index (CCI), and socioeconomic deprivation.

Results: 63.5% (174/274 patients) developed severe disease. Socioeconomic deprivation associated with severity, being most pronounced between the most and least deprived quartiles (OR 2.81, 95% CI 1.22 – 6.47, P = 0.015), after adjusting for age, sex and ethnicity. There was no association between obesity, diabetes status, ethnicity or CCI with COVID-19 severity. We found no evidence of temporal evolution of cases (P = 0.209) or clustering that would impact our findings.

Conclusion: The incidence of severe COVID-19 is high among patients on haemodialysis; this cohort should be considered high risk. There was strong evidence of an association between socioeconomic deprivation and COVID-19 severity. Other risk factors that apply to the general population may not apply to this cohort.

Strengths and Limitations:

- A multicentre centre study of thirty four haemodialysis units representative of urban and rural units
- Largest study to date looking at risk factors for COVID-19 severity among patients on haemodialysis
- Data collection was retrospective
- Sample size was limited by the number of COVID-19 cases, and the absence of protocolised testing of asymptomatic patients in the given time frame

Key words: Haemodialysis, COVID-19, SARS-CoV-2, Risk, Socioeconomic deprivation

Word Count: 3801

Figures: 2

Tables: 3

Introduction

Coronavirus disease 2019 (COVID-19) continues to exert a significant strain on healthcare systems worldwide (1). It presents as a clinical spectrum, with severe disease often manifesting as respiratory compromise leading to significant morbidity and mortality (2-4). Patients on haemodialysis are particularly at risk (5-10). Traditional public health measures do not apply due to their obligation to travel to and from enclosed units for regular treatment, often on public or shared transport. While the long term impacts of COVID-19 are still being characterised in this group, the risk of morbidity and mortality afforded by acute COVID-19 is clear (5-10).

The widespread dissemination of COVID-19 vaccinations has therefore been welcome among those receiving haemodialysis. Despite the successful roll out of vaccines globally, access is yet to become universal and vaccine hesitancy remains an issue even where they are readily available (11, 12). Understanding which patients on haemodialysis are most at risk of severe disease is thus an issue of continued importance; it would facilitate patient counselling, public health measures in the event of further outbreaks, and would inform the development of disease modelling and risk scores which are becoming increasingly important clinical decision aids (13).

Most studies that have investigated COVID-19 among those receiving haemodialysis examined risk of mortality, mostly reporting age, frailty, and co-morbidity burden as important predictors (14-19). Severe disease represents a different but important clinical outcome, conferring significant mental and physical morbidity, and may have different risk factors that associate with it (2, 20-23). Associations with this outcome have not been investigated in detail among patients receiving haemodialysis. Large studies that have investigated this among those receiving haemodialysis used hospitalisation as a proxy for disease severity (24, 25) - this may not always translate to severe disease. Especially early in the pandemic, admission was also prompted for logistical reasons, such being unable to dialyse a symptomatic patient with confirmed or suspected COVID-19 (26).

In this study, we chose to explore disease severity defined by the pragmatic and objective clinicopathological criteria set out by the RECOVERY trial (new oxygen requirement and/or a C-reactive protein level ≥ 75 mg/L) (27). We report the incidence of severe COVID-19 in patients on haemodialysis from thirty four dialysis units, managed by 5 tertiary centres in the United Kingdom, and investigate the applicability of accepted risk factors for severe COVID-19 in the general population for patients on maintenance haemodialysis.

Methods

Study design and participants

Data were collected retrospectively from thirty four haemodialysis units across the United Kingdom, from 1st March 2020 to 1st August 2020. Participants included adults (≥ 18 years) with end-stage kidney disease (ESKD) of any aetiology receiving maintenance haemodialysis at the time of data collection, with the SARS-CoV-2 virus confirmed on polymerase chain reaction (PCR) swab testing. The swabs were taken either in hospital, at dialysis units or from community testing, and for indications, including: development of symptoms suggestive of COVID-19; exposure to an individual with COVID-19; hospital admission screening (emergency and elective), or: routine clinical testing during inpatient hospital stay.

Following a recent directive from the UK Government Department of Health and Social Care on the Control of Patient Information (COPI) in response to COVID-19 (28), patient consent was not required. However, principles of the declaration of Helsinki, and the International Conference on Harmonisation Good Clinical Practice Guideline (ICH-GCP) were followed. The lead centre for this work was University Hospitals of Leicester NHS Trust (UHL) (registered project number 10802). Collection and sharing of anonymised patient data were approved with each participating renal network (appendix 1). Subject data were de-identified within their local centres and data anonymity was maintained throughout.

Patient and Public Involvement

No formal patient and public involvement was under taken for this study.

Outcomes of interest

The primary outcome of interest was the development of severe COVID-19 infection, defined as new oxygen requirement and/or a C-reactive protein level ≥ 75 mg/L (29). Admission to hospital during time of a positive SARS-CoV-2 PCR test, and 30-day mortality from date of a positive SARS-CoV-2 PCR test were also collected.

The primary exposures of interest were diabetes status (inclusive of all subtypes), body mass index (BMI), ethnicity, Charlson Co-morbidity Index (CCI) and socioeconomic deprivation. Socioeconomic deprivation was

identified through the UK government 'English indices of deprivation 2019' tool and was collected as deprivation ranks (30).

Secondary exposures of interest included: blood pressure, haemoglobin, history of renal transplantation, immunosuppressant use, medical blockade of the renin-angiotensin aldosterone system (RAAS) and vitamin D supplementation. Additional characteristics collected included: age, sex, date of progression to ESKD, dialysis vintage, dialysis access and location of dialysis.

Data collection

All data were collected from electronic hospital clinical records (laboratory results and observation charts). Medical records were requested to clarify any events that were uncertain from electronic documentation. Patient identifiers were removed from the data collection tool prior to transfer to UHL NHS Trust for analysis.

Statistical analysis

Data were locked prior to analysis using SPSS v26 for Windows IBM Corp. as per the pre-specified statistical analysis plan (appendix 2). Categorical data are presented as frequencies with percentages. Ethnicity was classified as Caucasian (includes British, Irish, Northern Irish, English, Scottish, Welsh, Cornish, white European, and any other white background) and non-Caucasian (all other ethnicity groups) for analysis. The CCI and socioeconomic deprivation rank were divided into quartiles. For socioeconomic deprivation rank, the first quartile represents the most deprived and the fourth quartile represents the least deprived. Distribution of continuous data were assessed visually using Shaprio-Wilk tests and Q-Q plots, and are presented as either mean with standard deviation, or median with interquartile range (IQR), as appropriate. Univariate analyses comparing categorical risk factors by COVID-19 severity were completed using Chi-square tests. Continuous risk factors were compared using independent T-tests or Mann-Whitney tests dependent upon data distribution.

Unadjusted odds ratios were calculated for risk factors associated with severe COVID-19 infection. For social deprivation ranks, the odds ratios were calculated by comparing non-severe and severe COVID-19 infection for the first to third quartiles, to the fourth quartile. Logistic regression analysis with adjustments for age, sex, and ethnicity (Caucasian and non-Caucasian) were planned for any primary exposure found to have statistically

significant relationship with COVID-19 severity. Data are rounded to 3 significant figures where appropriate. Patients with missing data were omitted from the analysis of that variable.

The influence of time on the incidence of severe and non-severe cases was explored, using the date of the first case of COVID-19 disease in our cohort as the reference. The median time in days from the first reported case was calculated for each new severe disease and non-severe disease case and were compared using a Mann-Whitney U test. Cumulative incidence of severe and non-severe cases over time was calculated as a percentage of total number of cases and explored.

Case cluster associations with disease severity were explored visually by plotting incident cases against time, for each dialysis unit, grouped by dialysis slots (Monday, Wednesday, Friday slots, or Tuesday, Thursday, Saturday slots), with overlapping shifts presented together, where this data was available.

Results

Five dialysis networks contributed to data collection, gathered from thirty four haemodialysis units, as outlined in Table 1. The total prevalent haemodialysis population was 2,899 patients; 274 had a positive SARS-CoV-2 viral PCR swab result during the 5-month data collection period, representing an overall incidence of infection of 9.45%. The 30-day mortality for the 274 patients with a positive SARS-CoV-2 viral PCR was 73 patients (26.6%).

Patients diagnosed with COVID-19 were categorised into groups of 'non-severe' (n = 77, 28.1%) or 'severe' (n = 174, 63.5%) COVID-19 infection. Severe cases thus represented 6% of the overall population at the time of data collection. Incomplete severity data were recorded for 23 patients who were excluded from further analysis. From the 251 patients included in the analysis, 67 (26.7%) died within 30-days of their positive SARS-CoV-2 swab result.

Baseline characteristics

Table 2 demonstrates the key demographic features. The outcome groups (non-severe COVID-19 and severe COVID-19) were well-matched with regard to age, sex, length of time with ESKD, dialysis vintage, dialysis access and location of routine haemodialysis. There were significant differences between the outcome groups for admission to hospital [$X^2(1, N = 251) = 86.8$, $P < 0.001$] and 30-day mortality [$X^2(1, N = 244) = 18.2$, $P < 0.001$] (Table 2).

Primary exposures of interest

On univariate analysis, there was no evidence of an association between diabetes status, ethnicity (Caucasian vs non-Caucasian), BMI or CCI with severe COVID-19. These exposures were well matched between the two outcome groups (table 3).

There was strong evidence of an association between socioeconomic deprivation and severe COVID-19. More patients living in the most deprived areas developed severe COVID-19 compared to those living in the least deprived areas. On unadjusted analysis by logistic regression, there was a greater risk of severe COVID-19 among the first quartile (OR 2.37, 95% CI 1.12 – 5.03, $P = 0.025$), second quartile (OR 2.42, 95% CI 1.14 –

5.13, $P = 0.021$) and third quartile (OR 2.57, 95% CI 1.18 – 5.57, $P = 0.017$) of socioeconomic deprivation, compared to the fourth quartile (the least deprived). On adjusted analysis (Figure 1), the evidence for an association persisted: first quartile (OR 2.81, 95% CI 1.22 – 6.47, $P = 0.015$), second quartile (OR 2.63, 95% CI 1.19 – 5.79, $P = 0.017$) and the third quartile (OR 2.74, 95% CI 1.24 – 6.05, $P = 0.012$).

Secondary exposures of interest

Most secondary exposures of interest were not significantly different between the outcome groups: previous renal transplantation, immunosuppressant therapy, RAAS blockade, and systolic blood pressure (Table 3). There was strong evidence of an association between vitamin D supplementation for mineral bone disease treatment (OR 2.43, 95% CI 1.35 – 4.38, P = 0.03) and severe COVID-19. There was also strong evidence of an association between haemoglobin level and severe COVID-19 [$t(249) = 2.19$, $P = 0.029$], with a mean haemoglobin level of 108g/L in the non-severe group, and 103g/L in the severe group (OR 0.981, 95% CI 0.964 – 0.998, $P = 0.031$).

Time dependency and clustering

There was no difference in the timing of severe and non-severe case presentations to imply a time dependent effect of our findings (Figure 2). The median time to a diagnostic PCR test for each new severe and non-severe case was 32 and 33 days respectively with respect to the first recorded positive test in our data set (Mann Whitney Test $P = 0.209$) (Figure 2).

Clustering was investigated in 15 of the 34 units due to data availability (supplementary figure 1). Whilst episodes of clustering seemed possible, this appeared to have no pattern of influence on disease severity. Given the small number of cases in each unit and dialysis slot that could have clustered, it was not possible to perform any statistical analysis to investigate this further (supplementary figure 1).

Discussion

In this multi-centre, retrospective, cross-sectional study, we investigated risk factors that associate with severe COVID-19 among haemodialysis patients. This study produced three key findings. We found strong evidence that socioeconomic deprivation associates with severe COVID-19 (defined as new oxygen requirement and/or a C-reactive protein level ≥ 75 mg/L) after adjusting for age, sex and ethnicity, while other risk factors reported in the general population may not apply to haemodialysis patients. This study also highlights the high incidence of severe COVID-19 and subsequent 30-day mortality amongst patients on haemodialysis.

The incidence of COVID-19 in our population matches national statistics for the period of data collection (31). Severe disease developed in 63.5% of those with COVID-19, considerably higher than in the general population, where it is estimated to be closer to 20% (32, 33). This finding corroborates previously published data arising from smaller cohorts across the world, despite variable definitions for disease severity (24, 34-39). This finding also adds credence to the notion that all haemodialysis patients should be managed as being at risk for severe disease. With COVID-19 vaccinations becoming readily available, these results should be used to encourage immunisations among this patient group, and prioritise vaccines for those receiving haemodialysis in areas where vaccine availability is yet to become universal. In the event of future COVID-19 outbreaks, further measures should include reinforcing social distancing, isolated dialysis when appropriate and rigorous infection prevention measures at all dialysis units.

The high incidence observed is likely to be multifactorial. The generalised immunosuppressed state of haemodialysis patients has been well documented and is further evidenced by their increased susceptibility to infections and muted responses to immunisations (40, 41). Dialysis patients are also obliged to spend prolonged periods of time in enclosed, populated spaces to receive their treatment; this may increase their exposure to SARS-CoV-2 viral particles and subsequent viral load (42), particularly if other asymptomatic patients yet to be tested are dialysing out of isolation within the same unit, as may have occurred early in the pandemic (43-45). Indeed, this has been observed in the context of other communicable diseases which propagate through droplet transmission (46-48). As viral load correlates with disease severity (49), these factors together may predispose the entire haemodialysis cohort to severe COVID-19.

Despite the high rate of severe COVID-19 among haemodialysis patients, a proportion did not develop severe disease. We subsequently interrogated our data to determine if risk factors that associate with severe COVID-19 in the general population could be applicable to our cohort. Our key finding was strong evidence of an association between socioeconomic deprivation and COVID-19 severity among patients on haemodialysis. Socioeconomic deprivation has long been established as a predictor of poor health outcomes, and this has been demonstrated in the context of COVID-19 (5, 50-53). We used the English Index of Multiple Deprivation (IMD) as a marker of social deprivation. The IMD is a weighted composite of seven domains (income, employment, education, health, crime, barriers to housing, and living environments) which assigns a rank to 32,844 areas in England, with a rank of one considered the most deprived on the index (30). We present strong evidence that the IMD associated with a greater risk of severe COVID-19, being most pronounced between the least and most deprived quartiles. This finding persisted after adjusting for age, sex and ethnicity (OR 2.81, 95% CI 1.22 – 6.47, $P = 0.015$). The Scottish Renal Registry recently demonstrated patients living in more deprived areas were more susceptible to contracting COVID-19 (54), and residence in a congregate setting conferred a 17-fold risk for developing COVID-19 in the United States of America (17), but to the best of our knowledge, this is the first study demonstrating a link between socioeconomic deprivation and COVID-19 severity in the haemodialysis population.

Determining the precise factors that account for the relationship between the IMD and COVID-19 severity among haemodialysis patients is beyond the scope of this study, however there are a number of potential contributors that could warrant further investigation. Household overcrowding is incorporated into the IMD as a contributing factor of social deprivation (30). As with dialysis units, it is possible that this contributes to a greater exposure to viral load, should another member of the household be COVID-19 positive (49-51). Additionally, we were unable to collect data on patient smoking status, which may confound this association. Indeed, smoking is a possible a risk factor for severe COVID-19, and smoking habits are four times as more likely in areas ranked as most deprived by the IMD (55, 56). Other factors that may explain this association are likely to be less COVID-19 specific; dialysis patients living in areas considered to be deprived have poorer survival rates (57, 58), and this may be reflective of the physiological stressors associated with socioeconomic deprivation. Exposure to noise pollution, crowding, threat of crime, poor nutrition, and other life pressures, including job and housing insecurity, can contribute to a state of chronic stress (59). This exerts negative impacts on immunity (60, 61) and can promote pro-inflammatory states which pre-dispose to cardiovascular

frailty (62, 63), perhaps accounting for the poor outcomes noted in this population.

Obesity, ethnicity and diabetes status predict severity in the general population (22, 23, 32, 64-68), however, we found no evidence of these factors associating with COVID-19 severity in haemodialysis patients. This finding is in keeping with results of smaller French (122 patients) and Chinese (154) studies (7, 69). We also investigated the Charlson Comorbidity index, a weighted index that predicts ten-year survival in patients with multiple comorbidities (70), as a risk factor for COVID-19 severity. The CCI has shown value in predicting severe COVID-19 in the general population (71-74), but again, we found no evidence of an association with severe COVID-19 among patients on haemodialysis. This finding contrasts with those reported by Stefan et al, who found a positive correlation between CCI and COVID-19 severity in a cohort of 37 Romanian dialysis patients (34). However, the definition of severity used was different and a proportion of the patients in this study received treatments that included glucocorticoids, hydroxychloroquine, lopinavir-ritonavir, and tocilizumab, which may have altered disease progression, confounding results. Other risk factors reported to be significant in the general population, including sex, cardiovascular disease and blood pressure were evenly matched in our severe and non-severe COVID-19 groups. These findings further corroborate the results of smaller previously published studies (7, 69). It is possible that the risk conferred by haemodialysis for severe COVID-19 far outweighs that of the established risk factors defined for the general population, minimising their effect sizes in this select cohort of patients.

We also noted strong evidence of an association between prescribed vitamin D supplementation and severe COVID-19 (OR 2.43, 95% CI 1.35 – 4.38, P = 0.03). Vitamin D prescription in the dialysis population is principally in its activated from, used for the management for chronic kidney disease-related mineral bone disease, and not for routine supplementation (75). Those supplemented with vitamin D are therefore at higher risk of hyperphosphataemia, secondary hyperparathyroidism and ultimately vascular calcification, all of which associate with poor outcomes (76). Rather than suggesting these data infer any causal relationship between vitamin D supplementation and development of a severe manifestation of COVID-19, it is more likely that this 'relationship' is driven by residual confounding of the indications for vitamin D supplementations and related co-morbidity. A difference was also noted in the haemoglobin levels between those with severe disease and non-severe disease (103g/L vs 108g/L, $P = 0.029$). Although both groups showed evidence of chronic kidney disease-related anaemia, they also appeared to be adequately treated and within the limits recommended by

international guidelines (77). As with socioeconomic deprivation, establishing if these links are causal are beyond the scope of this study, but are hypothesis generating, nevertheless.

We opted to investigate severity over the commonly reported metrics of total incidence and mortality, as we found it to be more representative of the burden placed on healthcare resources by COVID-19, and an important clinical outcome with regards to the physical and mental morbidity. Mortality among those with COVID-19 on haemodialysis has been widely reported on, with age, frailty and co-morbidity burden featuring as strong predictors (14, 17, 69). However, mortality is commonly reported as a death occurring within 28 or 30 days of a positive PCR test (78-82) and could therefore include mortalities not strictly attributable to COVID-19, particularly given the characteristics of those most at risk. Furthermore, risk factors for mortality may not be COVID-19 specific; this can be challenging to differentiate between and therefore act upon from a public health perspective. Incidence is increasingly being accounted for by asymptomatic patients who place little strain on healthcare services beyond the need to dialyse in isolation (43, 44). We found that COVID-19 severity as defined by the RECOVERY trial, associated with admission rates and mortality ($P < 0.001$), and was therefore an adequate, relevant and generalisable marker for severity with regards to the objectives of this study. We opted to use the RECOVERY trial's definition for COVID-19 severity as it provided a pragmatic and clinically relevant definition. Larger studies have investigated disease severity using hospital admission as a proxy (25, 26). We opted to explore a different definition of severity; early in the pandemic admissions occurred to facilitate the logistics of isolated dialysis for COVID-19 patients who were otherwise well, and therefore an admission *per se* may not be truly reflective of disease severity.

The limitations of our study lie in our sampling methods, sample size and cross-sectional design. The issue of collider (sampling) bias has been highlighted in studies related to COVID-19 (83). This arises from a risk of failing to appropriately identify COVID-19 cases. This may occur because; 1) certain symptomatic groups are systematically less likely to get tested for COVID-19, and 2) the prevalence of asymptomatic patients identifiable only through protocolised or opportunistic testing. The first issue could be considered mitigated in our study by virtue of our patients all being dialysis dependent. Every patient included would have presented to either a hospital or a dialysis unit for dialysis, where they would have been screened for COVID-19 symptoms as a matter of protocol. Thus unlike in the general population, all symptomatic patients would have been tested for COVID-19, reducing this risk of a sampling bias. There is a risk that the PCR tests performed returned a

false negative. Again, the cohort of patients we report on would have been subject to repeat testing on each visit if symptoms persisted, reducing the risk of false negatives contributing to collider bias (84)

Our study did exclude asymptomatic patients who would not have been tested for COVID-19 at all. This is a reflection of testing availability and protocols that were being followed early in the pandemic. Whilst the exclusion of this patient group could influence our findings, we believe this impact to be minimal; the burden of asymptomatic disease among haemodialysis patients in Midlands of the UK, where most participating units were based, was likely to have been low. We note a study from Oxford that was performed over a similar time period as our study found a prevalence of 1.8% of asymptomatic disease (85). A study from Canada, which had a case:population ratio similar to that of the UK over the same period reported even lower rates (86). We also note a study from London which quoted a prevalence of 12% of asymptomatic patients, but are aware the case burden of COVID-19 early in the pandemic was much higher in the capital than it was in the Midlands (87, 88).

This work therefore included all haemodialysis patients for whom data was available, who tested positive for the SARS-CoV-2 virus on a PCR test during the first wave of the United Kingdom's COVID-19 pandemic. Although this is one of the larger studies investigating severity among of COVID-19 among haemodialysis patients, the relatively small sample size available limited its ability to identify smaller effect sizes that may have been exerted by the investigated exposures. It also prevented us from providing further granularity with regards to both ethnicity and socioeconomic deprivation and their associations with severe COVID-19, prompting a restriction in our analysis to Caucasian vs non-Caucasian and quartiles of socioeconomic deprivation, respectively. Given this was a cross-sectional observational study, causality cannot be inferred, and indeed it is likely that social deprivation associates with other key determinants of COVID-19 severity, that was beyond the scope of this study.

Conclusion

We confirmed a high incidence of severe COVID-19 among patients on haemodialysis and found that risk factors that apply to the general population may not be applicable in the same way for patients on haemodialysis. For patients on haemodialysis socioeconomic deprivation appears to be more closely associated with COVID-19 severity, but further work is needed to establish whether there is because of a causal link, or whether there are confounding factors that account for this finding.

Contributorship Statement

HS, KLH and JOB designed the study. HS, KLH, SFA, SA, MCC, MH, RH, AK, HK, ML, HSL, KM, SN, BO, SS, and MT collected data. HS and KLH coordinated data collection. KLH performed the statistical analysis supervised by LG. HS, KLH and JOB interpreted the data. HS and KH wrote the manuscript supervised by JOB. SFA, MGB, MH, ML, JFM and SN critically revised the manuscript. All authors edited and approved the final manuscript. JOB guarantors this study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

All pseudonymised data collected will be shared in spreadsheet format. The statistical analysis plan has been included as an appendix.

Transparency Declaration

HS, KLH and JOB affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Dialysis network	Included dialysis units, n = 34 (%)	Prevalent dialysis patients, n = 2899 (%)	+ve SARS-CoV-2 swabs, n = 274 (%)	Non-severe COVID-19, n = 97 (%)	Severe COVID-19, n = 174 (%)
Leicester	9 (26.5)	762 (26.3)	74 (27.0)	7 (22.1)	42 (24.4)
Birmingham	1 (2.95)	1031 (35.6)	105 (38.3)	23 (42.9)	67 (38.5)
Nottingham	5 (14.7)	454 (15.7)	31 (11.3)	10 (13.0)	20 (11.5)
Stoke	3 (8.82)	271 (9.35)	22 (8.0)	7 (7.29)	15 (8.62)
Coventry	6 (17.7)	381 (13.1)	42 (15.3)	13 (14.3)	30 (17.2)

Table 1 - demonstrates the number of haemodialysis units for each participating dialysis network, with the proportion of positive SARS-CoV-2 nasopharyngeal swabs, and the proportion of non-severe and severe COVID-19 outcomes

Characteristic	Non-severe COVID-19 (n = 77)	Severe COVID-19 (n = 174)	Missing data, n (%)
Age, years, median (IQR)	70 (57 – 80)	68 (60 – 78)	0
Sex, female, n (%)	34 (44.2)	67 (39.4)	0
Ethnicity:-			
Mixed British, n (%)	43 (55.8)	94 (54.0)	
Any other white background, n (%)	1 (1.30)	3 (1.91)	
Indian or British Indian, n (%)	11 (14.3)	21 (12.1)	
Pakistani or British Pakistani, n (%)	7 (9.10)	18 (10.3)	
Bangladeshi or British Bangladeshi, n (%)	3 (3.90)	3 (1.70)	
Any other Asian background, n (%)	2 (2.60)	6 (3.45)	
Caribbean, n (%)	1 (1.30)	4 (2.30)	0
African, n (%)	0	1 (0.60)	
Mixed Black, n (%)	0	2 (1.10)	
Black British, n (%)	1 (1.30)	1 (0.60)	
Any other Black background, n (%)	5 (6.50)	14 (8.00)	
Chinese, n (%)	0	1 (0.60)	
Any other ethnic group, n (%)	2 (2.60)	0	
Not stated, n (%)	1 (1.30)	6 (3.40)	
Years since developing ESKD, median (IQR)	4 (2 – 7)	4 (2 – 8)	6 (2.39)
Dialysis vintage, years, median (IQR)	3 (2 – 7)	4 (2 – 7)	24 (9.56)
Hospital-based unit, n (%)	20 (26.0)	45 (25.9)	
Satellite unit, n (%)	55 (71.4)	125 (71.8)	1 (0.398)
Home haemodialysis, n (%)	2 (2.60)	3 (1.70)	
Arteriovenous fistula or graft, n (%)	54 (70.1)	135 (77.6)	1 (0.398)
Haemodialysis catheter, n (%)	23 (29.9)	38 (21.8)	
ESKD diagnosis:-			
Diabetes, n (%)	28 (36.4)	66 (37.9)	
Glomerulonephritis, n (%)	12 (15.6)	26 (14.9)	
Hypertension, n (%)	3 (3.90)	11 (6.30)	
Polycystic kidney disease, n (%)	2 (2.60)	9 (5.20)	0
Pyelonephritis, n (%)	1 (1.30)	3 (1.70)	
Renal vascular disease, n (%)	2 (2.60)	6 (3.40)	
Other, n (%)	18 (23.4)	26 (14.9)	
Uncertain aetiology, n (%)	11 (14.3)	27 (15.5)	
Admitted to hospital, n (%)*	25 (32.5)	156 (89.7)	0
Death, n (%)*	6 (7.80)	61 (35.1)	7 (2.79)

*Table 2 - baseline characteristics for the two outcome groups, *p < 0.001* determined by unadjusted analysis*

Characteristic	Non-severe COVID-19 (n = 71)	Severe COVID-19 (n = 170)	*P* - value	Missing data, n (%)
Primary Exposures				
Caucasian, n (%) Non-Caucasian, n (%)	44 (57.1) 33 (42.9)	97 (55.7) 77 (44.3)	0.891	0
Diabetes mellitus, n (%)	44 (57.1)	103 (59.2)	0.788	2 (0.797)
CCI first quartile (1 – 4), n (%) CCI second quartile (5 – 6), n (%) CCI third quartile (7), n (%) CCI fourth quartile (≥ 8), n (%)	11 (14.3) 25 (32.5) 13 (16.9) 28 (36.4)	26 (14.9) 44 (25.3) 40 (23.0) 64 (36.8)	0.[illegible]	0
BMI, kg/m^2, median (IQR)	27.7 (23.6 – 31.4)	28.5 (24.2 – 34.5)	0.[illegible]	24 (9.56)
Deprivation rank 1st quartile, n (%) Deprivation rank 2nd quartile, n (%) Deprivation rank 3rd quartile, n (%) Deprivation rank 4th quartile, n (%)	17 (22.1) 17 (22.1) 15 (19.5) 28 (36.4)	46 (26.4) 47 (27.0) 44 (25.3) 32 (18.4)	0.0[illegible]*	5 (1.99)
Secondary Exposures				
Previous renal transplant, n (%)	6 (7.80)	23 (13.2)	0.285	2 (0.797)
Immunosuppressant therapy, n (%)	5 (6.50)	20 (11.5)	0.246	83 (33.1)
Vitamin D supplementation, n (%)	46 (59.7)	134 (77.0)	0.005*	5 (1.99)
RAAS blockade	7 (9.10)	22 (12.6)	0.423	0
Haemoglobin, g/L, mean (SD)	108 (+/- 15)	103 (+/-16)	0.029*	2 (0.797)
Systolic blood pressure, mm/Hg, mean (SD)	142 (+/- 25)	136 (+/-28)	0.[illegible]74	6 (2.39)

*Table 3 - summary of the results for the primary and secondary exposures of interest. *denotes statistical significance (P < 0.05), determined by unadjusted analysis*

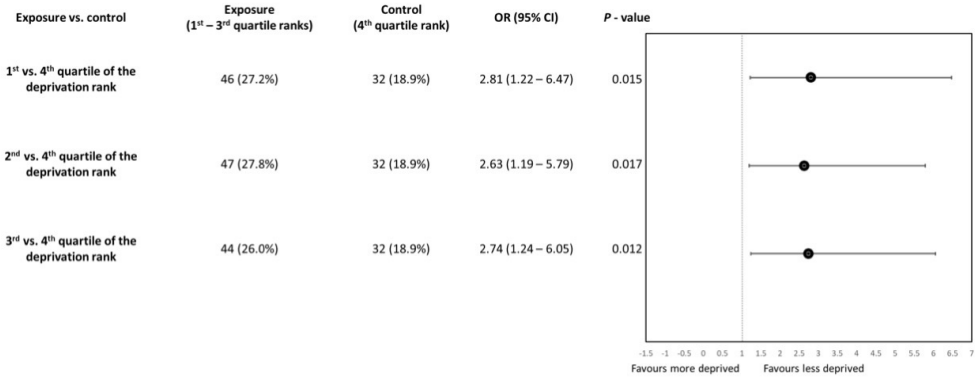
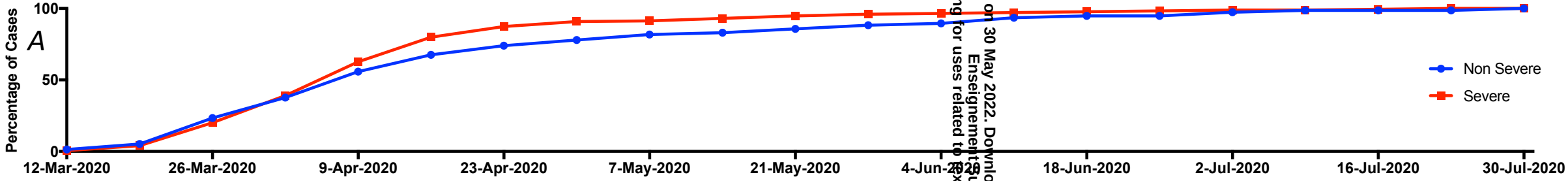
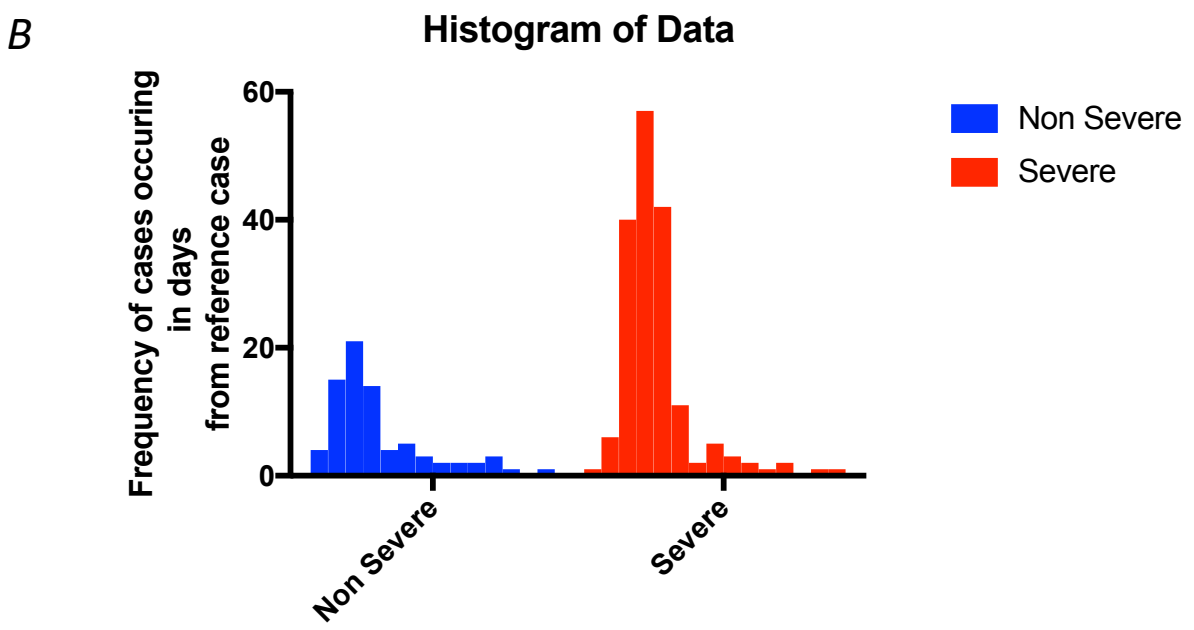


Figure 1 - Forest plot demonstrating the odds ratios on adjusted analysis when comparing the risk of developing severe COVID-19 between the most socially deprived (first to third deprivation ranks quartiles) and the least socially deprived areas (fourth deprivation rank quartiles).

107x60mm (300 x 300 DPI)





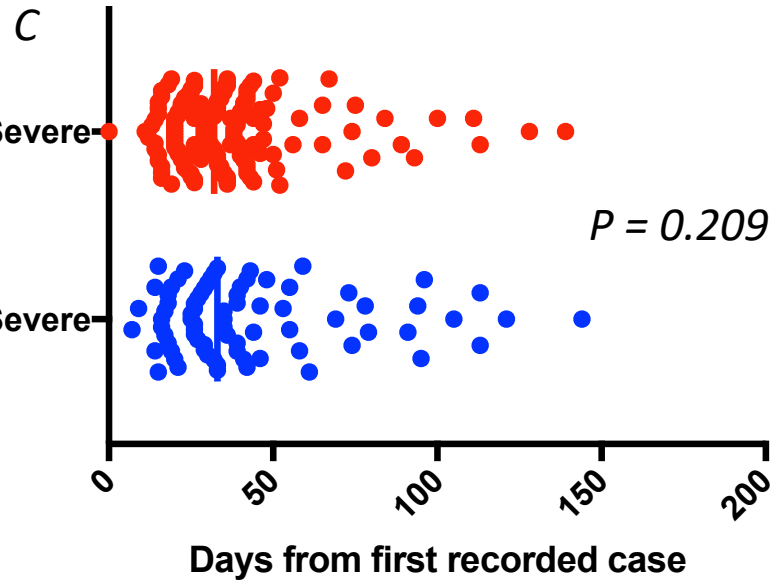


Figure 2: *The incidence of severe and non-severe cases over time. A) The cumulative percentage of cases over time for severe (N = 174, 100%) an non-severe cases (N = 77, 100%) was similar. B) Histogram showing frequency of cases in days relative to the reference case, defined as the first positive case in our study cohort. The data is not normally distributed, and as such was explored with non-parametric methods. C) The median number of days from the reference case for the presentation of severe and non severe cases was 32 and 33 respectively. A Mann Whitney test found this difference to be insignificant. Taken together, these data suggest that time dependency was unlikely to influence associations reported with disease severity.*

Project Registration Numbers for Participating Dialysis Networks

Dialysis Network	Project Registration Number
University Hospitals of Leicester NHS Trust	10802
Nottingham University Hospital NHS Trust	21-050C
University Hospitals of Birmingham NHS Trust	CARMS-16409
University Hospitals of North Midlands NHS Trust	CA41620
University Hospitals of Coventry and Warwickshire NHS Trust	10009

Risk Factors for Severe COVID-19 Among In-Centre Haemodialysis Patients.

Statistical Analysis Plan

Study Title: Risk factors for severe COVID-19 among in-centre haemodialysis patients.

Short Title: Severe COVID in ICHD patients.

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Prof. Laura Gray

Professor of Medical Statistics
University of Leicester

1. INTRODUCTION

1.1. STUDY BACKGROUND

Coronavirus disease 2019 (COVID-19) presents on a clinical spectrum, with severe disease requiring supplemental oxygenation, escalating to mechanical ventilation and even extra-corporeal membrane oxygenation (ECMO) in extreme cases. Factors influencing the severity of presentation has been rigorously interrogated in the general population, and include cardiovascular disease, diabetes mellitus, chronic lung disease, obesity, malignancy, immunosuppression and chronic kidney disease. The elucidation of these factors has directly informed public health advice, by defining at-risk patient groups who are advised to strictly social distance or shield, and is likely to guide rationing of the recently approved vaccinations.

Although those who require in-centre haemodialysis (ICHD) fall into the high risk category, not all develop severe disease. Understanding risk factors for severity of COVID19 among ICHD patients is of the utmost priority; traditional public health measures cannot apply to this group due to their obligation to travel to and from their units, and the need to interact with health care professionals at least three times a week. In this study, we report the incidence of COVID19 among HD patients in the midlands, a strongly multi-ethnic region in the United Kingdom, and explore risk factors for severity of infection, defining a cohort for whom added protective measures may need to be considered in the context of global easing of 'lockdowns', and perhaps who should be prioritised for vaccinations when they become available.

1.2. STUDY OBJECTIVES

This study aims to provide insights into unresolved questions regarding risk factors that may predispose to severe COVID19 among in-centre haemodialysis (ICHD) patients.

Hypothesis:

1. Obesity, diabetes, ethnicity are risk factors for severe COVID19 among ICHD patients

2. The Charlson Co-morbidity Score and Socioeconomic Deprivation are risk factors for severe COVID19 among ICHD patients

1.3. STUDY DESIGN

The study design is a multi-centre, retrospective cross-sectional observational study.

1.4. SAMPLE SIZE

Estimated sample size based on UK renal registry data is 350. This is the total number of patients with COVID19 in dialysis units based in the midlands between February 2020 to August 2020, and is therefore all the data available to us at present. Based on our pilot data of 69 patients, this sample should be adequate enough to detect the effect of BMI, Diabetes and Socioeconomic deprivation (as measured by the index of multiple deprivation (IMD)), however it may not be adequate enough to detect the effect of ethnicity or the Charlson Co-morbidity index. Sample size calculations were performed assuming an alpha of 0.5 and a power of 80% (https://clincalc.com/stats/samplesize.aspx):

Severe COVID in BMI >/=25 = 70%
Severe COVID in BMI <25 = 51%
Alpha 0.5, Power 80%
Total n = 206 (103 in each group)

Severe COVID in Diabetes = 76%
Severe COVID in non-diabetics = 45%
Alpha 0.5, Power 80%
Total n = 76 (38 in each group)

Severe COVID in White British = 58%
Severe COVID in other ethnicities = 53%
Alpha 0.5, Power 80%
Total n = 3100 (1550 in each group)

Severe COVID in Charlson Index >/= 5 = 55%
Severe COVID in Charlson Index < 5 = 50%
Alpha 0.5, Power 80%
Total n = 3130 (1565 in each group)

Severe COVID in lowest IMD deciles = 53%
Severe COVID in highest IMD deciles = 23%
Alpha 0.5, Power 80%
Total n = 80 (40 in each group)

1.5. STUDY POPULATIONS

All ICHD patients who tested positive for COVID19, on a hospital based real time reverse transcription quantitative polymerase chain reaction tests, were included in this study.

1.6. STATISTICAL ANALYSIS PLAN (SAP)

1.6.1. SAP OBJECTIVES

The objective of this SAP is to describe the statistical analyses to be carried out for the final analysis of this study.

1.8.2. General Principles

An alpha level of 0.05, and confidence intervals be set at 95% will be used for all statistical tests. Power of 0.8 was assumed when calculating sample sizes.

1.8.3. Software

Analyses will be carried out using SPSS, R, or Prism.

2. Analysis

2.1. Study Populations

All ICHD patients who tested positive for COVID19, on a hospital based real time reverse transcription quantitative polymerase chain reaction tests, will be included in this study.

These patients will be divided into those who had severe COVID19 (defined as respiratory support with supplemental oxygen or more, and/or a CRP of >75) and those who were able to oxygenate effectively on room air (no supplemental oxygen, or further interventions required).

2.2. Outcomes

2.2.1. Primary Outcome

The primary outcome of this study is COVID severity, as defined above in section 2.1. The effect of exposures on this outcome will be assessed in this study and has been detailed in section 2.3

2.3. **EXPOSURES**

2.3.1 Primary Exposures

The primary exposures of interest are:

1) Diabetes status (collected as a yes/no categorical variable), inclusive of all variants.

2) BMI collected as a continuous variable

3) Ethnicity, defined as a categorical variable based on office of national statistics categories.

4) The Charlson Comorbidity index

5) Social deprivation will be collected using the English Index of Multiple Deprivation rank and deciles, as an ordinal variable.

2.3.2 Exploratory Exposures

Exploratory exposures of interest will include association age, sex, dialysis vintage, dialysis access, renin-angiotensin inhibition, transplant status, immunosuppression status, haemoglobin, vitamin D supplementation and blood pressure.

2.4 ANALYSIS PLAN

2.4.1 Baseline data

Incidence of COVID-19 and Severe COVID-19 will be calculated against the total dialysis population belonging to each participating haemodialysis unit, during the time frame of data collection.

Continuous variables will be summarised by mean and standard deviation, minimum and maximum. Categorical variables will be summarised by N (%).

2.4.2 Exposure effect exploration

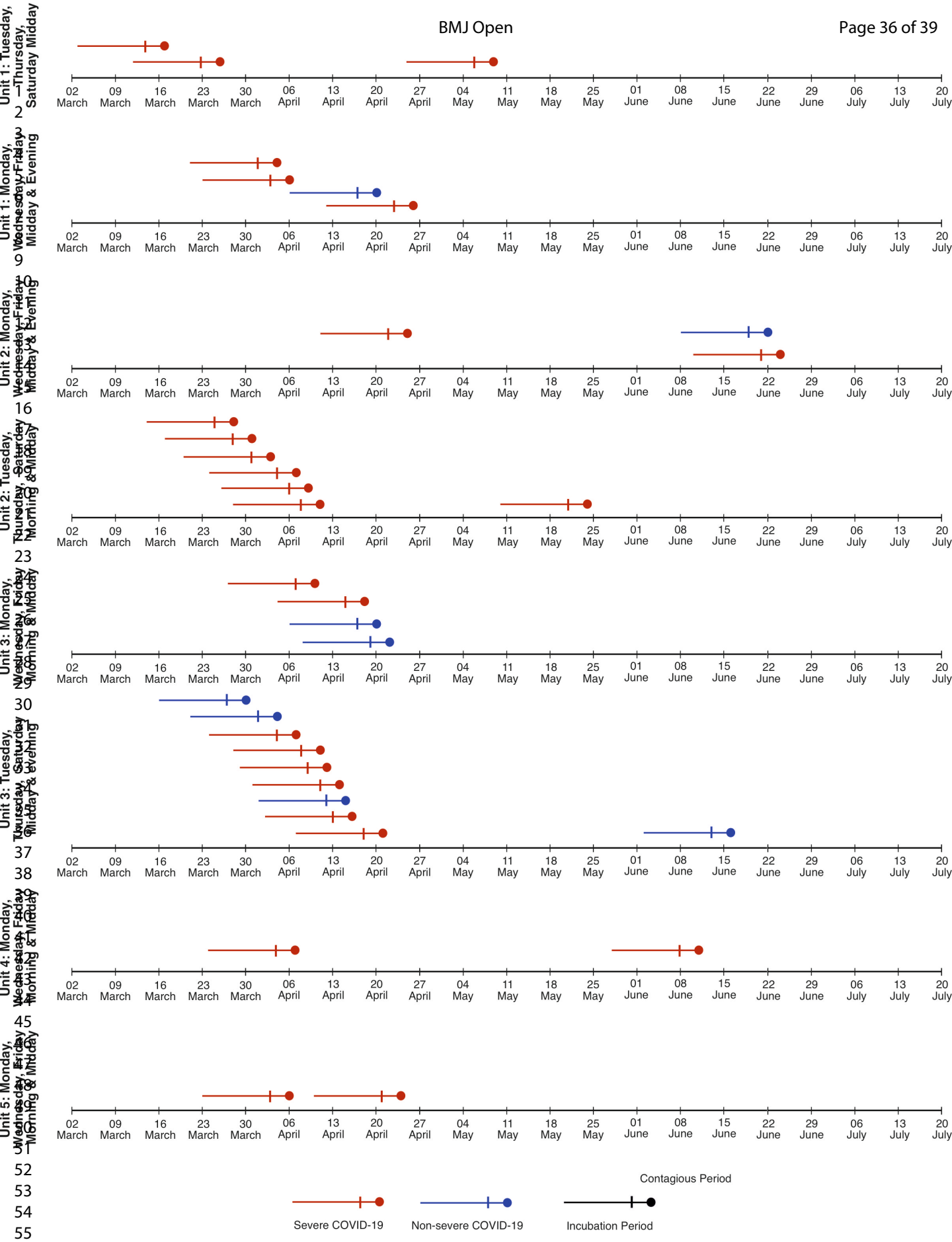
The incidence of severe COVID between exposed and non exposed groups, as defined in sections 2.3.1 and 2.3.2 will be compared. Continuous variables will be summarised by mean and standard deviation, minimum and maximum. Categorical variables will be summarised by N (%).

2.4.3.Modelling – adjusted and unadjusted

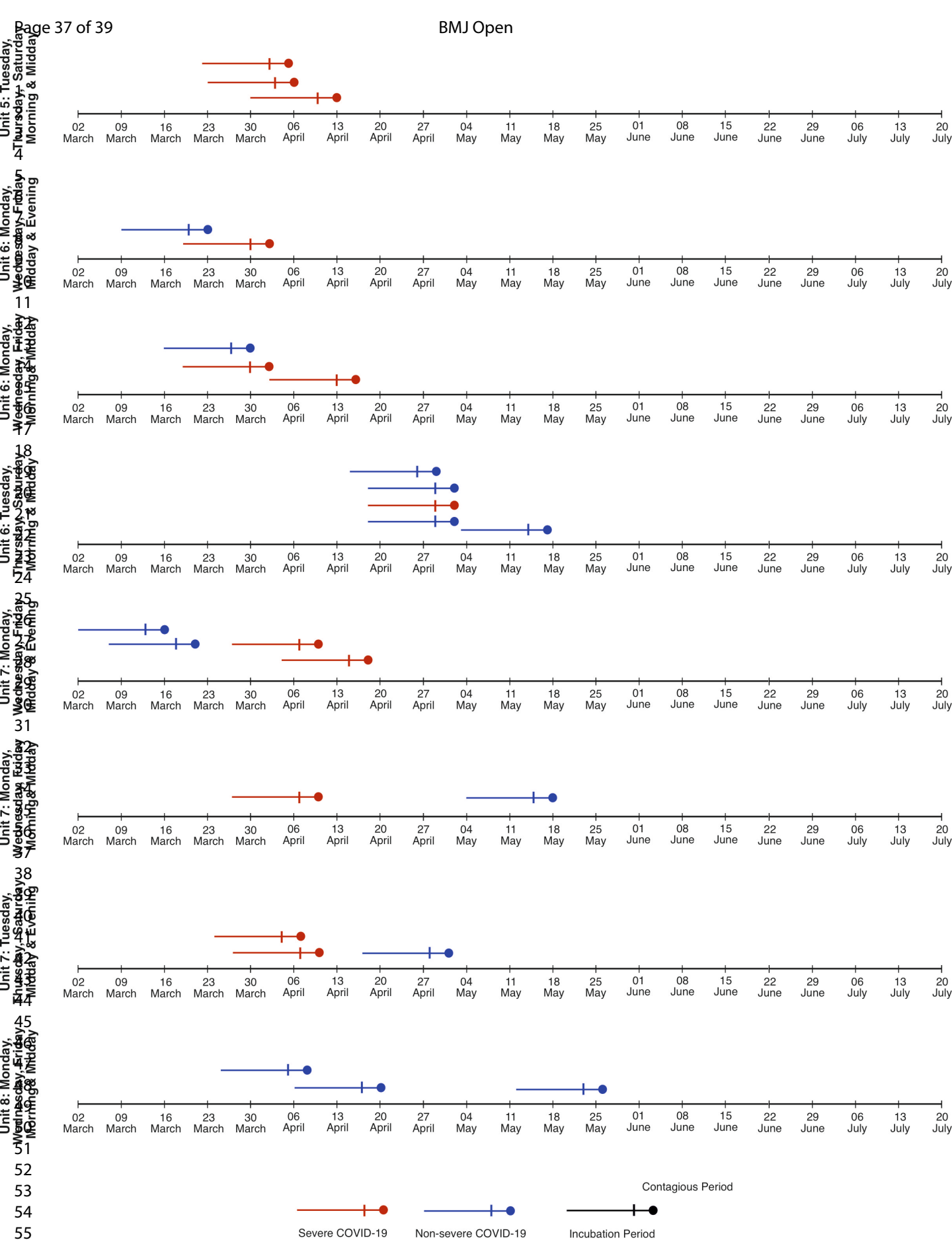
Risk factor effects on primary outcomes (severe COVID19) will be analysed using logistic regression models. Adjustments will be made for sex, age and ethnicity.

3. DOCUMENT HISTORY

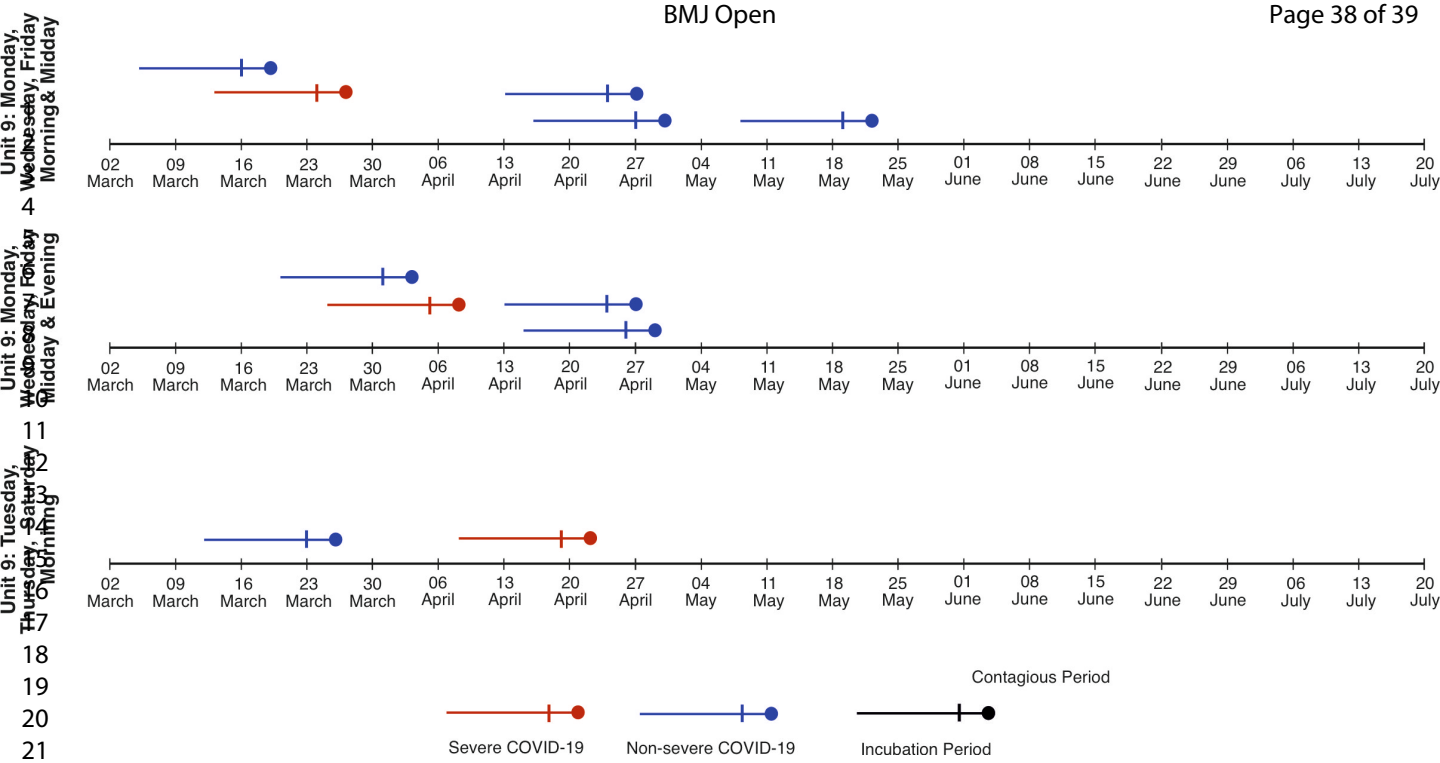
This is version 1.3 of the SAP for this study, dated 19th of December 2020, the fourth iteration of this document.



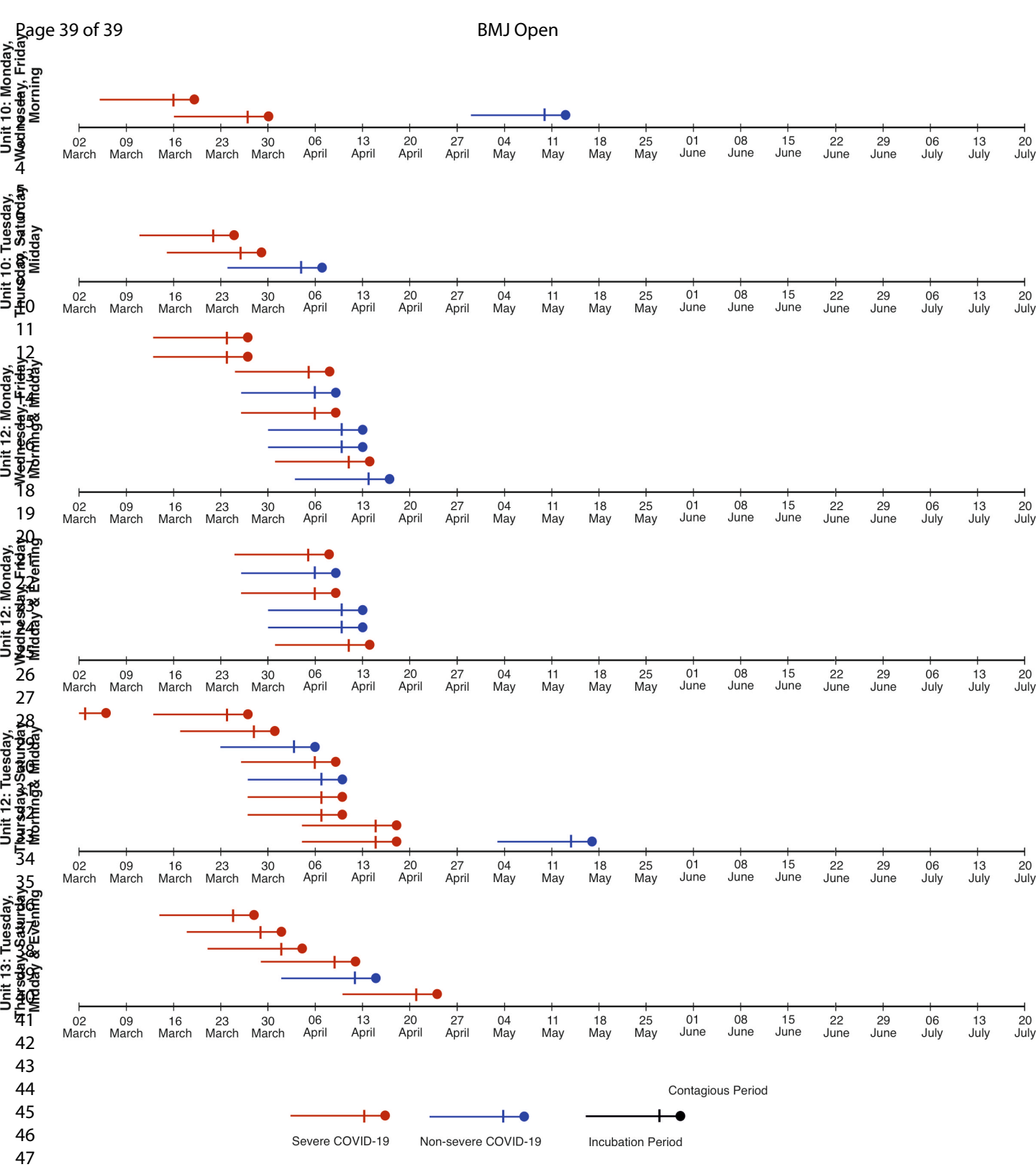
***Supplementary Figure 1A**: Incident cases of severe (red) and non-severe (blue) cases over time, grouped by dialysis unit and dialysis slots. Morning and Midday slots, and Midday and evening slots were grouped together to account for the risk of overlap, although this was avoided where possible. The dot represents the date of a positive PCR test conferring a diagnosis of COVID-19. The horizontal line represents the presumed incubation period of 14 days, and the vertical line represents the three day period in which infectivity would have been possible. Although certain clusters are visible, a relationship between clustering and severity is not consistent or evident.*



***Supplementary Figure 1B**: Incident cases of severe (red) and non-severe (blue) cases over time, grouped by dialysis unit and dialysis slots. Morning and Midday slots, and Midday and evening slots were grouped together to account for the risk of overlap, although this was avoided where possible. The dot represents the date of a positive PCR test conferring a diagnosis of COVID-19. The horizontal line represents the presumed incubation period of 14 days, and the vertical line represents the three day period in which infectivity would have been possible. Although certain clusters are visible, a relationship between clustering and severity is not consistent or evident.*



***Supplementary Figure 1C**: Incident cases of severe (red) and non-severe (blue) cases over time, grouped by dialysis unit and dialysis slots. Morning and Midday slots, and Midday and evening slots were grouped together to account for the risk of overlap, although this was avoided where possible. The dot represents the date of a positive PCR test conferring a diagnosis of COVID-19. The horizontal line represents the presumed incubation period of 14 days, and the vertical line represents the three day period in which infectivity would have been possible. Although certain clusters are visible, a relationship between clustering and severity is not consistent or evident.*



***Supplementary Figure 1D**: Incident cases of severe (red) and non-severe (blue) cases over time, grouped by dialysis unit and dialysis slots. Morning and Midday slots, and Midday and evening slots were grouped together to account for the risk of overlap, although this was avoided where possible. The dot represents the date of a positive PCR test conferring a diagnosis of COVID-19. The horizontal line represents the presumed incubation period of 14 days, and the vertical line represents the three day period in which infectivity would have been possible. Although certain clusters are visible, a relationship between clustering and severity is not consistent or evident.*

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6,21,22
Outcome data	15*	Report numbers of outcome events or summary measures	21,22
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7

		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.