Comparison of Outcomes of In-Centre Haemodialysis Patients between the 1st and 2nd COVID-19 Outbreak in England, Wales, and Northern Ireland: A UK Renal Registry Analysis

Manuela Savino\textsuperscript{a} Shalini Santhakumaran\textsuperscript{a} Christine S.M. Currie\textsuperscript{b} Bhakti S.S. Onggo\textsuperscript{b} Katharine M. Evans\textsuperscript{a} James F. Medcalf\textsuperscript{a, c, d} Dorothea Nitsch\textsuperscript{a, e, f} Retha Steenkamp\textsuperscript{a}

\textsuperscript{a}UK Renal Registry, Bristol, UK; \textsuperscript{b}Department of Mathematical Sciences, University of Southampton, Southampton, UK; \textsuperscript{c}University of Leicester, Leicester, UK; \textsuperscript{d}Leicester General Hospital, Leicester, UK; \textsuperscript{e}London School of Hygiene and Tropical Medicine, London, UK; \textsuperscript{f}Royal Free London NHS Foundation Trust, London, UK

Unadjusted survival at 28 days was similar in both waves (wave 1 75.6\% [95\% confidence interval [CI]: 73.7--77.5], wave 2 76.3\% [95\% CI 74.3--78.2]), but death occurred more rapidly after detected infection in wave 1. Long vintage treatment and not being on the transplant waiting list were associated with higher mortality in both waves. \textbf{Conclusions:} Risk of death of patients on ICHD treatment with COVID-19 remained unchanged between the first and second outbreaks. This highlights that this vulnerable patient group needs to be prioritized for interventions to prevent severe COVID-19, including vaccination, and the implementation of measures to reduce the risk of transmission alone is not sufficient.

Introduction

The COVID-19 pandemic has posed a major challenge to the safety of patients undergoing in-centre haemodialysis (ICHD) treatment, as well as to the organization of services provided by renal centres. Although regarded as clinically extremely vulnerable, patients on ICHD were not able to shield during the pandemic, because of their...
need to visit hospital regularly for their life-sustaining treatment [1, 2].

A previous UK Renal Registry (UKRR) analysis found that, up to 30 June 2020, unadjusted survival for ICHD patients in England and Wales at 1 week after date of positive COVID-19 test was 87.5% (95% confidence interval [CI]: 86.1–88.8) and 80.0% at 2 weeks (95% CI: 78.3–81.5) [3]. Relative risk of mortality of ICHD patients with COVID-19, compared to the general population with COVID-19, was 45.4 and was highest in younger adults [3].

COVID-19 has led to different pandemic “waves” over time, and recent studies have compared differences in infection rates and outcomes between the various waves. In the UK, studies have analysed differences between the first (March to August 2020) and second (September 2020 to January 2021) waves in the outcomes of the general population with COVID-19, finding a decline in COVID-19-related mortality in the second wave compared to the first, both in hospital and in the community [4, 5]. Reasons underlying this decline include a change in the case-mix of patients with more severe COVID-19, an increased proportion of younger and healthier people during the second wave [6], the introduction of policies to protect the most vulnerable groups, greater knowledge of available therapeutic aids [7], improved medical management to reduce admissions to intensive care [8–10], and finally increased testing capacity and detection of cases amongst the general population, motivated by the spread of variants with higher transmissibility.

Several guidelines and policies were developed during the first wave of the pandemic to protect patients on ICHD [11, 12], but to date, it is unclear the impact these have had in reducing transmission of COVID-19 and increasing survival of this vulnerable patient group in the second wave. The objective of this retrospective cohort study was to compare patient features, infection rates, and outcomes of patients on ICHD between the first and second waves of the COVID-19 pandemic in England, Wales, and Northern Ireland.

**Material and Methods**

**Study Population and Design**

This is a retrospective cohort study of all people aged ≥18 years receiving ICHD at 31 December 2019 in England, Wales, or Northern Ireland who were still alive and not in receipt of a kidney transplant on 31 December 2019 in England, Wales, or Northern Ireland.

**COVID-19 Infection Data**

Data on COVID-19 infections came from weekly returns from 1 March 2020 to 31 January 2021 submitted to the UKRR by UK renal centres in England, Wales, and Northern Ireland listing all ICHD patients with a positive polymerase chain reaction test. The COVID-19 infections were split into two “waves”: wave 1 from March to August 2020 and wave 2 from September 2020 to January 2021. We chose to end wave 2 on 31 January 2021 when the vaccination program was established in the kidney replacement therapy (KRT) population. For the main analysis, only the first infection was considered, but we present a description of patients who were reinfected (with at least 90 days between the test dates). We compared infection counts in the study cohort with UK general population data, obtained from the UK Government Coronavirus dashboard [13].

**Outcomes and Covariates**

Age, sex, ethnicity, Index of Multiple Deprivation [14] rank quintile from patient postcode, primary renal diagnosis (PRD), and whether the patient was on the transplant waiting list on 31 December 2019 were extracted from the UKRR database. Dates of death were obtained from the NHS Demographics Batch Service. For mortality following COVID-19 infection, we included all-cause mortality within 28 days of the test date. COVID-19 mortality in ICHD patients was compared with the general population using data published in the UK Office of National Statistics (ONS) on deaths where COVID-19 was mentioned on the death certificate [15].

**Ethics**

The UKRR collects patient data without consent under section 251 from the Health Research Authority’s Confidentiality Advisory Group. The data were pseudonymized prior to being analysed. This study was approved by the North East Newcastle & North Tyneside 1 Research Ethics Committee (16/NE/0042).

**Statistical Analysis**

The cumulative incidence of COVID-19 was calculated separately for wave 1 and wave 2, treating death and transplant as competing events. Multivariable Cox models were used to assess risk factors for positivity separately in wave 1 and wave 2, censoring patients who died or were transplanted with no positive test (i.e., estimating cause-specific hazards). Kaplan-Meier-unadjusted survival and multivariable Cox models were used to describe survival. Infection and mortality models were adjusted for age, sex, ethnicity, deprivation quintile, PRD (diabetic/non-diabetic), whether the patient was on the kidney transplant waiting list by 31 December 2019, and treatment vintage to investigate if time on renal replacement treatment was associated with an increased risk of mortality. Interactions were checked, and the assumption of proportional hazards was tested using log minus log plots.

The method of Cori et al. [16] was used to estimate the median and 95% credible interval (CrI) of the reproduction number (R) for cases in dialysis centres. A mean serial interval of 3.96 days was assumed [17, 18]. Due to the strong weekly pattern in the data, which records the arrival of positive results when patients attend for dialysis, we used a 7-day moving average of incidence.

Relative risk of death with COVID-19 infection for ICHD patients in England and Wales compared to the general population was calculated separately for each wave, by age and region. The risk in the ICHD population is the number of deaths recorded within 28 days of a positive COVID-19 test in the wave, divided by the number at risk at the start of the wave. The risk in the general pop-
All adult (≥18 years) RRT patients on in-centre haemodialysis at 31st December 2019 in England, Wales and N Ireland (n = 22,514)

Excluded:
- Died before 1st March 2020 (n = 656)
- Transplanted before 1st March 2020 (n = 278)

Final cohort (n = 21,580)

Wave 1 March to August 2020
Number at risk at start of wave (n = 21,580)

ICHD COVID-19 infections in wave (n = 2,105)
- Died without infection (n = 1,059)
- Changed modality without infection (n = 435)

(n = 17,981)

Transplant failed before start of wave 2 (n = 3)

Wave 2 September 2020 to January 2021
Number at risk at start of wave (n = 17,984)

ICHD COVID-19 infections in wave (n = 2,303)
- Died without infection (n = 60)
- Changed modality without infection (n = 400)

(n = 15,221)

Fig. 1. Flow chart describing the study cohort.
ulation is the number of deaths recorded in England and Wales during the wave where COVID-19 is mentioned on the death certificate [15], divided by the England and Wales mid-2019 population estimate [19]. The risk in the ICHD population was divided by the risk in the general population to obtain the relative risk. The age-specific estimates were used to calculate an overall age-standardized relative risk, with the mid-p method used to calculate the 95% CI. Analyses were conducted using SAS version 9.4,11, and 95% CIs are reported throughout this paper.

Results

Study Cohort

There were 22,514 people in England, Wales, and Northern Ireland receiving ICHD at the end of 2019. Of these, 656 died and 278 had a functioning transplant by the start of the study period, leaving 21,580 in the cohort (Fig. 1).

Incidence of COVID-19 Infection

There were a total of 4,408 people who had a positive COVID-19 test: 2,105 in wave 1 and 2,303 in wave 2. The peaks of infection occurred at the same time as for the general UK population (Fig. 2), but the wave 1 peak was much higher than wave 2 for ICHD patients. From the start of wave 1, cumulative infections rose sharply before flattening off at around 8 weeks (online suppl. Fig. 1; see www.karger.com/doi/10.1159/000523731 for all online suppl. material). In contrast, during wave 2 the rate of infections increased over the period. In addition to those infected in wave 1, further 1,059 patients died and 432 were successfully transplanted by 1 September 2020, leaving 17,984 at risk for the start of wave 2. Fifty-nine patients (1.3%) had a second positive test more than 90 days after the first (see online suppl. Table 1 for characteristics). The median time between infections was 227 days (interquartile range 159–270 days).

Risk Factors for COVID-19 Infection

Patients infected in wave 1 were older (median age 69 years, with 20% aged ≥80) compared to wave 2 (median age 67 with 16% aged ≥80) (Table 1). In wave 1, the risk of infection increased consistently with age (p < 0.001). People aged 18–39 had a 30% lower risk of infection (95% CI 13–43%) compared to 60–79-year-olds, and those aged over 80 had a 9% higher risk (95% CI: −3% to 22%) (Table 2).
wave 2, the 40–59-year-olds were at the highest risk, and those aged over 80 had a 16% (95% CI: 5–36%) lower risk than those aged 60–79. Non-white ethnicities were more likely to be infected than white ethnicities in both waves, but the differences were larger in wave 1, particularly for black people. In wave 1, black patients comprised 18% of infections and were more than twice as likely to be infected compared to white patients (adjusted HR 2.12 [95% CI: 1.87–2.39]). Black patients were 35% more likely than white patients to be infected in wave 2 (adjusted HR 1.35 [95% CI: 1.18–1.53]) and accounted for 13% of infections, closer to the 12% seen in the overall cohort. People with diabetes as PRD were more likely to be infected, particularly in wave 1 (HR 1.49 [95% CI: 1.35–1.63] in wave 1, 1.21 [95% CI: 1.1–1.32] in wave 2). People on the waiting list for a transplant at the end of 2019 were less likely to be infected in wave 1 (HR 0.79 [95% CI: 0.69–0.91]), but this was not the case for wave 2 (HR 0.98 [95% CI: 0.87–1.1]).

The median value of R peaked in mid-March 2020 at 2.94 (95% CrI: 1.41–5.31), excluding the summer months when the number of cases was too low to accurately estimate R (Fig. 3). The highest median value in wave 2 was 2.17 in early September 2020, but with high uncertainty due to the small number of cases amongst the study cohort (95% CrI: 0.36–6.80).

**Table 1.** Demographics of study cohort and of people with COVID-19 infection in wave 1 and wave 2

| Variable                                      | ICHD adults end 2019 (n = 21,580) | ICHD adults with COVID-19 in wave 1 (n = 2,105) | ICHD adults with COVID-19 in wave 2 (n = 2,303) |
|-----------------------------------------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|
| Age, years                                    | Median (IQR)                      | 68 (56–77)                                     | 69 (58–78)                                     | 67 (56–76)                                     |
| 18–39, %                                      | 7                                 | 5                                             | 6                                             |
| 40–59, %                                      | 26                                | 24                                            | 27                                            |
| 60–79, %                                      | 49                                | 51                                            | 50                                            |
| ≥80, %                                        | 18                                | 20                                            | 16                                            |
| Male, %                                       | 62                                | 62                                            | 62                                            |
| Ethnicity, %                                  | White                             | 70                                            | 54                                            | 60                                            |
| Asian                                         | 15                                | 24                                            | 23                                            |
| Black                                         | 12                                | 18                                            | 13                                            |
| Other                                         | 4                                 | 5                                             | 4                                             |
| Area-level deprivation quintile, %           | 1 – least deprived                | 12                                            | 10                                            | 11                                            |
| 2                                             | 15                                | 13                                            | 14                                            |
| 3                                             | 19                                | 20                                            | 17                                            |
| 4                                             | 24                                | 27                                            | 26                                            |
| 5 – most deprived                             | 29                                | 30                                            | 33                                            |
| PRD diabetic nephropathy                      | 28                                | 39                                            | 33                                            |
| Waitlisted for kidney transplant at 31 Dec 2019 | 17                                | 14                                            | 16                                            |
| Vintage, %                                    | ≤2015                             | 44                                            | 44                                            | 43                                            |
| 2016–2018                                     | 38                                | 39                                            | 38                                            |
| 2019                                          | 18                                | 17                                            | 18                                            |

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**COVID-19 Outcomes and Features of Patients on ICHD**

**Wave Two Survival after COVID-19 Infection**

At 28 days after infection, unadjusted survival was similar in both waves (wave 1 75.6% [95% CI: 73.7–77.5], wave 2 76.3% [95% CI: 74.3–78.2]), but death occurred more quickly in wave 1 (Fig. 4). The median survival time was 7 days in wave 1 and 10 days in wave 2. The pattern was similar for age- and sex-adjusted survival (online suppl. Fig. 2).

In wave 1, there was strong evidence that increasing age was associated with increased mortality: those aged...
≥80 years had a mortality risk of 5.9 times that of those aged 18–39 years (Table 3). Ethnicity and PRD (diabetic vs. non-diabetic) were not associated with mortality in wave 1. Patients on dialysis for more than 5 years had higher mortality risk (53% wave 1, 50% wave 2) compared to patients who started dialysis during the last year. Those patients on the waiting list for a kidney transplant at the end of 2019 had a lower risk of mortality to COVID-19 compared to patients not on the waiting list (HR 0.44 wave 1, 0.50 wave 2). In wave 2, younger diabetic patients (40–59 years of age) had a higher risk of mortality compared to non-diabetic patients; the mortality risk of diabetes was similar for other age groups. Black patients on ICHD with COVID-19 had a lower mortality risk in wave 2 than white patients. Deprivation was not associated with mortality in either wave and not included in the mortality models.

**Risk of Mortality Compared to the General Population**
Compared to the general population in England and Wales, the age-standardized relative risk of mortality amongst ICHD patients was 8.95 (95% CI: 8.14–9.67) in wave 1 and 8.43 (95% CI: 7.71–9.20) in wave 2. Age-specific relative risks were similar between waves except for those aged over 80, who had relatively higher mortality in the first wave (RR 4.02, 95% CI: 3.5–4.7) than during the second wave (RR 2.70, 95% CI: 2.2–3.3), Table 4. COVID-19 mortality was consistently much higher in the ICHD population than the general population which suggests that temporal trends differed by region. ICHD mortality was relatively higher in the first wave for the West Midlands (wave 1 RR 29.5 [95% CI: 23.6–36.9] vs. wave 2 RR 20.3 [95% CI: 15.4–26.7]), London (wave 1 RR 40.7 [95% CI: 35.6–46.5] vs. wave 2 RR 33.5 [95% CI: 28.2–39.8]), and Wales (wave 1 RR 27.5 [95% CI: 18.7–40.2] vs. wave 2 RR 15.0 [95% CI: 9.7–23.2]). Other regions showed the opposite: the North West (wave 1 RR 16.2 [95% CI: 12.1–21.5]).

### Table 2. Hazard ratios for COVID-19 infection in wave 1 and wave 2, from multivariable Cox regression

| Variable                                      | Level     | Wave 2 (1 Sep 2020 to 31 Jan 2021) (N = 17,363) | 95% limits for HR | HR 95% limits for HR | HR 95% limits for HR |
|-----------------------------------------------|-----------|------------------------------------------------|------------------|----------------------|----------------------|
| Age                                           | 18–39     | 0.7                                            | 0.57             | 0.87                 | 0.92                 |
|                                               | 40–59     | 0.86                                           | 0.77             | 0.96                 | 1.04                 |
|                                               | 60–79     | 1                                               | 1                | 1                    | 1                    |
|                                               | 80+       | 1.09                                           | 0.97             | 1.22                 | 0.84                 |
| Sex                                           | Male      | 1                                               | 1                | 1                    | 0.88                 |
|                                               | Female    | 0.97                                           | 0.88             | 1.06                 | 0.96                 |
| Ethnicity                                     | White     | 1                                               | 1                | 1                    | 1                    |
|                                               | Asian     | 1.98                                           | 1.77             | 2.21                 | 1.91                 |
|                                               | Black     | 2.12                                           | 1.87             | 2.39                 | 1.35                 |
|                                               | Other     | 1.78                                           | 1.45             | 2.19                 | 1.4                  |
| Area-level deprivation quintile               | 1 – least deprived | 1 | 1 | 1 | 1 |
|                                               | 2         | 1.06                                           | 0.88             | 1.27                 | 1.02                 |
|                                               | 3         | 1.21                                           | 1.02             | 1.44                 | 0.98                 |
|                                               | 4         | 1.21                                           | 1.02             | 1.43                 | 1.15                 |
|                                               | 5 – most deprived   | 1.12 | 0.95 | 1.32 | 1.19 |
| Diabetes as PRD                               | Non-diabetic | 1 | 1 | 1 | 1 |
|                                               | Diabetic   | 1.49                                           | 1.35             | 1.63                 | 1.21                 |
| Waitlisted for transplant at 31 Dec 2019      | No        | 1                                               | 0.79             | 0.69                 | 0.91                 |
|                                               | Yes       | 1                                               | 0.91             | 0.69                 | 0.98                 |
| Year of dialysis start                        | ≤2015     | 1.09                                           | 0.96             | 1.23                 | 1.03                 |
|                                               | 2016–2018 | 1.05                                           | 0.93             | 1.19                 | 1.01                 |
|                                               | 2019      | 1                                               | 1                | 1                    | 0.9                  |

729 patients (3%, the same for those with and without infection) were excluded due to missing data. PRD, primary renal disease.
Fig. 3. Incidence and R₀ calculation for all renal centres in England, Wales, and Northern Ireland.

Fig. 4. Twenty-eight-day crude survival for ICHD COVID-19 patients.
In our study, we found that unadjusted survival at 28 days after infection of ICHD patients with COVID-19 was similar in both waves at about 76%, but death occurred more quickly after infection in wave 1. R peaked in March 2020 and decreased in line with the first national lockdown; thereafter, it increased again in September 2020 but with no further increases during the second wave. Regional patterns of mortality risk when compared to the general population varied markedly and were not consistent with COVID-19 incidence, especially during wave 2.

The COVID-19 pandemic has led the UK through three national lockdowns, 1st lockdown between 26 March 2020 (week 4) to 23 June 2020 (week 17), 2nd lockdown between 5 November 2020 (week 9) and 2 December 2020 (week 13), and 3rd lockdown from 6 January 2021 (week 18) [20]. These national lockdowns were each characterized by different types of restrictive measures, and therefore, they had different effects on transmission of COVID-19 within the community [21]. Whilst in the first lockdown, in line with international practice, stricter measures were used, including closure of schools, in the second and third lockdowns the measures were less re-

### Table 3. Hazard ratios for death up to 28 days after COVID-19 infection

| Variable                                      | Patients wave 1, n | Deaths wave 1, n | Patients wave 2, n | Deaths wave 2, n | Hazard ratio wave 1a | 95% CI wave 1 | Hazard ratio wave 2a | 95% CI wave 2 |
|-----------------------------------------------|-------------------|-----------------|-------------------|-----------------|----------------------|--------------|----------------------|--------------|
| Age group (years)                             |                   |                 |                   |                 |                      |              |                      |              |
| 18–39                                         |                   |                 |                   |                 |                      |              |                      |              |
| 40–59                                         |                   |                 |                   |                 |                      |              |                      |              |
| 60–79                                         |                   |                 |                   |                 |                      |              |                      |              |
| ≥80                                           |                   |                 |                   |                 |                      |              |                      |              |
| Sex                                           |                   |                 |                   |                 |                      |              |                      |              |
| Female                                        |                   |                 |                   |                 |                      |              |                      |              |
| Male                                          |                   |                 |                   |                 |                      |              |                      |              |
| Ethnicity                                     |                   |                 |                   |                 |                      |              |                      |              |
| White                                         |                   |                 |                   |                 |                      |              |                      |              |
| Asian                                         |                   |                 |                   |                 |                      |              |                      |              |
| Black                                         |                   |                 |                   |                 |                      |              |                      |              |
| Other                                         |                   |                 |                   |                 |                      |              |                      |              |
| PRD                                           |                   |                 |                   |                 |                      |              |                      |              |
| Non-diabetic                                  |                   |                 |                   |                 |                      |              |                      |              |
| Diabetic                                      |                   |                 |                   |                 |                      |              |                      |              |
| Vintage                                       |                   |                 |                   |                 |                      |              |                      |              |
| ≤2015                                         |                   |                 |                   |                 |                      |              |                      |              |
| 2016–2018                                     |                   |                 |                   |                 |                      |              |                      |              |
| 2019                                          |                   |                 |                   |                 |                      |              |                      |              |
| Waitlisted for kidney transplant at 31 Dec 2019|                   |                 |                   |                 |                      |              |                      |              |
| Yes                                           |                   |                 |                   |                 |                      |              |                      |              |
| No                                            |                   |                 |                   |                 |                      |              |                      |              |
| Age-diabetes interaction                      |                   |                 |                   |                 |                      |              |                      |              |
| Diabetic versus non-diabetic                  |                   |                 |                   |                 |                      |              |                      |              |
| 18–39                                         |                   |                 |                   |                 |                      |              |                      |              |
| 40–59                                         |                   |                 |                   |                 |                      |              |                      |              |
| 60–79                                         |                   |                 |                   |                 |                      |              |                      |              |
| ≥80                                           |                   |                 |                   |                 |                      |              |                      |              |

All variables in the table were mutually adjusted for each other. PRD, primary renal diagnosis. a Hazard ratios and CIs with fitted without the age-PRD interaction term.
### Table 4. Relative risk of death with COVID-19 for ICHD patients compared to the general population, by wave, age group, and region

| Wave            | England and Wales COVID-19 deaths per 10,000a | ICHD COVID-19 deaths per 10,000b | relative risk ICHD/E&W COVID-19 death rates | 95% CI       | Wave            | England and Wales COVID-19 deaths per 10,000a | ICHD COVID-19 deaths per 10,000b | relative risk ICHD/E&W COVID-19 death rates | 95% CI       |
|-----------------|---------------------------------------------|---------------------------------|---------------------------------------------|-------------|-----------------|---------------------------------------------|---------------------------------|---------------------------------------------|-------------|
| **Age group (years)** |                                             |                                 |                                             |             | **Age group (years)** |                                             |                                 |                                             |             |
| 20–39           | 0.20                                        | 48.38                           | 244.53                                      | 115.8–516   | 0.24                                        | 49.22                           | 203.93                                      | 91.2–456   |
| 40–59           | 2.05                                        | 111.93                          | 54.54                                       | 42.5–70     | 2.47                                        | 149.19                          | 60.47                                       | 47.8–76    |
| 60–79           | 15.00                                       | 274.92                          | 18.33                                       | 16.3–20.6   | 19.37                                       | 356.47                          | 18.40                                       | 16.5–20.6  |
| 80+             | 107.10                                      | 430.70                          | 4.02                                        | 3.5–4.7     | 130.24                                      | 352.18                          | 2.70                                        | 2.2–3.3    |
| **Region**      |                                             |                                 |                                             |             | **Region**                                  |                                             |                                 |                                             |             |
| North East      | 10.70                                       | 182.37                          | 17.04                                       | 10.8–27     | 12.01                                       | 192.31                          | 16.02                                       | 9.8–26.1   |
| North West      | 11.03                                       | 177.95                          | 16.13                                       | 11.7–22.3   | 12.88                                       | 142.66                          | 16.42                                       | 10.8–26.1  |
| Yorkshire and The Humber | 8.96                                 | 200.00                          | 22.33                                       | 16.4–30.4   | 11.32                                       | 240.67                          | 21.26                                       | 15.6–28.9  |
| East Midlands   | 8.33                                        | 155.09                          | 18.61                                       | 12.4–27.9   | 11.69                                       | 216.69                          | 18.53                                       | 12.7–26.9  |
| West Midlands   | 10.03                                       | 296.18                          | 29.52                                       | 23.6–36.9   | 11.76                                       | 238.66                          | 20.30                                       | 15.4–26.7  |
| East of England | 8.28                                        | 151.52                          | 18.30                                       | 12.5–26.8   | 11.78                                       | 340.83                          | 28.95                                       | 22–38      |
| London          | 9.61                                        | 391.13                          | 40.70                                       | 35.6–46.5   | 9.08                                        | 304.40                          | 33.53                                       | 28.2–39.8  |
| South East      | 8.15                                        | 222.33                          | 27.28                                       | 20.5–36.2   | 11.07                                       | 318.51                          | 28.78                                       | 22.3–37.1  |
| South West      | 5.23                                        | 78.93                           | 15.08                                       | 8.8–25.9    | 6.75                                        | 182.56                          | 27.04                                       | 18.6–39.3  |
| Wales           | 8.19                                        | 224.91                          | 27.46                                       | 18.7–40.2   | 13.67                                       | 204.92                          | 14.99                                       | 9.7–23.2   |

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*a* Number of deaths in England and Wales recorded on 1 March to 28 August 2020 (wave 1) or 29 August 2020 to 29 January 2021 (wave 2) with COVID-19 cited on the death certificate, divided by the England and Wales mid-2019 population estimate. *b* Number of deaths recorded for tests within 28 days of a positive COVID-19 test in wave 1 (March to August 2020) or wave 2 (September 2020 to January 2021) in the England and Wales ICHD 2019 prevalent cohort still on ICHD at the time of test, divided by the England and Wales ICHD 2019 prevalent cohort at risk at the start of the wave.
restrictive and allowed, albeit with social distancing rules and hygiene prevention in place, more opportunities for social interactions. Throughout, in response to the high number of ICHD patients with COVID-19 and with the intention of protecting this vulnerable group of patients, renal centres implemented over time a range of strategies to try to reduce the risk of COVID-19 transmission in dialysis units [11, 12, 22]. In line with international practices, the strategies used to reduce risk ranged from cohorting test-positive patients to dialysis slots followed by immediate subsequent cleaning of all facilities/equipment, implementation of the use of suitable personal protective equipment for staff and patients, as well as social distancing in all the phases of interaction with the patients that usually occur during the dialysis treatment. These range from using individual rather than shared transport of the patients to the dialysis units to seating arrangements in the waiting rooms upon arrival in the unit until the dialysis treatment can be started. Additionally, amongst the measures taken, many units have implemented systematic screening all patients regardless of the presence of symptoms. Whilst in the first wave, particularly the first 3 months, dialysis units were able to test only all symptomatic patients, from May 2020 onward some units were already starting to screen asymptomatic patients. A recent survey conducted across all the UK units found that more than 60% of the 57 respondent units carried out systematic testing of patients irrespective of symptoms [23].

In our study, we found that following the adoption of those measures R reduced and, despite the huge peak of COVID-19-positive patients in December 2020, remained lower during the second wave. Since there was COVID-19 screening testing for ICHD patients, regardless of symptom status, we anticipated that mortality would be lower as more patients without symptoms would be found. In reality, our analysis shows that the mortality risk of ICHD patients with COVID-19 remained essentially unchanged between the first and second waves.

To date, not many studies have compared the outcomes of dialysis patients during the pandemic and its different waves. However, a recent study in Germany found that amongst dialysis patients during spring 2020, there was a 1.4% prevalence of COVID-19 which declined during the summer. Despite the adoption of hygiene measures in dialysis centres in December 2020, COVID-19 prevalence had increased again to 1.9%. Also, like our study, mortality remained high and at 20% throughout the pandemic [24].

Unfortunately, our study does not include data on rates of patient admission to intensive care units and relative need for mechanical ventilation and other intensive treatments. However, public data from the Intensive Care National Audit and Intensive Centre (ICNARC) [25] allow us to see that, in the UK, the ICU admission rate for patients with renal disease remained essentially unchanged between different waves at approximately 1.7%. In our study, the risk of positivity for patients treated with ICHD was mainly influenced by socio-economic factors in both waves and improved slightly in wave 2. In contrast, risk of COVID-19-related mortality amongst ICHD patients in both waves was not associated with socio-economic deprivation but linked to conditions of greater basal frailty. In this study, both length of time on KRT and waiting list for transplantation were used as surrogate indicators of basal general health status [26–29]. We found that, in both waves, risk of mortality was lower amongst those waitlisted for transplantation and higher for those who had spent more than 5 years on KRT. Only in the second wave, we also found an interaction between diabetic status and age, which indicates an increased risk in younger patients with diabetes. However, these differences may also reflect selection of patients who did not catch the disease in the first wave. The time between infection and death was shorter in the first wave, especially during the first 3 months of the pandemic, probably because during that period testing was reserved for symptomatic patients only and therefore the disease was detected later.

Relative risk of mortality in ICHD patients with COVID-19 was higher compared to general population with COVID-19 in both waves; however, regional differences in mortality risk did not mirror the incidence of COVID-19 in the general population. Instead, the pattern suggests that mortality from COVID-19 in the second wave in ICHD patients was lower in settings where the general population had experienced more deaths during the first wave, whilst settings which had had a lower mortality from COVID-19 in the general population during the first wave had higher mortality from COVID-19 amongst ICHD patients in the second wave. Moreover, some regional variation in mortality may be due to renal centre-specific measures and policies being implemented differently across centres.

Additionally, during the first wave, the number of deaths amongst dialysis patient who died without having had a positive test for COVID-19 was much higher than in the second wave (1,059 in wave 1 vs. 60 in wave 2). Reasons for this are currently unclear, and future analyses may clarify whether this was the result of an increased
pressure on the healthcare system during the first wave with a lack of resources or also the result of a smaller testing capacity in the first wave with a larger number of untested COVID-19-related deaths.

Strengths and Limitations
To our knowledge, this is one of the first studies that, using a large database, compare the outcomes of patients on dialysis treatment between the first two waves of COVID-19. In our study, we could not use data on comorbidities; however, the included data on PRD, transplant waiting list status, and length of time on treatment were used as indicators of general baseline health status.

Numbers of positive cases used to calculate R were relatively low, and we could not use data for both general population and dialysis units’ staff; however, the R calculation in our study is useful to understand differences in transmission of the disease in dialysis units between the two waves and in response to policies adopted. Unfortunately, it was not possible to include incident patients in 2020; however, clinicodemographic characteristics of the wave 1 survivor cohort did not differ from those of the original cohort (online suppl. Table 2). This reassures that the exclusion of the new starters in 2020 was likely to have had a small effect on the results shown.

Conclusion
This study confirms that patients treated with ICHD represent a highly vulnerable group of patients whose risk of death from COVID-19 has remained unchanged between the first and second waves of the pandemic despite the extensive testing in the second wave. This supports that this group of patients should continue to be prioritized for vaccination against COVID-19.

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References
1 Li KK, Woo YM, Stirrup O, Hughes J, Ho A, Da Silva Filipe A, et al. Genetic epidemiology of SARS-CoV-2 transmission in renal dialysis units – a high risk community-hospital interface. J Infect. 2021 Apr;83(1):96–103.
2 Wee LE, Concejiao EP, Sim XYJ, Aung MK, Tan KY, Wong HM, et al. Minimizing intra-hospital transmission of COVID-19: the role of social distancing. J Hosp Infect. 2020 Jun;105(2):113–5.
3 Savino M, Casula A, Santhakumaran S, Pitcher D, Wong E, Magadi W, et al. Sociodemographic features and mortality of individuals on haemodialysis treatment who test positive for SARS-CoV-2: A UK Renal Registry data analysis. PLoS One. 2020 Oct;15(10):e0241263.
4 Mahon J, Oke J, Heneghan C. Declining death rate from COVID-19 in hospitals in England. The Centre for Evidence-Based Medicine; 2020. Available from: https://www.cebm.net/covid-19-declining-death-rate-from-covid-19-in-hospitals-in-england/ (accessed July 6, 2021).

5 Office for National Statistics (ONS); Sutherland E, Headicar J, Delong P. Coronavirus (COVID-19) infection survey technical article: waves and lags of COVID-19 in England. 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19infectionsurveytechnicalarticle/wavesandlagsofcovid19inenglandjune2021 (accessed July 8, 2021).

6 UK Government. Coronavirus (COVID-19) in the UK. 2021. Available from: https://coronavirus.data.gov.uk/ (accessed June 8, 2021).

7 RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 – preliminary report. N Engl J Med. 2021 Feb;384:693–704.

8 REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19. JAMA. 2020 Oct;324(13):1317–29.

9 ICNARC (Intensive Care National Audit and Research Centre). Reports. 2021. Available from: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports (accessed March 3, 2021).

10 Karagiannidis C, Windisch W, McAuley DF, Welte T, Busse R. Major differences in ICU admissions during the first and second COVID-19 wave in Germany. Lancet Respir Med. 2021 May;9(5):e47–8.

11 UK Kidney Association. COVID-19 UKKA resources. 2020. Available from: https://uk-kidney.org/health-professionals/covid-19/ukka-resources (accessed May 20, 2021).

12 National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: dialysis service delivery. NICE Guideline [NG160]; 2020. Available from: https://www.nice.org.uk/guidance/ng160 (accessed February 5, 2021).

13 UK Government. Coronavirus (COVID-19) in the UK. Available from: https://coronavirus.data.gov.uk/details/download (accessed May 25, 2021).

14 Ministry of Housing, Communities & Local Government. English indices of deprivation. 2019. Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019 (accessed January 27, 2021).

15 Office for National Statistics (ONS). Deaths registered weekly in England and Wales, provisional, 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/weeklyprovisionalfiguresondeathsregisteredinenglishandwales (accessed May 25, 2021).

16 Cori A, Ferguson NM, Fraser C, Cauchemez S. A new framework and software to estimate time-varying reproduction numbers during epidemics. Am J Epidemiol. 2013 Nov 1;178(9):1505–12.

17 Du Z, Xu X, Wu Y, Wang L, Cowling BJ, Meyers LA. Serial interval of COVID-19 among publicly reported confirmed cases. Emerg Infect Dis. 2020 Jun;26(6):1341–3.

18 Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. Int J Infect Dis. 2020 Apr;93:284–6.

19 Office for National Statistics (ONS). Population estimates. 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates (accessed May 25, 2021).

20 Institute for government. Timeline of UK government coronavirus lockdowns. 2021. Available from: https://www.instituteforgovernment.org.uk/charts/uk-government-coronavirus-lockdowns (accessed June 28, 2021).

21 Haug N, Geyrhofer L, Londei A, Dervic E, Desvars-Larrive A, Loreto V, et al. Ranking the effectiveness of worldwide COVID-19 government interventions. Nat Hum Behav. 2020 Dec;4:1303–12.

22 KQuIP COVID-19 Haemodialysis Patient Safety Working Group. Recommendations for minimising the risk of transmission of COVID-19 in adult haemodialysis units. 2021. Available from: https://www.thinkkidneys.nhs.uk/kquip/wp-content/uploads/sites/5/2020/07/Recommendations-for-minimising-risk-of-transmission-of-COVID-19-on-UK-haemodialysis-units-FINAL-V E R S I O N - W I T H - F L O W - CHARTS-300620.pdf (accessed March 8, 2021).

23 KQuIP COVID-19 Haemodialysis Patient Safety Working Group. Minimising the risk of transmission of COVID-19 in adult UK haemodialysis units – the KQuIP COVID-19 haemodialysis ensuring patient safety working group’s response to the pandemic. 2021. [publication in progress].

24 Hoxha E, Suling A, Turner JE, Haubitz M, Floege J, Huber TB, et al. Coronavirus-disease-2019-Pandemie aus nephrologischer Perspektive [Coronavirus disease 2019 pandemic from a nephrological perspective]. Internist. 2021 Jul;62(7):718–24.

25 Intensive Care National Audit and Research Centre. ICNARC case mix programme database. Available from: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports (accessed December 1, 2021).

26 Reese PP, Shults J, Bloom RD, Mussell A, Harhay MN, Abt P, et al. Functional status, time to transplantation, and survival benefit of kidney transplantation among wait-listed candidates. Am J Kidney Dis. 2015 Nov;66(5):837–45.

27 Tennankore KK, Gunaratnam L, Suri RS, Yoohana S, Walsh M, Tangri N, et al. Frailty and the kidney transplant wait list: protocol for a multicenter prospective study. Can J Kidney Health Dis. 2020 Sep.

28 Chertow GM, Johansen KL, Lew N, Lazarus JM, Lowrie EG. Vintage, nutritional status, and survival in hemodialysis patients. Kidney Int. 2000 Mar;57(3):1176–81.

29 Sumida K, Yamagata K, Iseki K, Tsubakihara Y. Different impact of hemodialysis vintage on cause-specific mortality in long-term hemodialysis patients. Nephrol Dial Transplant. 2016 Feb;31(2):298–305.