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[1]* MD, Shalini Santhakumaran[1] PhD, Christine S.M. Currie[2] PhD, Bhakti S.S. Onggo[2] PhD, Katharine M. Evans[1] PhD, James F. Medcalf[1,3,4] MSc MD, Dorothea Nitsch[1,5,6] MSc Dr.med, Retha Steenkamp[1] PhD.

[1] UK Renal Registry

[2] University of Southampton

[3] University of Leicester

[4] Leicester General Hospital

[5] London School of Hygiene and Tropical Medicine

[6] Royal Free London NHS Foundation Trust

*Corresponding author

E-mail: Manuela.Savino@gstt@nhs.uk

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ABSTRACT

Introduction

This retrospective cohort study compares in-centre haemodialysis (ICHD) patients' outcomes between the 1st and 2nd wave of the COVID-19 pandemic in England, Wales and Northern Ireland.

Methods

All people aged ≥18 years receiving ICHD at 31/12/2019, who were still alive and not in receipt of a kidney transplant at 1 March and who had a positive polymerase chain reaction (PCR) test for SARS-CoV-2 between 01/03/2020 and 31/01/2021 were included. The COVID-19 infections were split into two 'waves': wave1 from March to August 2020, and wave2 from September 2020 to January 2021.

Cumulative incidence of COVID-19, multivariable Cox models for risk of positivity, median and 95% credible interval of reproduction number in dialysis units were calculated separately for wave1 and wave2. Survival and hazard ratios for mortality were described with age and sex adjusted Kaplan Meier plots and multivariable Cox proportional models.

Results

4,408 ICHD patients had COVID-19 during the study period. Unadjusted survival at 28 days was similar in both waves [wave1 75.6% (95% CI 73.7-77.5), wave2 76.3% (95% CI 74.3-78.2)], but death occurred more rapidly after detected infection in wave1. Long vintage treatment and not being on the transplant waiting list were associated with higher mortality in both waves.

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 prioritised 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 organisation 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 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% 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-August 2020) and second (September 2020-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] and improved medical management to reduce admissions to intensive care [8,9,10], and finally, increased testing capacity and detection of cases among 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 31st December 2019 in England, Wales or Northern Ireland who were still alive and not in receipt of a kidney transplant at 1 March 2020.

COVID-19 infection data

Data on COVID-19 infections came from weekly returns from 1 March 2020 - 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 (PCR) test. The COVID-19 infections were split into two 'waves': wave1 from March to August 2020, and wave2 from September 2020 to January 2021. We chose to end wave2 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 re-infected (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 (IMD) [14] rank quintile from patient postcode, primary renal disease (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 the UK Office of National Statistics (ONS) on deaths where COVID-19 was mentioned on the death certificate [15].

Ethics

The UK Renal Registry (UKRR) collects patient data without consent under section 251 from the Health Research Authority's Confidentiality Advisory Group. The data were pseudonymised 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 wave1 and wave2, treating death and transplant as competing events. Multivariable Cox models were used to assess risk factors for positivity separately in wave1 and wave2, 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, primary renal diagnosis (diabetic/non-diabetic), whether the patient was on the kidney transplant waiting list by 31st 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 seven-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 population 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-standardised relative risk, with the mid-p method used to calculate the 95% confidence interval.

Analyses were conducted using SAS version 9.4,11 and 95% confidence intervals (95% CI) 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 (figure 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 (figure 2) but the wave1 peak was much higher than wave2 for ICHD patients. From the start of wave1, cumulative infections rose sharply before flattening off at around 8 weeks (supplementary figure 1). In contrast, during wave2 the rate of infections increased over the period. In addition to those infected in wave1, a further 1,059 patients died and 432 were successfully transplanted by 1 September 2020, leaving 17,984 at risk for the start of wave2. Fifty-nine patients (1.3%) had a second positive test more than 90 days after the first (see supplementary table 1 for characteristics). The median time between infections was 227 days (interquartile range 159 to 270 days).

Risk factors for COVID-19 infection

Patients infected in wave1 were older (median age 69 years, with 20% aged ≥80) compared to wave2 (median age 67 with 16% aged ≥80) (table 1). In wave1, the risk of infection increased consistently with age ($p<0.001$). People aged 18-39 had a 30% lower risk of infection (95% confidence interval (CI) 13% to 43%) compared to 60-79 year olds, and those aged over 80 had a 9% higher risk (95% CI -3% to 22%) (table 2). In wave2, the 40–59 year-olds were at the highest risk, and those aged over 80 had a 16% (95% CI 5% to 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 wave1, particularly for black people. In wave1, 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 to 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 to 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 wave1 (HR 1.49 (95% CI1.35 to 1.63) in wave1, 1.21 (95% CI 1.1 to 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 wave1 (HR 0.79 (95% CI 0.69 to 0.91)), but this was not the case for wave2 (HR 0.98 (95% CI 0.87 to 1.1)).

The median value of R peaked in mid-March 2020 at 2.94 (95% CrI 1.41 to 5.31), excluding the summer months when the number of cases was too low to accurately estimate R (figure 3). The highest median value in wave2 was 2.17 in early September 2020, but with high uncertainty due to the small number of cases among the study cohort (95% CrI 0.36 to 6.80).

28-day survival after COVID-19 infection

At 28 days after infection, unadjusted survival was similar in both waves (wave1 75.6% (95% CI 73.7 to 77.5), wave2 76.3% (95% CI 74.3 to 78.2), but death occurred more quickly in wave1 (figure 4). The median survival time was 7 days in wave1 and 10 days in wave2. The pattern was similar for age and sex adjusted survival (supplementary figure 2).

In wave1, 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) was not associated with mortality in wave 1. Patients on dialysis for more than 5 years had higher mortality risk (53% wave1, 50% wave2) 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 wave1, 0.50 wave2). In wave2 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 wave2 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-standardised relative risk of mortality among ICHD patients was 8.95 (95% CI 8.14-9.67) in wave1 and 8.43 (95% CI 7.71-9.20) in wave2. 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 to 4.7) than during the second wave (RR 2.70, 95% CI 2.2 to 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 (wave1 RR 29.5 (95% CI 23.6 to 36.9) vs wave2 RR 20.3 (95% CI 15.4 to 26.7)), London (wave1 RR 40.7 (95% CI 35.6 to 46.5) vs wave2 RR 33.5 (95% CI 28.2 to 39.8)) and Wales (wave1 RR 27.5 (95% CI 18.7 to 40.2) vs wave2 RR 15.0 (95% CI 9.7 to 23.2)). Other regions showed the opposite: the North West (wave1 RR 16.2 (95% CI 11.7 to 22.3) vs wave2 RR 32.0 (95% CI 25.6 to 40.1)), the East of England (wave1 RR 18.3 (95% CI 12.5 to 26.8) vs wave2 RR 29.0 (95% CI 22.0

to 38.0)) and the South West (wave1 RR 15.1 (95% CI 8.8 to 25.9) vs wave2 27.0 (95% CI 18.6 to 39.3)).

Discussion

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 wave1. 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 wave2.

The COVID-19 pandemic has led the UK through three national lockdowns, 1st lockdown between 26th March 2020 (week 4) to 23rd June 2020 (week 17), 2nd lockdown between 5th November 2020 (week 9) and 2nd December 2020 (week 13) and 3rd lockdown from 6th January 2021 (week 18) [20]. These national lockdowns were each characterised by different types of restrictive measures and therefore they had different effects on transmission of COVID-19 within the community [21]. While 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 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 (PPE) 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, among the measures taken, many units have implemented systematic screening all patients regardless of the presence of symptoms. While in the first wave, particularly the first 3 months, dialysis units were able to test only all symptomatic patients, from May 2020 onwards 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 wave.
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 among 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 wave2. In contrast risk of COVID-19 related mortality among ICHD patients in both waves was not associated with socioeconomic 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 [26,27,28,29]. We found that, in both waves, risk of mortality was lower among 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 among 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 among dialysis patient who died without having had a positive test for COVID-19 was much higher than in the second wave (1059 in wave1 vs 60 in wave2). Reasons for this are currently unclear, 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.

STRENGHTS AND LIMITATIONS

To our knowledge, this is one of the first studies that, using a large database, compares 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 wave1 survivor cohort did not differ from those of the original cohort (supplementary 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 wave of the pandemic despite the extensive testing in the second wave. This supports that this group of patients should continue to be prioritised for vaccination against COVID-19.

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Ethical statement
On behalf of the Renal Association, the UK Renal Registry (UKRR) collects patient data without consent under section 251 of the NHS Act (2006), granted by the Health Research Authority's Confidentiality Advisory Group (ref 16/CAG/0064). Data are always pseudonymised prior to being analysed. The UKRR database has approval for research studies from the North East Newcastle & North Tyneside 1 Research Ethics Committee (16/NE/0042).

Conflict of interest statement
The authors have no competing interests to declare.

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Authors' contributions

Dr Manuela Savino	Joint first author (conception of the work, data interpretation, writing draft of the manuscript, critical revision before submission, corresponding author)
Dr Shalini Santhakumaran	Joint first author (conception of the work, data analyses and interpretation, writing draft of the manuscript, critical revision before submission)
Prof. Christine Currie	Co-author (data analyses and interpretation, critical revision before submission)
Prof. Stephan Onggo	Co-author (data analyses and interpretation, critical revision before submission)
Dr Katharine Evans	Co-author (writing draft of the manuscript, data interpretation, critical revision before submission)
Prof. James Medcalf	Joint last author (supervision, critical revision before submission)
Prof. Dorothea Nitsch	Joint last author (supervision, critical revision before submission)
Dr. Retha Steenkamp	Joint last author (data analyses, curation and interpretation, supervision and critical revision before submission)

Data availability statement
The data underlying this article are available from the UKRR through the UKRR's data application process – see https://renal.org/audit-research/how-access-data/ukrr-data. For any data access queries, contact ukrr-research@renalregistry.nhs.uk.

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Figures Legend

Fig 1: Flowchart describing the study cohort

Fig 2 Weekly COVID-19 log infection counts in the study population and the UK general population

Fig 3. Incidence and R_0 calculation for all renal centres in England, Wales and Northern Ireland

Fig 4. 28 day crude survival for ICHD COVID-19 patients

Supplementary Fig 1. Cumulative incidence of COVID-19 in the study cohort comparing wave 1 and wave 2

Supplementary Fig 2. 28 day age, sex adjusted survival for ICHD COVID-19 patients