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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

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Keywords
COVID-19 · Dialysis · End-stage kidney disease · Haemodialysis · Wave 1 and wave 2

Abstract
Introduction: This retrospective cohort study compares in-centre haemodialysis (ICHD) patients' outcomes between the 1st and 2nd waves of the COVID-19 pandemic in England, Wales, and Northern Ireland. ***Methods:*** All people aged ≥18 years receiving ICHD at 31 December 2019, who were still alive and not in receipt of a kidney transplant at 1 March and who had a positive polymerase chain reaction test for SARS-CoV-2 between 1 March 2020 and 31 January 2021, were included. 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. 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 wave 1 and wave 2. 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 (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. ***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

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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 at 1 March 2020.

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-

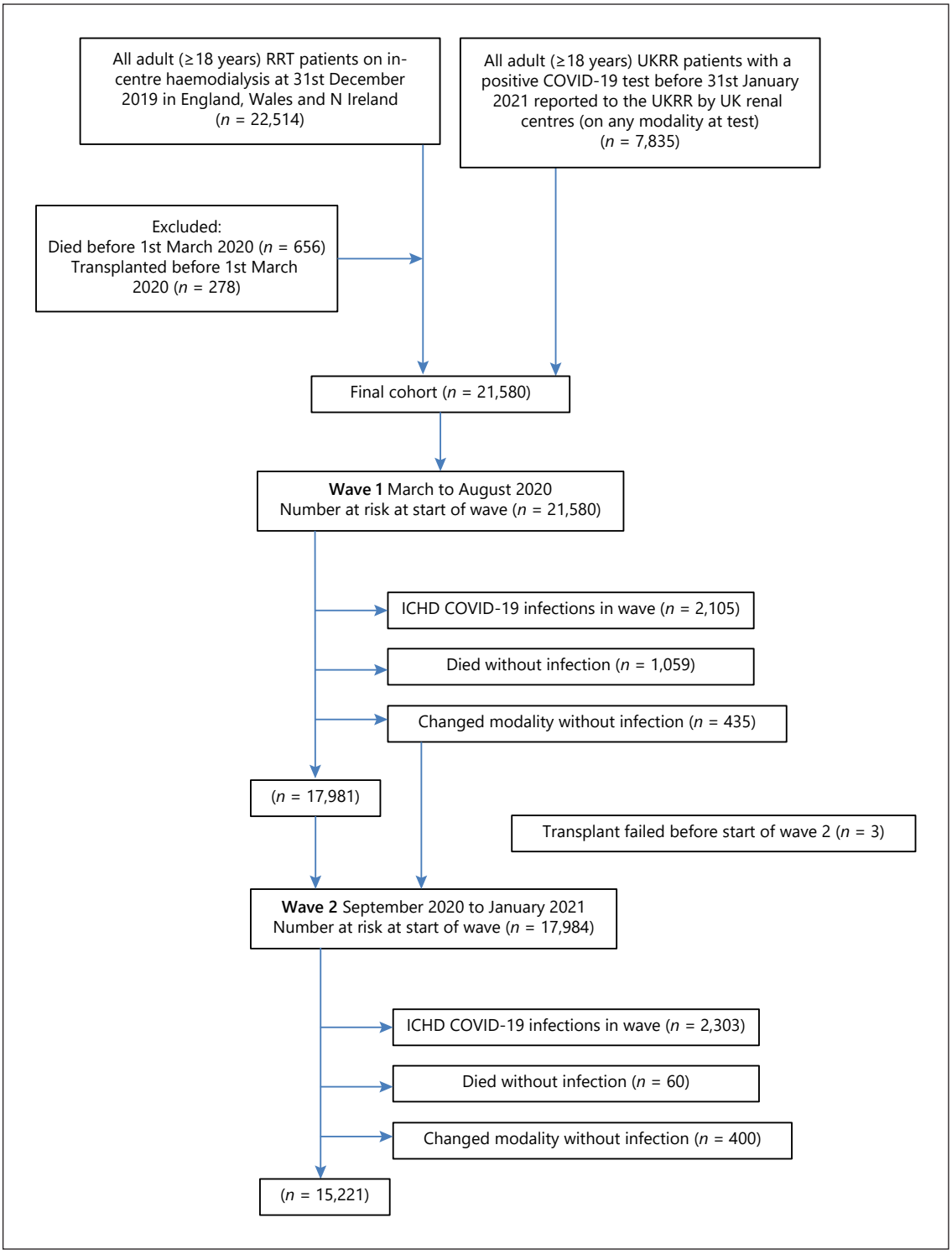

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Fig. 1. Flow chart describing the study cohort.

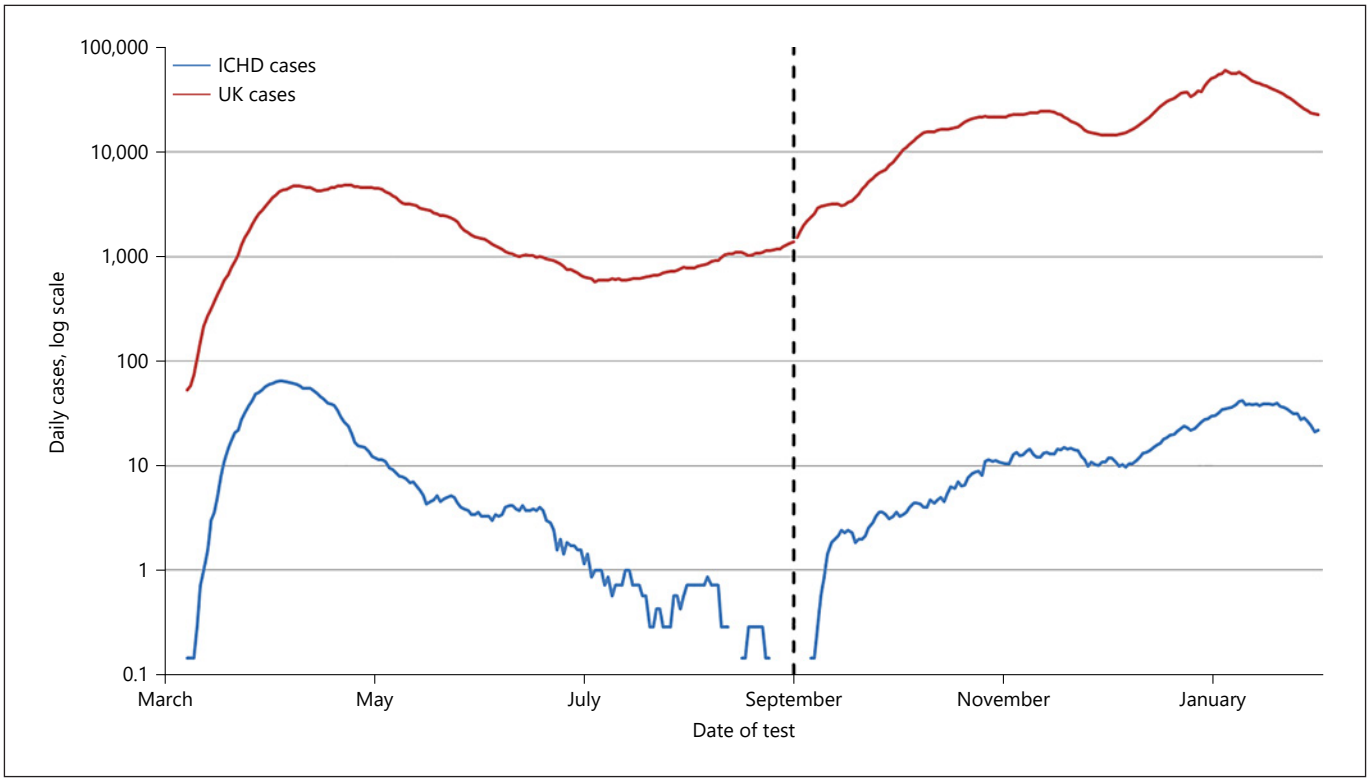

Fig. 2. Weekly COVID-19 log infection counts in the study population and the UK general population.

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). In

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)[a]	ICHD adults with COVID-19[b] in wave 1[c] (n = 2,105)[d]	ICHD adults with COVID-19[b] in wave 2[c] (n = 2,303)[d]
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

ICHD, in-centre haemodialysis; PRD, primary renal diagnosis. [a] Percentages exclude missing data: there were 3% of patients with missing ethnicity, 3% with missing PRD, and <1% with missing deprivation. [b] For UK renal centres that submitted patients with COVID-19 to the UKRR. [c] Wave 1: 1 March to 31 August 2020; wave 2: 1 September 2020 to 31 January 2021. [d] Percentages exclude missing data: wave 1 – there were 3% with missing ethnicity and 3% with missing PRD; wave 2: 4% with missing ethnicity and 3% with missing PRD.

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).

Twenty-Eight-Day 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

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		
Age	18–39	0.7	0.57	0.87	0.92	0.77	1.1
	40–59	0.86	0.77	0.96	1.04	0.94	1.15
	60–79	1			1		
	80+	1.09	0.97	1.22	0.84	0.74	0.95
Sex	Male	1			1		
	Female	0.97	0.88	1.06	0.96	0.88	1.04
Ethnicity	White	1			1		
	Asian	1.98	1.77	2.21	1.91	1.72	2.12
	Black	2.12	1.87	2.39	1.35	1.18	1.53
	Other	1.78	1.45	2.19	1.4	1.13	1.72
Area-level deprivation quintile	1 – least deprived	1			1		
	2	1.06	0.88	1.27	1.02	0.86	1.22
	3	1.21	1.02	1.44	0.98	0.83	1.15
	4	1.21	1.02	1.43	1.15	0.99	1.34
	5 – most deprived	1.12	0.95	1.32	1.19	1.02	1.38
Diabetes as PRD	Non-diabetic	1			1		
	Diabetic	1.49	1.35	1.63	1.21	1.1	1.32
Waitlisted for transplant at 31 Dec 2019	No	1			1		
	Yes	0.79	0.69	0.91	0.98	0.87	1.1
Year of dialysis start	≤2015	1.09	0.96	1.23	1.03	0.91	1.15
	2016–2018	1.05	0.93	1.19	1.01	0.9	1.14
	2019	1			1		

729 patients (3%, the same for those with and without infection) were excluded due to missing data. PRD, primary renal disease.

≥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:

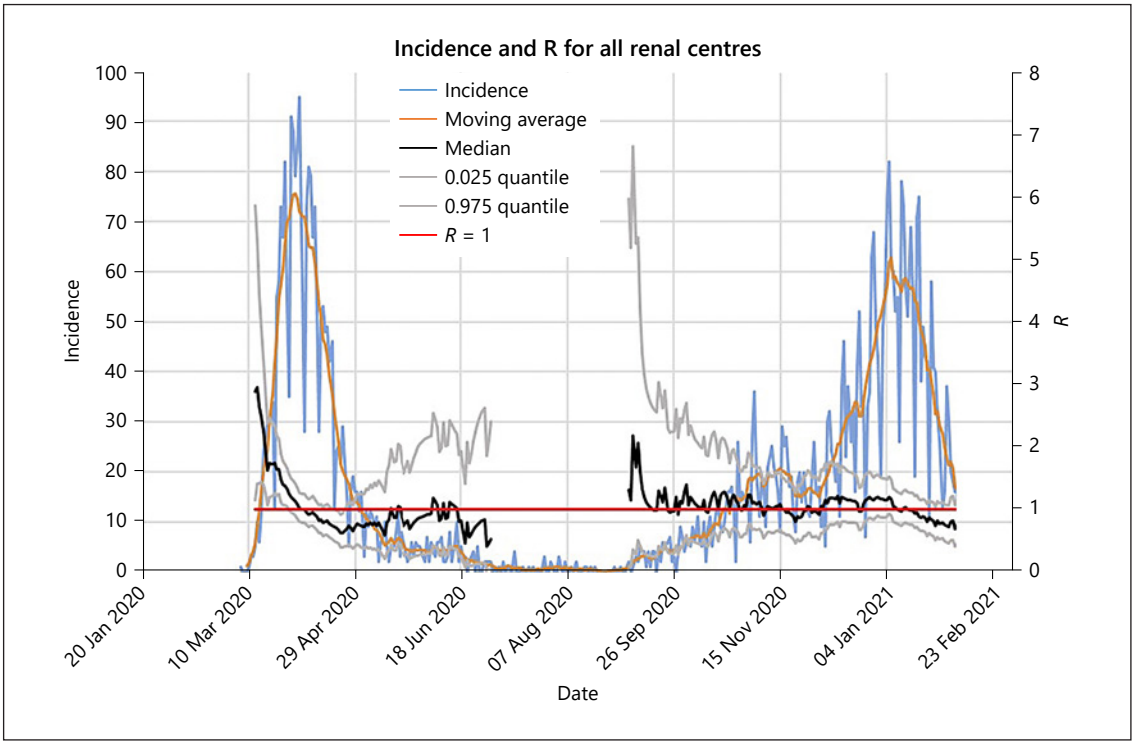

Fig. 3. Incidence and R_0 calculation for all renal centres in England, Wales, and Northern Ireland.

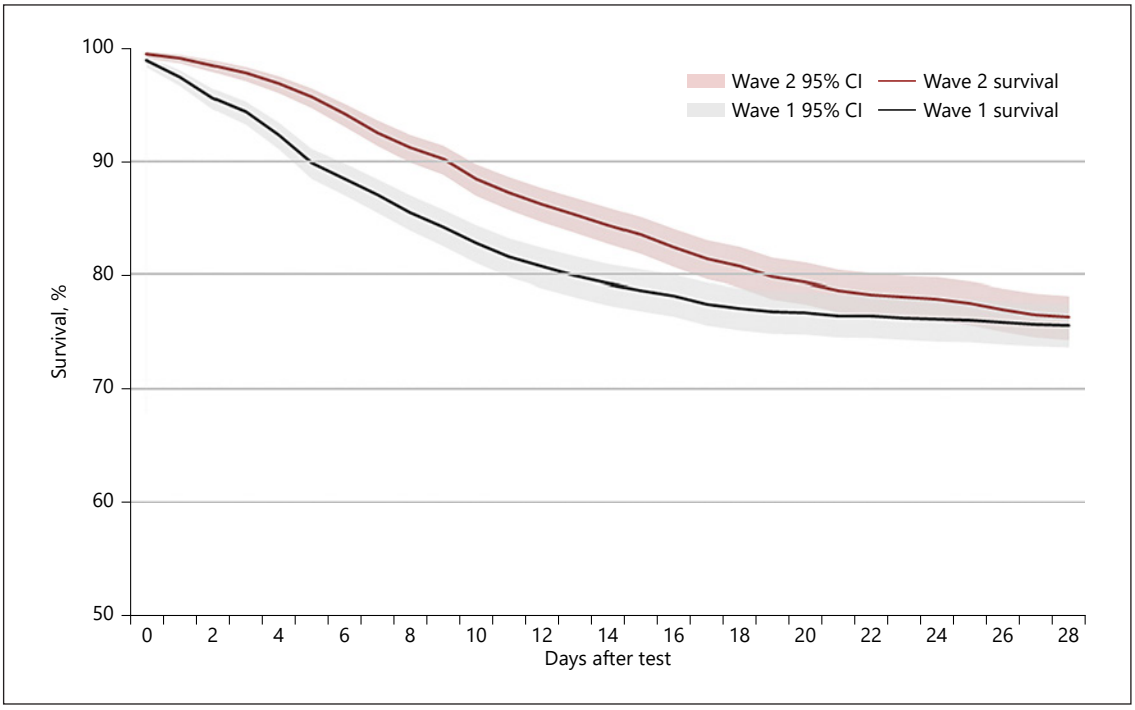

Fig. 4. Twenty-eight-day crude survival for ICHD COVID-19 patients.

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 1[a]	95% CI wave 1	Hazard ratio wave 2[a]	95% CI wave 2
Age group (years)								
18–39	95	6	131	4	1			
40–59	479	60	589	60	1.93	0.83–4.46		
60–79	1,011	258	1,080	275	3.65	1.62–8.23		
≥80	394	158	350	111	5.87	2.58–13.33		
Sex								
Female	750	168	818	147	1		1	
Male	1,229	314	1,332	303	1.21	1.00–1.46	1.22	1.00–1.48
Ethnicity								
White	1,067	266	1,286	307	1		1	
Asian	466	130	487	98	1.24	1.00–1.54	0.84	0.66–1.06
Black	350	66	284	33	0.88	0.67–1.16	0.56	0.39–0.80
Other	96	20	93	12	1.03	0.65–1.62	0.65	0.37–1.16
PRD								
Non-diabetic	1,210	287	1,450	279	0.86	0.71–1.04		
Diabetic	769	195	700	171	1			
Vintage								
≤2015	875	247	936	200	1.53	1.16–2.00	1.50	1.13–1.98
2016–2018	767	168	827	183	1.14	0.86–1.52	1.31	0.99–1.74
2019	337	67	387	67	1		1	
Waitlisted for kidney transplant at 31 Dec 2019								
Yes	274	25	354	29	0.44	0.29–0.67	0.50	0.34–0.73
No	1,705	457	1,796	421	1		1	
Age-diabetes interaction								
Diabetic versus non-diabetic								
18–39							2.55	0.26–24.54
40–59							3.43	2.03–5.79
60–79							1.07	0.84–1.37
≥80							1.17	0.74–1.85

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.

11.7–22.3] vs. wave 2 RR 32.0 [95% CI: 25.6–40.1]), the East of England (wave 1 RR 18.3 [95% CI: 12.5–26.8] vs. wave 2 RR 29.0 [95% CI: 22.0–38.0]), and the South West (wave 1 RR 15.1 [95% CI: 8.8–25.9] vs. wave 2 27.0 [95% CI: 18.6–39.3]).

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 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-

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Table 4. Relative risk of death with COVID-19 for ICHD patients compared to the general population, by wave, age group, and region

	Wave 1				Wave 2			
	England and Wales COVID-19 deaths per 10,000[a]	ICHD COVID-19 deaths per 10,000[b]	relative risk		England and Wales COVID-19 deaths per 10,000[a]	ICHD COVID-19 deaths per 10,000[b]	relative risk	
			ICHD/E&W COVID-19 death rates	95% CI			ICHD/E&W COVID-19 death rates	95% CI
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								
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	412.66	32.03	25.6–40.1
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

[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.

strictive 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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Statement of Ethics

On behalf of the Renal Association, the 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 pseudonymized 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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Author Contributions

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