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ORIGINAL ARTICLE

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Hospital admissions for severe infections in people with chronic kidney disease in relation to renal disease severity and diabetes status

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Summary

Background: Immunosuppressive agents are being investigated for the treatment of chronic kidney disease (CKD) but may increase risk of infection. This was a retrospective observational study intended to evaluate the risk of hospitalized infection in patients with CKD, by estimated glomerular filtration rate (eGFR) and proteinuria status, aiming to identify the most appropriate disease stage for immunosuppressive intervention.

Methods: Routine UK primary-care and linked secondary-care data were extracted from the Clinical Practice Research Datalink. Patients with a record of CKD were identified and grouped into type 2, type 1 and nondiabetes cohorts. Time-dependent, Cox proportional hazard models were used to determine the likelihood of hospitalized infection.

Results: We identified 97 839 patients with a record of CKD, of these 11 719 (12%) had type 2 diabetes**.** In these latter patients, the adjusted hazard ratios (aHR) were 1.00 (95% CI: 0.80-1.25), 1.00, 1.03 (95% CI: 0.92-1.15), 1.36 (95% CI: 0.20-1.54), 1.82 (95% CI: 1.54-2.15) and 2.41 (95% CI: 1.60-3.63) at eGFR stages G1, G2 (reference), G3a, G3b, G4 and G5, respectively; and 1.00, 1.45 (95% CI: 1.29-1.63) and 1.91 (95% CI: 1.67-2.20) at proteinuria stages A1 (reference), A2 and A3, respectively. All aHRs (except G1 and G3a) were significant, with similar patterns observed within the non-DM and overall cohorts.

Conclusions: eGFR and degree of albuminuria were independent markers of hospitalized infection in both patients with and without diabetes. The same patterns of hazard ratios of eGFR and proteinuria were seen in CKD patients regardless of diabetes status, with the risk of each outcome increasing with a decreasing eGFR and increasing proteinuria. Infection risk increased significantly from eGFR stage G3b and proteinuria stage A2 in type 2 diabetes. Treating type 2 DM patients with CKD at eGFR stages G1-G3a with immunosuppressive therapy may therefore provide a favourable risk-benefit ratio (G1-G3a in type 2 diabetes; G1-G2 in nondiabetes and overall cohorts) although the degree of proteinuria needs to be considered.

KEYWORDS
albuminuria, chronic kidney disease, eGFR, infection

1 | INTRODUCTION

Diabetic nephropathy is the leading cause of chronic kidney disease (CKD) in all developed and most developing countries.[1] Gradual destruction of the kidney glomeruli in patients with type 1 and type 2 diabetes causes declining renal function, manifesting as decreased glomerular filtration rate (GFR), proteinuria[2] and hypertension.[3]

At present, relevant renal treatments focus on inhibiting the progression of nephropathy by maintaining good metabolic and hemodynamic control. Glycemic control is an important factor in reducing the microvascular complications that lead to nephropathy: the UK Prospective Diabetes Study (UKPDS) showed that diabetic patients receiving glucose-lowering treatment who achieved good glycemic control were less likely to progress to end-stage renal disease (ESRD).[4] Antihypertensives such as angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) also play a role in slowing the progression of kidney disease by inhibiting the renin-angiotensin-aldosterone system. The ADVANCE trial reported reduced onset of microalbuminuria and no progression to nephropathy from existing microalbuminuria in patients with type 2 diabetes treated with the ACE inhibitor perindopril combined with indapamide,[5] while a trial conducted by Brenner et al[6] found that the risk of ESRD was reduced by 28% in patients with type 2 diabetes receiving the ARB losartan.

However, there is emerging evidence that inflammatory processes and immune activation play an important role in the progression of diabetic nephropathy.[7,8] Therefore, new therapeutic strategies for slowing or reversing the decline in kidney function and progression to ESRD have been proposed that would target the immune system itself in order to minimize inflammation.[9-12] Such an approach may, however, bring with it an increased risk of infection, which is a recognized complication of kidney disease[13,14] and, separately, of diabetes.[15] Therefore, a careful evaluation of the risk-benefit profile of using such therapies in patients with diabetic nephropathy is warranted.

Currently, there are limited data available describing the true incidence of infections in the diabetic nephropathy population specifically, and how this varies by CKD stage and the degree of proteinuria. McDonald et al[16] demonstrated an association between decreased renal function and community-acquired lower respiratory tract infection, pneumonia and sepsis in patients with diabetes and CKD, identifying proteinuria as an independent risk marker. However, this study was limited in that it excluded subjects younger than 65 years.

Here, our objectives were to characterize the risk of severe infection in adult patients with CKD in type 2 diabetes, with similar data for those with nondiabetes and type 1 diabetes for completeness, in order to determine how severe infections varied by eGFR stage and severity of proteinuria. Furthermore, we aimed to identify where infection risk was lowest, in order to identify the most appropriate stage in which to intervene with immunosuppressants.

2 | METHODS

2.1 | Study design and data sources

Data for this retrospective cohort study were from the UK Clinical Practice Research Datalink (CPRD),[17] a governmental research service that provides anonymized electronic health records gathered directly from primary-care practices throughout the UK.

The CPRD collects data from nearly 700 primary-care practices, representing 7% of practices in the UK National Health Service (NHS). Over 98% of the UK population is registered with an NHS primary-care practice; care is free of charge. The primary-care practitioner (general practitioner [GP]) acts as a gateway to care and is the first point of contact for nonemergency health concerns, referring the patient to secondary care as necessary.

At July 2015, CPRD contained data from more than 13 million research-quality patients. Recorded data include demographics, clinical symptoms and diagnoses, tests ordered in primary care, assessments (such as blood pressure, body mass index), prescriptions and referrals to secondary care. For approximately 50% of patients in CPRD, linked secondary-care data are available from the Hospital Episode Statistics (HES),[18] including inpatient diagnoses and procedures. These linked patients have been found to be representative of the entire CPRD data set, which is, in turn, considered representative of the UK population as a whole in terms of age and sex.[17,19] Diagnoses in CPRD primary-care and HES data are encoded using the Read (Clinical Terms) and ICD-10 dictionaries, respectively.

Approval for this study was granted by the CPRD Independent Scientific Advisory Committee, reference number 017_191R.

2.2 | Study population

Patients were included if their patient-level information and practice-recording systems were classed as being of acceptable research quality by CPRD. Patients were also required to be eligible to have their records linked to the HES data set. The observation period began in 1997 and ended in 2014. The following patient selection criteria were also applied:

- At least one recorded diagnosis of CKD
- Two or more positive (<90 mL/min/1.73 m^2) estimated glomerular filtration rates (eGFR) 91-730 days apart
- Registration at the practice for 365 days or more at index date (defined as the earlier of the patient's first positive eGFR or proteinuria test). Positive proteinuria tests that were on the same day or had the same consultation identifier as a record of urinary tract infection were excluded.

- Aged 40 years or older at index date (25 years or older for patients with type 1 diabetes)
- No prior dialysis, kidney transplant, or cancer at index date.

Patients were grouped in the following cohorts: type 1 diabetes (T1DM), type 2 diabetes (T2DM) or no diabetes (non-DM) based on their history prior to index date.

The selection criteria were modelled from a previous study conducted by Schneider et al.[20]

Members of the type 1 diabetes (T1DM) cohort were further required to be aged 25 years or older at index date and to have at least one prescription for insulin with no other glucose-lowering agent, no record of type 2 diabetes, a diabetes presentation date on or before their index date and at least one of the following:

- At least one diagnosis of type 1 diabetes using a diagnostic code other than a Read code for "insulin-dependent diabetes mellitus" (a term that may be misapplied to patients with type 2 diabetes receiving insulin therapy)
- At least one diagnosis of type 1 diabetes and aged 30 years or younger at diabetes presentation (earlier of first insulin or first diagnosis)

Members of the type 2 diabetes (T2DM) cohort were required to be aged 40 years or older at index date and to have a diagnostic record of T2DM or at least one prescription for a glucose-lowering therapy other than insulin, no record of secondary diabetes and a diabetes presentation on or before their index date. Patients identified by metformin prescription alone were excluded if they had a diagnosis of polycystic ovarian syndrome.

- At least one diagnosis of type 1 diabetes, aged 31-39 at diabetes presentation and a body mass index (BMI) at presentation ≤25 kg/m^2.

Members of the nondiabetes (non-DM) cohort were required to be aged 40 years or older at index date, to have no record of diabetes or glucose-lowering therapy in the data source and to have no more than one record of glycosylated haemoglobin (HbA1c) ≥6.5% (47.5 mmol/mol).

For all cohort members, the end of data follow-up was calculated as the earliest of: the patient's death or transfer-out date, their practice's last data-collection date, the patient's individual HES linkage date and the end of the linkage scheme (31 March 2014); censoring occurred at first dialysis, kidney transplant, cancer or death for those who underwent renal replacement therapy or died during the study period.

2.3 | Study end-points

For all cohorts, the study end-points were:

- Event rates for all admissions to hospital with a primary diagnosis of infection
- Time to first admission for infection, stratified by eGFR and proteinuria category
- Adjusted risk of first admission for infection by eGFR category and proteinuria level

Glomerular filtration rate values were estimated from serum creatinine test results by means of the CKD Epidemiology Collaboration (CKD-EPI) equation,[21] incorporating its adjustment for black ethnicity where this could be identified from CPRD or HES data.

Tests for microalbuminuria and proteinuria (collectively termed proteinuria hereafter) are recorded in the CPRD primary-care data in five different test "entities," 3 of which: albumin-creatinine ratio, urine microalbumin and urine biochemistry record both quantitative and qualitative results, while another two: urinalysis—protein and urine dipstick for protein contain qualitative results only. Test data are accompanied by Read codes, which may provide more information about the nature of the test or of its result, and data qualifiers (such as "normal," "negative," "+++").

To address the challenge of identifying specific measures of proteinuria with appropriate units of measurement from the three quantitative entities, we extended the approach of Liang et al[22] by classifying each test entity, unit of measurement and accompanying Read code as specific, nonspecific, or conflicting with respect to each of these measures in turn: albumin-creatinine ratio, protein-creatinine ratio, albumin excretion rate, protein excretion rate, spot albumin and spot protein. Records were selected if at least one dimension was specific for a measure, with no conflicting dimension. Exceptions to this rule were: (a) where the Read code dimension was conflicting but the unit was specific; and (b) for spot albumin, where the entity was conflicting (albumin-creatinine ratio) but the unit of measurement was specific.

Qualitative results were identified from the qualitative test entities and also from quantitative records that did not meet any of the rules listed above or had no numeric result entered. In addition, clinical records from CPRD and HES were included as qualitative results if their respective Read or ICD-10 codes indicated negative or positive proteinuria.

Eight categories of infection plus all-cause infection were considered, as selected and defined by Dalrymple et al[14]: genitourinary, gastrointestinal, pulmonary, skin and soft tissue, sepsis, bone and joint, endocarditis, and bacteremia. Hospitalizations for each infection category were identified from the linked HES data by appropriate ICD-10 code, where that infection was listed as the main reason (primary diagnosis) for the admission.

The eGFR and proteinuria data were derived from CPRD and HES records. In accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines,[23] the severity of CKD was graded into six categories, from G1: normal or high to G5: kidney failure, based on the patient's eGFR measurements (Table S1). Classification of proteinuria severity was also based on a KDIGO classification, from A1: normal to mildly increased to A3:

severely increased, with a fourth category, A23, added to encompass qualitative results from which the extent of abnormality could not be determined (Table S2).[20]

Patients' baseline values for BMI, weight, height, systolic and diastolic blood pressure, creatinine and—for the diabetes cohorts—HbA1c were identified from the nearest record to index date, provided this was no more than 365 days before or 30 days after index date and searching in the following order: −30 days, +30 days, −365 days. Baseline smoking and alcohol status were identified from the nearest record prior to index date; if no such status was recorded, the nearest status following index date was used.

2.4 | Statistical methods

Baseline characteristics for each of the three cohorts: T2DM, non-DM and T1DM were summarized. Event rates for all admissions to hospital with a primary diagnosis of infection were calculated per 1000 patient years' (pkpy) follow-up.

For each cohort, Kaplan-Meier curves for time to first hospitalization for infection of any type were stratified by the patient's baseline eGFR and proteinuria category at or nearest to infection admission. Cox proportional hazard models were used to estimate adjusted hazard ratios (aHR) for time to first admission, adjusting for eGFR category (reference G2, "mildly decreased") and proteinuria level (reference A1, "normal to mildly increased") in quarterly updated time-dependent models. Where appropriate, the models were adjusted for age, gender, baseline body mass index (BMI), baseline blood pressure, glycosylated haemoglobin (HbA1c), smoking status, diabetes cohort, index year and prior comorbidities (coronary heart disease [CHD], congestive heart failure [CHF], hypertension cerebrovascular disease, dementia, other neurological disorders, chronic obstructive pulmonary disease [COPD], chronic liver disease and any antihypertensives [ACE/ARB] in the year prior). The eGFR level G2 was chosen as the referent because there were small numbers of patients with an eGFR of G1 ("normal or high") at index date. These analyses were carried out using the R statistical computing environment,[24] using the Therneau and Patricia survival package.[25]

3 | RESULTS

3.1 | Baseline characteristics

A total of 97 839 patients with CKD fulfilled the selection criteria, comprising 85 934 patients in the non-DM cohort, 11 719 in the T2DM cohort and 186 in the T1DM cohort. Baseline characteristics for the three cohorts are detailed in Table 1. Mean age was highest in the non-DM cohort (69.7 years, SD = 11.2), followed by the T2DM cohort (67.0 years, SD = 10.2) and the T1DM cohort (47.9 years, SD = 13.7, $P < 0.001$). There were slightly more males than females in the T2DM and T1DM cohorts: 53.5% and 57.0%, respectively; the non-DM cohort had more females: 59.3%. As expected, the duration of diabetes was higher in the T1DM cohort than in the T2DM cohort: 20.64 years vs 3.23 years, respectively ($P < 0.001$).

Of the 97 839 study patients, 99.1% were identified by (and had their index date set by) their first positive eGFR test. Most patients identified by eGFR had a baseline value of G2 (50.0% in non-DM, 60.1% in T2DM and 54.3% in T1DM, $P < 0.001$).

3.2 | Crude hospitalization rates for infection

Rates of hospital admission for infection were higher in the T2DM cohort, at 33.3 admissions per 1000 patient years (pkpy), than in the non-DM cohort (24.9 admissions pkpy) and T1DM cohort (24.0 pkpy, $P < 0.001$, Table 2). Examining admissions by infection type, hospitalization rates in the T2DM cohort were higher than in the non-DM cohort for genitourinary infection (10.5 vs 7.3 pkpy, $P < 0.001$, respectively), pulmonary infection (7.8 vs 6.6 pkpy, $P < 0.001$,), skin and soft tissue infection (5.9 vs 2.9 pkpy, $P < 0.001$,), sepsis (1.5 vs 0.9 pkpy, $P < 0.001$,) and bone and joint infection (1.2 vs 0.2 pkpy, $P < 0.001$,). Patients with T1DM had a higher rate of skin and soft tissue infection (11.6 pkpy) than did patients in the T2DM (5.9 pkpy) and non-DM cohorts (2.9 pkpy, $P < 0.001$ Table 2).

3.3 | Unadjusted risk of progression to hospital admission

The T1DM cohort comprised only 186 patients and therefore its Kaplan-Meier graphs are difficult to interpret (Figure 1A,E).

Examining the T2DM cohort by eGFR category, median time to infection could only be calculated for the categories G3a, G3b and G5 (Figure 1B); these were 16.8 years in G3a, 15.0 years in G3b and 6.5 years in G5, respectively. Patients with a proteinuria level of A2 had a median time to infection of 16.7 years (Figure 1F).

In the non-DM cohort, median time to infection was 15.0 years in the G4 category and 10.9 years in the G5 category (Figure 1C). Examining non-DM patients by proteinuria category (Figure 1G), there was a clear distinction between proteinuria levels after 5 years.

The Kaplan-Meier graphs for all patients combined (Figure 1D,H) are almost identical to the non-DM plots because 87.8% of the combined cohort patients had no diabetes.

3.4 | Adjusted risk of progression to hospital admission

Adjusting for age, gender, baseline BMI, baseline blood pressure, HbA1c, smoking status, diabetes cohort, index year and prior comorbidities and examining all CKD patients together, we found no difference in infection rates between patients in eGFR categories G1 and the referent category G2 (aHR = 1.03, 95% CI: 0.90-1.17). However, in the G3a category the aHR was 1.18 (1.13-1.23), in G3b,

TABLE 1 Baseline characteristics for the type 1 diabetes (T1DM), type 2 diabetes (T2DM) and nondiabetes (non-DM) cohorts

	Non-DM	T2DM	T1DM	Overall	*P*-value
N	85 934	11 719	186	97 839	
Age, mean (SD), y	69.67 (11.2)	66.98 (10.2)	47.85 (13.7)	69.3 (11.2)	<0.001
Male, n (%)	35 006 (40.7)	6271 (53.5)	106 (57.0)	41 383 (42.3)	<0.001
Duration of diagnosed diabetes, median (IQR), y	—	3.23 (0.8-8.6)	20.64 (14.1-30.7)	3.3 (0.8-9.0)	<0.001
Duration of diagnosed renal disease, median (IQR), y	4.25 (2.2-6.6)	4.72 (2.7-7.0)	2.95 (0-5.6)	4.3 (2.2-6.6)	<0.001
BMI, mean (SD), kg/m^2	27.48 (5.0)	30.04 (5.9)	25.88 (3.8)	28.1 (5.4)	<0.001
Systolic BP, mean (SD), mm Hg	148.27 (21.4)	146 (20.0)	138.95 (21.7)	147.9 (21.3)	<0.001
Diastolic BP, mean (SD), mm Hg	83.16 (11.6)	80.97 (10.8)	78.25 (11.8)	82.9 (11.6)	<0.001
Smoking status, n (%)					
Never	48 261 (56.2)	6104 (52.1)	97 (52.2)	54 462 (55.7)	<0.001
Ex-smoker	23 211 (27.0)	3561 (30.4)	38 (20.4)	26 810 (27.4)	
Current	13 782 (16.0)	2016 (17.2)	50 (26.9)	15 848 (16.2)	
Missing	680 (0.8)	38 (0.3)	1 (0.5)	719 (0.7)	
Alcohol status, n (%)					
Never	16 426 (19.1)	2904 (24.8)	27 (14.5)	19 357 (19.8)	<0.001
Ex-drinker	1619 (1.9)	353 (3.0)	6 (3.2)	1978 (2.0)	
Current	62 316 (72.5)	7966 (68.0)	141 (75.8)	70 423 (72.0)	
Missing	5573 (6.5)	496 (4.2)	12 (6.5)	6081 (6.2)	
HbA1c, median (IQR), %	5.7 (5.3-6.0)	7.5 (6.6-9.0)	9.0 (7.9-10.5)	7.38 (6.4-8.8)	<0.001
HbA1c, median (IQR), mmol/L	38.8 (34.4-42.0)	58.5 (48.6-74.9)	74.9 (62.3-90.7)	57.19 (46.5-72.7)	<0.001
Serum creatinine, mean (SD), µmol/L	105.0 (32.1)	101.1 (30.0)	117.5 (59.2)	104.55 (32.0)	<0.001
GP contacts in prior year, median (IQR)	5 (3-9)	8 (4-14)	7 (3-12)	5 (3-10)	<0.001
Index date = 1st positive eGFR, n (%)	85 727 (99.8)	11 036 (94.2)	151 (81.2)	96 914 (99.1)	<0.001
eGFR category at index date, n (%)					
G1	—	—	—	—	<0.001
G2	42 889 (50.0)	7043 (60.1)	101 (54.3)	50 033 (51.1)	
G3a	30 359 (35.4)	2725 (23.3)	19 (10.2)	33 103 (33.8)	
G3b	10 034 (11.7)	972 (8.3)	15 (8.1)	11 021 (11.3)	
G4	2169 (2.5)	276 (2.4)	14 (7.5)	2459 (2.5)	
G5	276 (0.3)	20 (0.2)	2 (1.1)	298 (0.3)	
Index date = 1st positive proteinuria, n (%)	253 (0.3)	844 (7.2)	38 (20.4)	1135 (1.2)	<0.001
Proteinuria status at index date, n (%)					
A1	—	—	—	—	<0.001
A2	63 (0.1)	505 (4.3)	15 (8.0)	583 (0.6)	
A23	61 (0.1)	145 (1.2)	7 (3.8)	213 (0.2)	
A3	129 (0.2)	194 (1.7)	16 (8.6)	339 (0.4)	

1.57 (1.49-1.65), in G4, 2.28 (2.12-2.44) and in G5, 3.74 (3.16-4.42). Risks of infection were higher in proteinuria levels A2 (aHR = 1.35, 1.26-1.44), A23 (aHR = 1.28, 1.13-1.44) and A3 (aHR = 1.74, 1.58-1.91) than in A1.

When compared with the non-DM cohort, those in the T1DM cohort had the highest risk of infection (aHR = 2.84, 1.88-4.30), followed by T2DM (aHR = 2.33, 2.11-2.57). There was no difference in infection rates between gender (Table S3).

TABLE 2 Rates of hospital admission with infection as the primary diagnosis

	Non-DM		T1DM		T2DM		
	N	Crude event rate, pkpy	N	Crude event rate, pkpy	N	Crude event rate, pkpy	*P*-value
Patients	85 934	–	186	–	11 719	–	
Patient years	646 908	–	1459	–	95 935	–	
Hospital admissions							
Any listed infection	16 101	24.9	35	24.0	3198	33.3	<0.001
Genitourinary	4707	7.3	7	4.8	1011	10.5	<0.001
Gastrointestinal	4440	6.9	3	2.1	604	6.3	<0.001
Pulmonary	4251	6.6	4	2.7	746	7.8	<0.001
Skin and soft tissue	1902	2.9	17	11.6	567	5.9	<0.001
Sepsis	597	0.9	2	1.4	147	1.5	<0.001
Bone and joint	144	0.2	2	1.4	112	1.2	<0.001
Endocarditis	53	0.1	0	0	9	0.1	<0.001
Bacteremia	7	0.0	0	0	2	0.0	<0.001

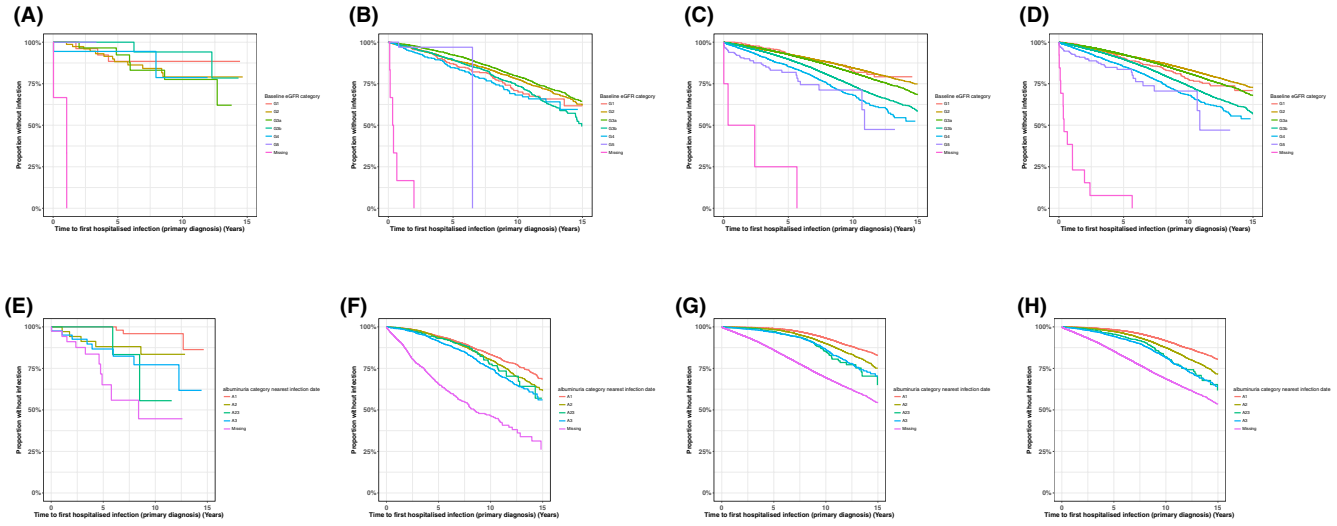

FIGURE 1 A, Time to first hospitalized infection in T1DM cohort by eGFR category. B, Time to first hospitalized infection in T2DM cohort by eGFR category. C, Time to first hospitalized infection in non-DM cohort by eGFR category. D, Time to first hospitalized infection in overall cohort by eGFR category. E, Time to first hospitalized infection in T1DM cohort by proteinuria category. F, Time to first hospitalized infection in T2DM cohort by proteinuria category. G, Time to first hospitalized infection in non-DM cohort by proteinuria category. H, Time to first hospitalized infection in overall cohort by proteinuria category

3.5 | Adjusted risk of progression to hospital admission by diabetes status

Adjusted models were run for the T2DM and non-DM cohorts (Figure 2). The proposed models were inappropriate in the T1DM cohort due to low numbers.

Within the T2DM cohort, there was no significant difference between G1 (aHR = 1.00, 0.80-1.25) and G3a (aHR = 1.03, 0.92-1.15) compared with the reference G2. However, there was an association between worsening eGFR and infection rates in categories G3b (aHR = 1.36, 1.20-1.54), G4 (aHR = 1.82, 1.54-2.15) and G5 (aHR = 2.41, 1.60-3.63). In the non-DM cohort, there was no significant difference between G1 (aHR = 0.94, 0.80-1.11) and the reference G2, but infection rates increased in this cohort from categories G3a to G5: the adjusted hazard ratio for G3a was 1.21 (1.15-1.27), for G3b, 1.61 (1.52-1.71), for G4, this was 2.40 (2.21-2.60) and for G5, 4.15 (3.44-5.00).

Within the T2DM cohort, aHRs for the positive proteinuria categories A2, A23 and A3 were all significant (Figure 2). There was an association between worsening proteinuria and infection rates in categories A2 (aHR = 1.45, 1.29-1.63), A2/3 (aHR = 1.31, 1.10-1.57) and A3 (aHR = 1.91, 1.67-2.20) compared with A1. A similar pattern was seen within the non-DM cohort (Figure 2), with the aHR

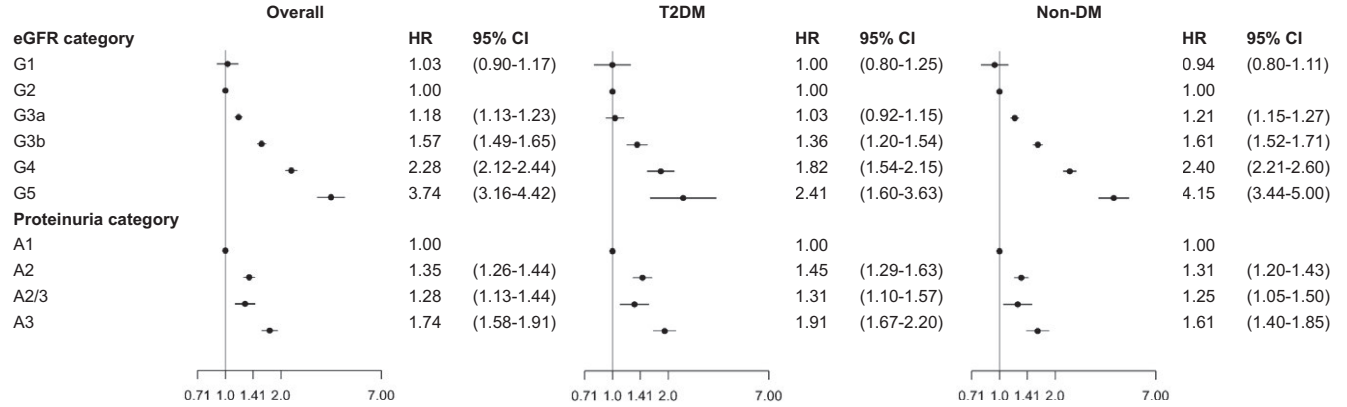

FIGURE 2 Adjusted hazard ratios for eGFR (reference: G2) and proteinuria (reference: A1) categories from T2DM and non-DM Cox models

for A2 being 1.31 (1.20-1.43), A23, 1.25 (1.05-1.50) and A3, 1.61 (1.40-1.85).

4 | DISCUSSION

In this study the severity of renal morbidity, as measured by eGFR and proteinuria, were both associated with an increase in infection rates, and that this association was independent. McDonald et al[16] published a study similar to ours that looked at the associations between CKD and the incidence of infection in patients with diabetes aged 65 and older. They found that there was an association between eGFR category and rates of lower respiratory tract infection and sepsis. Their results have been validated in our study of a larger population of patients aged 40 and older (25 and older for those with type 1 diabetes) with and without diabetes.

Much of the current rationale for intervention in patients with diabetes and kidney disease is directed towards use of ACE inhibitors, angiotensin receptor blockers and other vascular interventions to reduce the risk of progression both to end-stage renal failure and to cardiovascular events including ischaemic events and cardiac failure. The increasing burden of sepsis with worsening burden of renal impairment is rarely considered by clinicians. As potential immunosuppressive interventions for CKD emerge that may reduce the fibrosis associated with worsening diabetic nephropathy,[26] the worsening burden of infection as nephropathy progresses, potentially related to the loss of immunoglobulins via the kidney due to increased glomerular permeability, should be considered in the risk-benefit evaluation of any therapy. Here, hospitalized infection risk within the type 2 diabetes cohort was seen to rise as the severity of CKD worsened from G3b to G5 (G3a-G5 in overall and nondiabetes) and proteinuria stages A2-A3. Treating patients at eGFR stages G1-G3a with immunosuppressive therapy may therefore provide a favourable risk-benefit ratio (G1-G3a in type 2 diabetes; G1-G2 in nondiabetes and overall cohorts), although further studies are required to explore this.

These data and the study design had a number of strengths and limitations. The study included routine observations from a very large number of people, from a national, real-world setting. Infection rates were compared with those in patients with mildly decreased kidney function or mild kidney damage, who might already be experiencing a high number of hospitalized infections. There was no standardization of the timing of observations such as eGFR and proteinuria. We believe that this will have introduced noise but not bias because there is inherent variability in the monitoring of kidney function in routine care. In identifying the members of our diabetes cohorts, we may have selected patients having an aetiology other than diabetes for their CKD. A limited range of infections was included in the definition, which may have led to bias, and in addition, the impact of socioeconomic status on the risk of severe infection was not factored in.

Since approximately 2006, there has been considerable variability in the calibration of serum creatinine measurements in UK laboratories, with methodology changes and the piecemeal introduction of isotope-dilution mass spectrometry (IDMS) reference assays. The use of IDMS standards is believed to have led to a slight but systematic downward shift in serum creatinine values, with a corresponding upward shift in eGFR values. This has implications for our study, by affecting the apparent trajectory of individual patients' eGFR histories, which might in turn have been incorrectly related to the infection outcome. This could be considered an additional limitation of the study.

Although this study separately analysed the effect of renal impairment and proteinuria on the risk of hospitalization for infection, an analysis of the interaction between stage of renal function and stage of proteinuria was also conducted. However, when adjusting for eGFR category and proteinuria combinations, the model was overparametrized, and despite all possible combinations being tested (eg, A1 × G1, A1 × G2 etc.), no combination showed any significance. This can be explained by the large proportion of missing data for proteinuria category.

In summary, it has already been established that patients with chronic kidney disease (CKD), particularly ESRD, have an increased incidence of infections, particularly those resulting in hospitalizations and death.[13,27] There is also some evidence that patients with predialysis CKD also have a higher risk of infections (as measured by infection-related hospitalizations) which correlates to degree of renal function decline.[14,16] Patients with diabetes may have an additional risk of infection due to their underlying metabolic disease.

The current study demonstrates that eGFR and degree of albuminuria are independent markers of hospitalized infection in both patients

with and without diabetes, and validates and extends previous work in a larger and more diverse population.[16] The same patterns of hazard ratios of eGFR and proteinuria were seen in CKD patients with type 2 diabetes and no diabetes, with the risk of each outcome increasing with a decreasing eGFR and increasing proteinuria. Our findings have therefore emphasized the relationship between eGFR and proteinuria and their impact on the risk of serious infection. Furthermore, they highlight the importance of monitoring and managing both, regardless of diabetes status, and that both should be considered when evaluating the risk-benefit profile of disease-specific therapies.

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AUTHOR CONTRIBUTIONS

C.J.C., P.A., L.J., S.J-J. and E.B. designed the study; E.B. and S.J-J. conducted the data extraction; E.B. and C.J.C. analysed the data; E.B., N.P., S.J-J., P.A., M.J., L.J., L.A.S. and C.J.C. drafted and revised the article; all authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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