ORIGINAL RESEARCH

Patient Characteristics and Outcomes of Hospitalized Chronic Kidney Disease Patients with and without Type 2 Diabetes Mellitus: Observations from the German Claims Data-Based Cohort of the CaReMe-CKD Multinational Study

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Introduction: Type 2 diabetes mellitus (T2DM) is a leading cause of chronic kidney disease (CKD) globally. Both conditions substantially worsen patients' prognosis. Current data on German in-hospital CKD cohorts are scarce. The multinational CaReMe study was initiated to evaluate the current epidemiology and healthcare burden of cardiovascular, renal and metabolic diseases. In this substudy, we share real-world data on CKD inpatients stratified for coexisting T2DM derived from a large German hospital network.
Methods: This study used administrative data of inpatient cases from 89 Helios hospitals from 01/01/2016 to 28/02/2022. Data were extracted from ICD-10-encoded discharge diagnoses and OPS-encoded procedures. The first case meeting a previously developed CKD definition (defined by ICD-10- and OPS-codes) was considered the index case for a particular patient. Subsequent hospitalizations were analysed for readmission statistics. Patient characteristics and pre-defined endpoints were stratified for T2DM at index case.
Results: In total, 48,011 patients with CKD were included in the present analysis (mean age ± standard deviation, 73.8 ± 13.1 years; female, 44%) of whom 47.9% had co-existing T2DM. Patients with T2DM were older (75 ± 10.6 vs 72.7 ± 14.9 years, p < 0.001), but gender distribution was similar to patients without T2DM. The burden of cardiovascular disease was increased in patients with T2DM, and index and follow-up in-hospital mortality rates were higher. Non-T2DM patients were characterised by more advanced CKD at baseline. Patients with T2DM had consistently higher readmission numbers for all events of interest, except for readmissions due to kidney failure/dialysis, which were more common in non-T2DM patients.
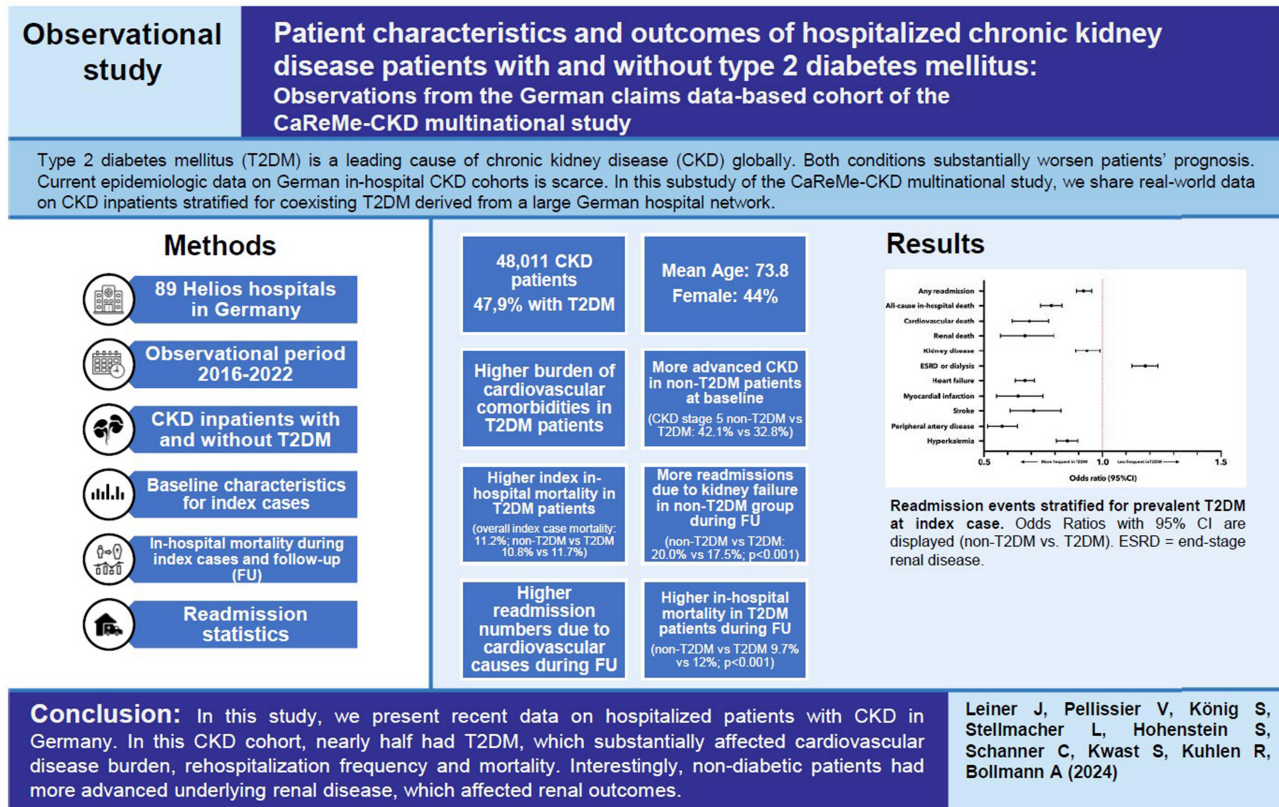**Conclusion:** In this study, we present recent data on hospitalized patients with CKD in Germany. In this CKD cohort, nearly half had T2DM, which substantially affected cardiovascular disease burden, rehospitalization frequency and mortality. Interestingly, non-diabetic patients had more advanced underlying renal disease, which affected renal outcomes.
Keywords: chronic kidney disease, type 2 diabetes mellitus, administrative data, in-hospital mortality, kidney failure, rehospitalization

Introduction

Chronic kidney disease (CKD) is a significant global health issue, with a prevalence of 9%–13%.[1–3] Associated mortality in patients with CKD is predominantly due to the increased cardiovascular risk.[1,3,4] Type 2 diabetes mellitus (T2DM) is a common cause of CKD. Through microvascular alterations, it leads to a specific form of glomerulopathy, known as diabetic kidney disease (DKD).[5] CKD prevalence in patients with T2DM varies across European countries,[6,7] ranging from 15.4% to 41.5%.[8] DKD often progresses to kidney failure and is considered the leading cause of kidney failure worldwide.[9,10] Co-existence of both T2DM and CKD significantly increases cardiovascular mortality.[5,11] However, the

Graphical Abstract

Observational study

Patient characteristics and outcomes of hospitalized chronic kidney disease patients with and without type 2 diabetes mellitus: Observations from the German claims data-based cohort of the CaReMe-CKD multinational study

Type 2 diabetes mellitus (T2DM) is a leading cause of chronic kidney disease (CKD) globally. Both conditions substantially worsen patients' prognosis. Current epidemiologic data on German in-hospital CKD cohorts is scarce. In this substudy of the CaReMe-CKD multinational study, we share real-world data on CKD inpatients stratified for coexisting T2DM derived from a large German hospital network.

Methods
- 89 Helios hospitals in Germany
- Observational period 2016-2022
- CKD inpatients with and without T2DM
- Baseline characteristics for index cases
- In-hospital mortality during index cases and follow-up (FU)
- Readmission statistics

- 48,011 CKD patients 47,9% with T2DM
- Mean Age: 73.8 Female: 44%
- Higher burden of cardiovascular comorbidities in T2DM patients
- More advanced CKD in non-T2DM patients at baseline (CKD stage 5 non-T2DM vs T2DM: 42.1% vs 32.8%)
- Higher index in-hospital mortality in T2DM patients (overall index case mortality: 11.2%; non-T2DM vs T2DM 10.8% vs 11.7%)
- More readmissions due to kidney failure in non-T2DM group during FU (non-T2DM vs T2DM: 20.0% vs 17.5%; p<0.001)
- Higher readmission numbers due to cardiovascular causes during FU
- Higher in-hospital mortality in T2DM patients during FU (non-T2DM vs T2DM 9.7% vs 12%; p<0.001)

Results

Readmission events stratified for prevalent T2DM at index case. Odds Ratios with 95% CI are displayed (non-T2DM vs. T2DM). ESRD = end-stage renal disease.

Conclusion: In this study, we present recent data on hospitalized patients with CKD in Germany. In this CKD cohort, nearly half had T2DM, which substantially affected cardiovascular disease burden, rehospitalization frequency and mortality. Interestingly, non-diabetic patients had more advanced underlying renal disease, which affected renal outcomes.

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true origin of CKD can only be reliably identified through kidney biopsy.[5,12] Hence, for some patients with T2DM, a non-diabetic cause of the underlying CKD cannot be ruled out.[5] Non-diabetic kidney disease (NDKD) is a common cause of CKD, with hypertension being the most common non-diabetic cause.[1,13,14] Population-based studies have demonstrated NDKD patients to be at increased risk for long-term adverse cardiovascular and renal outcomes.[13,15] However, when compared to CKD patients with coexisting diabetes, patients with NDKD tend to have lower event rates and more favourable outcomes.[16,17] This is consistent with the DAPA-CKD trial, where patients with both CKD and T2DM consistently had higher event rates[18,19] for the primary outcome measure.

Few recent European population-based studies have yet examined the epidemiology, characteristics, and respective in-hospital outcomes of hospitalised CKD patients with and without coexisting T2DM.[20–23] The multinational CaReMe study was initiated to report on the current epidemiology and healthcare burden of cardiovascular, renal and metabolic diseases using healthcare data from 12 countries. In a recent CaReMe-CKD analysis, the prevalence of diabetes (including type 1 diabetes mellitus) was 38–39% among 2.4 million included patients.[2] Aim of the present study was an analysis and comparative characterisation of a German in-hospital cohort of the CaReMe-CKD study, stratified for coexisting T2DM, over a 5-year observational period. Patient characteristics, comorbidity burden and in-hospital outcomes were evaluated, highlighting differences between patients with and without T2DM.

Methods
Data Source
In this retrospective observational cohort study, we analysed administrative (claims) data from 89 hospitals in Germany's Helios network – primary, secondary, tertiary care centres and specialty care centres – that included inpatient cases

between 01/01/2016 and 02/28/2022. The study used the International Statistical Classification of Diseases and Related Health Problems (ICD-10-GM [German Modification]) codes to identify patients with CKD and relevant comorbidities at hospital discharge, and Operations and Procedures codes (OPS [German adaptation of the International Classification of the Procedures in Medicine of the World Health Organization, version 2017]) to identify in-hospital medical procedures from administrative data. In-hospital death was defined by the type of hospital discharge. Hospital categories were extracted from administrative data. Supplemental Table 1 provides detailed information on the ICD-10-GM and OPS codes used. Patients ≥18 years of age with complete inpatient treatment, meeting one of the following CKD definition criteria, were included:

- Main discharge diagnosis of CKD
- Main diagnosis of acute kidney injury with a secondary diagnosis of CKD
- Any CKD-associated procedure indicating dialysis (according to OPS codes, Supplemental Table 1) with CKD as the main or secondary diagnosis at hospital discharge.

The index case was defined as the first case of each patient meeting the inclusion criteria. Patients with type 1 diabetes mellitus were excluded. The study did not differentiate between incident and prevalent CKD.

Study Variables

Baseline characteristics, including demographic and comorbidity information, were stratified for T2DM at the index case. In case of multiple codes for CKD stage, the most severe stage was considered. Kidney failure was defined as either CKD stage 5 or by ICD-10-GM/OPS codes indicating dialysis (Supplemental Table 1). Additionally, we calculated a modified Elixhauser comorbidity weighted score excluding the components "diabetes mellitus, complicated" and "diabetes mellitus, uncomplicated" to reduce confounding.[24,25] Supplemental Table 2 describes ICD−10-GM codes used to calculate the Elixhauser comorbidity weighted score.

For longitudinal analysis of readmission events during the observational period, only the first readmission per endpoint for one particular patient was included. Patients with incident T2DM during follow-up (FU) were counted as non-diabetic and patients with incident type 1 diabetes mellitus were excluded for this analysis. Pre-defined readmission event rates (for definitions, see Supplemental Table 3) were compared between stratification groups.

Statistical Analysis

Administrative data were extracted from QlikView (*QlikTech, Radnor, Pennsylvania, USA*); all statistical analyses were performed within the R environment. No statistical comparison of baseline characteristics was performed as per STROBE guidelines for observational analyses.[26] Readmission events were analysed as follows:

- As a time-to-first-event analysis (duration between the index case and the first occurrence of a given event). Median readmission time in days [25–75% quantiles] and P-values from negative-binomial regression adjusted for age are reported.
- As a cumulative event rate (percentage of index patients readmitted with a given endpoint during the FU period). N (%), odds ratios (OR) [95% confidence interval, CI] and P-values from Fisher's exact test are reported. ORs [95% CI] are displayed in a Forest plot.
- As a cumulative event rate per 100 patient-years.
- As a Cox regression analysis for selected endpoints (any readmission, readmission for kidney failure/dialysis, in-hospital mortality during FU, readmission for heart failure, readmission for kidney disease) adjusted for age, gender, T2DM status, Elixhauser comorbidity weighted score at baseline, hospital category (primary/secondary care centre, tertiary care centre, specialty care centre). FU was right censored at the date of in-hospital death if occurred during FU, except for the endpoint "in-hospital mortality".

Ethical Considerations

Patient data were stored in a double-pseudonymised form. Data use was approved by the local ethics committee of the University of Leipzig (AZ 010/21-ek) and the Helios Kliniken GmbH data protection authority. Considering the retrospective analysis of double-pseudonymised administrative clinical routine data, individual informed consent was not obtained. The study followed the STROBE guidelines for observational analyses.

Results

In total, 89 hospitals contributed inpatient cases to the database (33.4% primary care/secondary care centres; 34.3% tertiary care centres; 32.3% specialty care centres). A total of 48,011 patients (female, 44%; mean age ± standard deviation, 73.8 ± 13.1 years) fulfilled the pre-defined CKD definition. Of these, 22,994 (47.9%) had co-existing T2DM at the time of index hospitalization. Patients with T2DM were older (72.7 ± 14.9 vs 75 ± 10.6 years) and had a higher burden of comorbidities, especially cardiovascular diseases (CVD). Hypertension (71.8%) and heart failure (46%) were the most common comorbidities in the overall cohort and within stratification groups (Table 1). In patients with CKD and T2DM, baseline prevalences of complications associated with T2DM were 16.4% for diabetic neuropathy, 3.6% for diabetic retinopathy and 1.5% for diabetic foot complications. The underlying CKD was more advanced in the non-T2DM group as indicated by the prevalence of CKD stage 5 (42.1% vs 32.8%) and kidney failure (52.7% vs 47.5%) as defined above. Prevalence of acute kidney injury (AKI) was higher in the T2DM group at index case (54% vs 59.1%). Total index case in-hospital mortality was 11.2%, with a higher proportion of renal deaths compared to cardiovascular

Table 1 Baseline Characteristics of CKD Patients Stratified for Prevalent T2DM

	Total Cohort	Prevalent T2DM % (n)	No T2DM % (n)
Number of patients	48,011	47.9% (22,994)	52.1% (25,017)
Age, mean±SD (years)	73.8±13.1	75±10.6	72.7±14.9
Female sex	44% (21,107)	44.1% (10,145)	43.8% (10,962)
Elixhauser comorbidity weighted score#, mean±SD	18.6 (11.4)	18.3 (11.5)	18.8 (11.3)
Chronic kidney disease	//	//	//
CKD stage 1	0.3% (163)	0.3% (67)	0.4% (96)
CKD stage 2	6.4% (3074)	6.1% (1414)	6.6% (1660)
CKD stage 3	29.4% (14,128)	30.8% (7078)	28.2% (7050)
CKD stage 4	20.4% (9778)	21% (4838)	19.7% (4940)
CKD stage 5	37.6% (18,073)	32.8% (7539)	42.1% (10,534)
CKD - stage unspecified	0.3% (143)	50 (0.2%)	93 (0.4%)
Acute kidney injury	56.4% (27,086)	59.1% (13,589)	54% (13,497)
Kidney failure	50.2% (24,108)	47.5% (10,926)	52.7% (13,182)
Kidney transplant	1.4% (693)	0.7% (162)	2.1% (531)
Diabetes mellitus type 2	47.9% (22,994)	100% (22,994)	//
Diabetic neuropathy	7.9% (3772)	16.4% (3772)	//
Diabetic eye complications	1.7% (827)	3.6% (827)	//
Diabetic foot / peripheral angiopathy	0.7% (354)	1.5% (354)	//

(*Continued*)

Table 1 (Continued).

	Total Cohort	Prevalent T2DM % (n)	No T2DM % (n)
Cardiovascular disease*	89.3% (42,886)	93% (21,377)	86% (21,509)
Heart failure	46% (22,072)	51.9% (11,941)	40.5% (10,131)
CAD	29.4% (14,133)	35.1% (8065)	24.3% (6068)
(Previous) AMI	9.2% (4437)	11.2% (2572)	7.5% (1865)
AF /atrial flutter	32.4% (15,541)	35.5% (8171)	29.5% (7370)
Bradycardia / conduction disorder	5.6% (2668)	6.6% (1521)	4.6% (1147)
Ventricular arrhythmia	1.8% (881)	2.1% (491)	1.6% (390)
Hypertension	71.8% (34,471)	74.6% (17,155)	69.2% (17,316)
(Previous) Stroke	6.6% (3147)	7.8% (1804)	5.4% (1343)
Peripheral artery disease	10.8% (5198)	14.7% (3389)	7.2% (1809)
Major organ specific bleeding	10.3% (4961)	10.5% (2424)	10.1% (2537)
Cancer	7.6% (3667)	6.2% (1423)	9% (2244)
COPD	10.6% (5083)	11.8% (2703)	9.5% (2380)
Liver disease	7% (3369)	8.1% (1865)	6% (1504)
Outcomes (index case)			
All-cause in-hospital mortality	11.2% (5395)	11.7% (2698)	10.8% (2697)
Renal death	7.1% (3423)	7.2% (1648)	7.1% (1775)
Cardiovascular death	1.9% (895)	2.2% (510)	1.5% (385)

Notes: Baseline characteristics of CKD patients with and without T2DM. Only the most relevant comorbidities are shown. [#]Modified by excluding the component "diabetes mellitus, complicated" and "diabetes mellitus, uncomplicated". *Sum of codes from all subcategories (some of those are not shown here) according to Supplemental Table 1.
Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation; T2DM, type 2 diabetes mellitus.

deaths (7.1% vs 2.2%, for definition, see Supplemental Table 3) and a significant difference in all-cause in-hospital mortality between T2DM and non-T2DM patients (10.8% vs 11.7%). This was mainly caused by a between-group discrepancy in cardiovascular death rates (1.5% vs 2.2%; Table 1).

Circa fifty percent of the total cohort (n = 24,046) was rehospitalized at least once during FU (Table 3). Median (25%–75%) time from discharge of the index case until the last observed readmission event was 331 (92–776) while the mean number (±standard deviation) of readmissions per patient was 3.08 ± 3.08. Time-to-event analyses revealed a median (25%–75%) time to first readmission (any readmission) of 76 (24–239) days with no significant difference within stratification for T2DM (non-T2DM vs T2DM: 76 [24–244] vs 76 [24–235] days; p = 0.175; Table 2). Figure 1 shows plots of time-to-event analyses. There were no other significant differences in time-to-event analyses for individual readmission events except for the pre-defined endpoints "kidney disease" (non-T2DM vs T2DM: 111 [37–362] vs 136 [41–393.5]; p = 0.048; Table 2) and "peripheral artery disease" (non-T2DM vs T2DM: 269 [84.5–644.2] vs 239 [86–573]; p = 0.038; Table 2). The most common reason for hospital readmission was kidney failure/dialysis (18.8% in the overall cohort). This endpoint occurred more frequently in the non-T2DM group (20.0% vs 17.5%; OR [95% CI] 1.179 [1.125, 1.234]; p < 0.001). Patients with T2DM showed higher rehospitalization rates due to cardiovascular comorbidities (Table 3, Figure 2) as well as higher all-cause (non-T2DM vs T2DM: 9.7% vs 12.0%; OR [95% CI] 0.782 [0.738, 0.829]; p < 0.001), cardiovascular (2.4% vs 3.4%; OR [95% CI] 0.691 [0.619, 0.771]; p < 0.001) and renal (1.0% vs 1.5%, OR

Table 2 Time-to-First-Readmission Analysis Stratified for T2DM

Readmission Cause	Overall Cohort	T2DM	No T2DM	P value
Any readmission	76 [24–239]	76 [24–235]	76 [24–244]	0.175
All-cause in-hospital death	268 [65–671]	286 [71–685]	245.5 [59–649.2]	0.251
CV death	274 [77–663]	313 [83–692.8]	242 [71.5–608]	0.056
Renal death	191 [43–549]	209 [46–588]	152 [37.2–499.8]	0.494
Kidney disease	122 [39–373.2]	136 [41–393.5]	111 [37–362]	0.048
Kidney failure or dialysis	93 [31–287.2]	93 [31–287]	93 [31–289]	0.087
HF	169 [50–485]	177 [55–495]	163.5 [46–476]	0.457
AMI	320 [113–678]	334 [113–681.2]	299 [114–674]	0.694
Stroke	364 [120.5–735]	392 [108–746.5]	346 [141.2–710.8]	0.694
Peripheral artery disease	254 [85.5–593.5]	239 [86–573]	269 [84.5–644.2]	0.038
Hyperkalemia	209 [61–537]	224 [63–551]	193 [59–519.2]	0.095

Notes: Shown is the median duration between index case discharge and the first admission for a given event (days, median [25–75%]). P-values derived from negative binomial regression.
Abbreviations: AMI, acute myocardial infarction; CV, cardiovascular; HF, heart failure; T2DM, type 2 diabetes mellitus.

Table 3 Cumulated Readmission Events of the CKD Cohort Stratified by T2DM

Readmission Cause	Overall Cohort, % (n)	T2DM, % (n)	No T2DM, % (n)	OR (95% CI)	P value
Any readmission					
Any type of admission	50.1% (24,046)	51.2% (11,765)	49.1% (12,281)	0.920 (0.888; 0.954)	<0.001
Emergency admission	37.1% (17,824)	39.3% (9029)	35.2% (8795)	0.839 (0.808; 0.870)	<0.001
All-cause in-hospital death					
Any type of admission	10.8% (5190)	12.0% (2770)	9.7% (2420)	0.782 (0.738; 0.829)	<0.001
Emergency admission	8.3% (3979)	9.3% (2138)	7.4% (1841)	0.775 (0.726; 0.827)	<0.001
CV death					
Any type of admission	2.9% (1369)	3.4% (778)	2.4% (591)	0.691 (0.619; 0.771)	<0.001
Emergency admission	2.1% (1032)	2.6% (588)	1.8% (444)	0.689 (0.607; 0.781)	<0.001
Renal death					
Any type of admission	1.2% (591)	1.5% (341)	1% (250)	0.671 (0.567; 0.793)	<0.001
Emergency admission	0.9% (452)	1.2% (267)	0.7% (185)	0.634 (0.522; 0.769)	<0.001
Kidney disease					
Any type of admission	12.4% (5968)	12.8% (2947)	12.1% (3021)	0.934 (0.885; 0.987)	<0.001
Emergency admission	6.7% (3211)	7.6% (1741)	5.9% (1470)	0.762 (0.709; 0.819)	<0.001
Kidney failure or dialysis					
Any type of admission	18.8% (9012)	17.5% (4017)	20% (4995)	1.179 (1.125; 1.234)	<0.001
Emergency admission	11.8% (5687)	11.5% (2642)	12.2% (3045)	1.068 (1.010; 1.129)	0.021
HF					
Any type of admission	9.7% (4659)	11.5% (2649)	8.0% (2010)	0.671 (0.631; 0.713)	<0.001
Emergency admission	7.4% (3565)	8.9% (2045)	6.1% (1520)	0.663 (0.618; 0.710)	<0.001

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Table 3 (Continued).

Readmission Cause	Overall Cohort, % (n)	T2DM, % (n)	No T2DM, % (n)	OR (95% CI)	P value
AMI					
Any type of admission	1.5% (719)	1.8% (422)	1.2% (297)	0.643 (0.551; 0.748)	<0.001
Emergency admission	1.3% (603)	1.5% (351)	1.0% (252)	0.656 (0.556; 0.775)	<0.001
Stroke					
Any type of admission	1.5% (723)	1.8% (407)	1.3% (316)	0.710 (0.610; 0.825)	<0.001
Emergency admission	1.3% (637)	1.6% (357)	1.1% (280)	0.718 (0.611; 0.843)	<0.001
Peripheral artery disease					
Any type of admission	3.1% (1467)	3.9% (897)	2.3% (570)	0.574 (0.515; 0.640)	<0.001
Emergency admission	1.5% (703)	1.9% (427)	1.1% (276)	0.590 (0.504; 0.688)	<0.001
Hyperkalemia					
Any type of admission	13.1% (6289)	14.1% (3233)	12.2% (3056)	0.851 (0.806; 0.897)	<0.001
Emergency admission	9.3% (4463)	10.3% (2364)	8.4% (2099)	0.799 (0.751; 0.851)	<0.001

Notes: The presented percentages refer to proportion of patients with an observed event during follow-up. Only the first readmission per patient during the observational period was considered for this analysis.
Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; CV, cardiovascular; HF, heart failure; OR, odds ratio; T2DM, type 2 diabetes mellitus.

[95% CI] 0.671 [0.567, 0.793]; p < 0.001) in-hospital mortality during FU. Hyperkalaemia was more common in patients with T2DM during the FU period (12.2% vs 14.1%; OR [95% CI] 0.851 [0.806, 0.897]; p < 0.001). Most rehospitalization events were emergency readmissions.
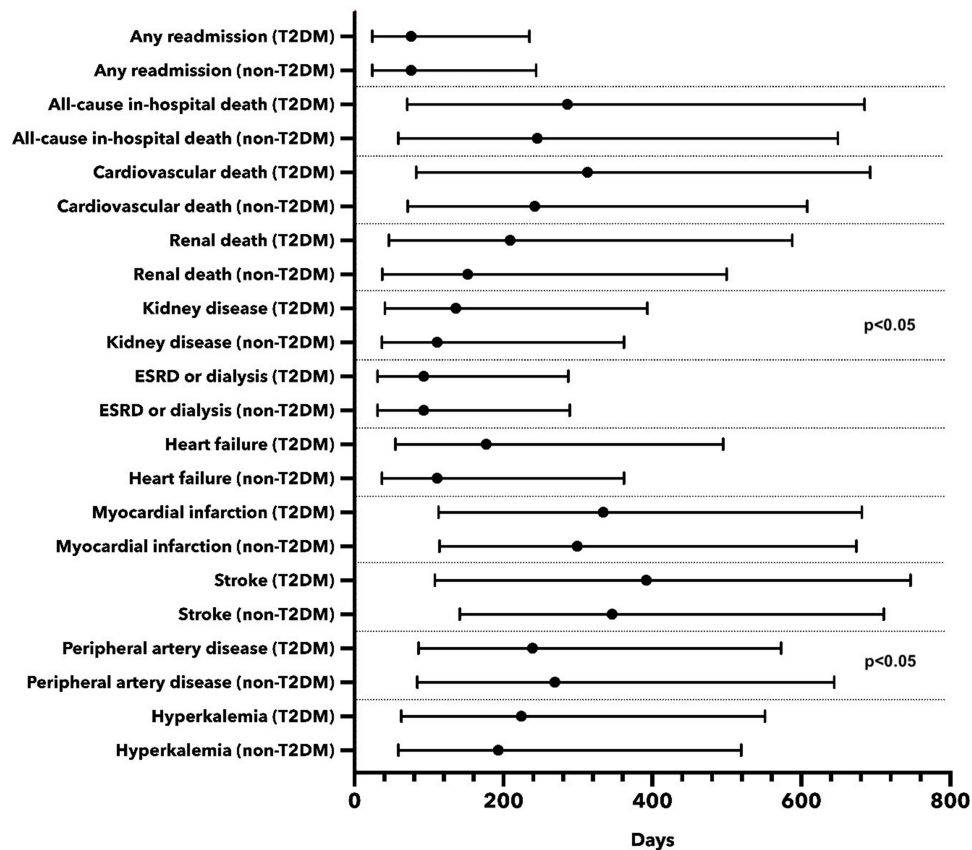
Figure 1 Time-to-first-readmission analyses stratified for prevalent T2DM at index case. Shown is the median duration between index case discharge and the first admission for a given event (days, median [25–75%]). For detailed numbers see Table 2.
Abbreviations: ESRD, end-stage renal disease (= kidney failure); T2DM, type 2 diabetes mellitus.
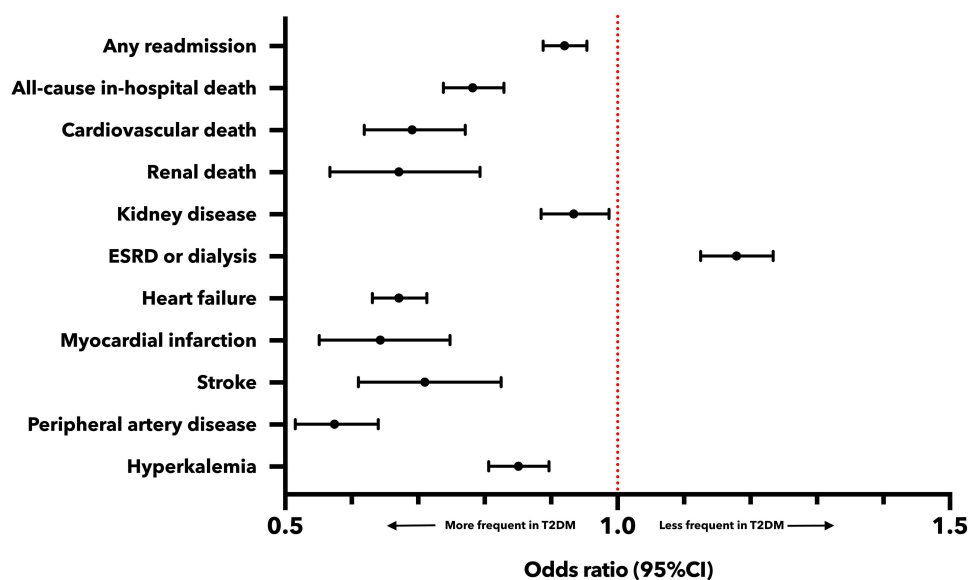
Figure 2 Readmission events stratified for prevalent T2DM at index case. Odds ratios with 95% CI are displayed (non-T2DM vs T2DM). For detailed numbers see Table 3.
Abbreviations: ESRD, end-stage renal disease (= kidney failure); T2DM, type 2 diabetes mellitus.

In Cox regression analysis, presence of T2DM was associated with a higher risk for all combined readmission events during FU, readmission for heart failure, readmission for "kidney disease" (according to Supplemental Table 3) and in-hospital mortality during FU (Supplemental Table 4). However, presence of T2DM was not associated with an increased risk for the endpoint kidney failure/dialysis (hazard ratio [95% CI] 0.996 [0.955, 1.039]; p = 0.868). Treatment in tertiary care centres and specialty care centres as well as male sex were associated with increased risk for this endpoint. Increased age was not associated with a higher risk for readmission for kidney failure/dialysis or the endpoint "kidney disease".

Figure 2 displays the corresponding OR, and Table 3 provides detailed numbers for all cumulated readmission events. Supplemental Table 4 shows results from Cox regression analyses. Supplemental Table 5 shows event rates per 100 patient-years.

Discussion

The present sub-analysis of the CaReMe-CKD study provides real-world in-hospital data up to 2022 of patients in Germany with and without T2DM. We highlight the following main findings: hospitalised patients with CKD represent a high-risk population, characterized by a high burden of comorbidities, particularly related to cardiovascular issues. These patients often experience adverse events such as rehospitalizations and in-hospital death. Prevalence of T2DM leads to a significant increase in the burden of CVD, which consequently has a substantial effect on mortality. However, deaths attributed to the underlying renal disease were the primary factor contributing to in-hospital mortality among index cases. In our cohort, hospitalised CKD patients without T2DM were younger but presented with more advanced kidney disease, as indicated by the proportion of patients with CKD stage 5/kidney failure at baseline and the higher number of rehospitalizations due to kidney failure/dialysis during FU. With this analysis, we emphasize the need to focus on patients with DKD as well as NDKD in everyday clinical practice to continuously optimise therapy and halt the progression of the underlying renal disease and prevent adverse outcomes. To the best of our knowledge, this is currently the largest analysis of real-world data analysing characteristics and outcomes of hospitalized CKD patients in Germany.

Our study once more highlights the interplay between diabetes mellitus, CKD and CVD and its consequences for patients' prognosis among a large cohort of inpatients. Taken together, these conditions pose a serious challenge for healthcare systems worldwide.[1,27] Various pathophysiological mechanisms such as liberation of mediators of inflammation and fibrosis in patients with diabetic metabolic disorders promoting both CKD and CVD have been described.[27–30] However, promising therapeutic targets also emerge from the shared pathophysiology within the triad of cardiovascular,

renal and metabolic disease opening up novel treatment options that have been shown to significantly improve outcomes, leading to a paradigm shift in medical therapy for these patient cohorts.[27,31,32] Intensified risk factor control with respect to hypertension, dyslipidaemia and hyperglycaemia has also been shown to reduce the risk for major adverse cardio-vascular events in patients with DKD,[33] which once more emphasizes the importance of an adequate patient management within the triad of CKD, diabetes mellitus and CVD.

For our analysis, we aimed to establish a homogenous cohort of patients with CKD and evaluate the influence of T2DM on patient outcomes. Therefore, we excluded patients with type 1 diabetes mellitus as they generally have younger age and a diverse risk profile.[34] T2DM prevalence was 47.9%, which is slightly higher than the overall diabetes prevalence reported in the CaReMe-CKD global study.[2] In the 2021 US renal data system report, diabetes (including type 1 diabetes mellitus) was present in ~50% of insured individuals with CKD.[35] In the German cohort of the multinational Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps),[36] a prospective cohort including ~1800 patients with stage 3 and 4 CKD and a comparable demographic profile (median age, 75 years; female, 42%), 42% of patients had diabetes, which is comparable with our reported prevalence.[37] The German Chronic Kidney Disease (GCKD) prospective study established one of the largest European CKD cohorts with over 5000 patients.[38,39] The lower mean age in this cohort of 60 years might explain the reported lower diabetes prevalence of 35%. Nevertheless, CVD burden was pronounced in both GCKD and CKDopps study populations, with significant differences between patients with and without diabetes.[37,39] The prevalence of heart failure in our cohort was 46%, which is considerably higher than the 13% reported for CKDopps.[37] This difference could be attributed to the fact that our analysis included only inpatients and the majority had terminal kidney failure, and the risk of heart failure increases with CKD severity.[40] We also observed high prevalence of coronary heart disease and atrial fibrillation, which are common causes of heart failure.[41] Notably, CKDopps and GCKD trials excluded patients with kidney failure and recruitment occurred in the outpatient setting; hence, cohorts must be cautiously compared.

Patients with T2DM showed very low rates of diabetic eye complications (diabetic retinopathy) in comparison to previous published data.[42] Within the disease management program for T2DM in Germany, a structured screening program for diabetic retinopathy is recommended every 1–2 years,[43] however, a lack of screening for this complication was previously reported.[44,45] Hence, diabetic retinopathy is likely to be significantly underdiagnosed in our cohort, especially considering that patients were hospitalised with CKD during the index cases, where screening for diabetic retinopathy is unlikely to be part of routine patient assessment.

Most patients presented with CKD stage 5 (37.6%) with a significant difference between T2DM (32.8%) and non-T2DM (42.1%) patients. To accurately identify the patient cohort with kidney failure, we used an augmented definition that included dialysis-specific OPS codes (Supplemental Table 1). Per this definition, kidney failure was present in 50% of the total cohort. In-hospital mortality during index case was 11.2% and 10.8% during FU for the total cohort. In the German CKDopps trial, which excluded patients with CKD stage 5, the underlying CKD progressed to kidney failure in 24.9% of patients at a median FU 29 months and 24.4% died.[37] Among other variables, diabetes was identified as a predictor of kidney failure and death. In the significantly younger GCKD patient cohort, all-cause mortality was 7.2%[46] and 11.8% in 4 years and 6.5 years of FU,[47] respectively. CVDs were major drivers of mortality in both CKDopps and GCKD.[37,46,47] In accordance with the high baseline prevalence of advanced CKD in our claims data-based cohort, deaths attributed to renal causes, according to the pre-defined endpoints, were the major driver of index in-hospital mortality albeit cardiovascular death was more frequently observed during FU. To the best of our knowledge, large representative studies with specific focus on German in-hospital populations with CKD are lacking. Therefore, when comparing outcomes of our study to the available data, it is important to consider the composition of cohorts. Patients in our study were predominantly hospitalised because of the underlying renal pathology (see CKD definition in section "Methods") suggesting a severe disease state. Our study included inpatient data only, so it was not possible in a meaningful way to differentiate between incident and prevalent CKD. A high proportion of patients with prevalent CKD is, however, likely as most patients presented with CKD stage 5 or kidney failure (per the above mentioned definition) at index hospitalization.

One of the key findings of this study is that despite a lower mean age, non-T2DM patients had more advanced underlying CKD. This was indicated by the prevalence of CKD stage 5/kidney failure at baseline and differences in the cumulative

number of readmission events for kidney failure/dialysis during FU. In adjusted Cox regression analysis, T2DM was not associated with an increased risk for rehospitalizations for kidney failure/dialysis. Previous investigations have consistently identified diabetes as a major risk factor for severe CKD and progression to kidney failure.[16,17,37,39] However, NDKD patients also represent a high-risk population, as reported in a retrospective study by Menon et al, where 56% of the NDKD cohort patients advanced to kidney failure (median FU, 88 months) and 22% died (median FU, 123 months).[15] A recent claims data-based analysis from the United States reported an event rate of 10.3/100 patient-years for the composite kidney outcome (end-stage renal disease/kidney failure/dialysis) and 4.0/100 for heart failure hospitalizations, which compares well with our data.[13] In 2004, Germany introduced a structured disease management program for patients with diabetes, which includes regular (quarterly or half-yearly) check-ups at the treating general practitioner.[48,49] Less advanced CKD and better renal outcomes in T2DM patients could be due to better FU in the outpatient setting compared to non-T2DM patients. We recommend evaluating the possibilities of establishing disease management programs for patients with CKD as presently, no such care program exists in Germany. Importantly, data on the true cause of the underlying renal disease were not available in our administrative database due to the unavailability of kidney biopsy results. The cause of CKD in patients with T2DM might also be non-diabetic;[5] however, this influence could not be investigated in our study. Due to the higher burden of especially cardiovascular comorbidities in the CKD-T2DM cohort, more frequent hospitalizations also *prior* to the index hospitalization can be expected. Therefore, a closer monitoring of renal function and initiation of therapeutic interventions during those hospitalizations is likely in this cohort, which may be a possible influencing factor explaining our observation of less advanced renal disease in the CKD-T2DM cohort.

In line with the increased CVD burden at the index case, we also observed more and earlier rehospitalizations due to CVD in patients with T2DM during FU. The prevalence of AKI in the overall cohort at index case was high with a significant difference between T2DM and non-T2DM patients. AKI is associated with increased long-term mortality risk.[50,51] A large meta-analysis by Odutayo et al provided additional evidence of an increased risk for cardiovascular adverse events in patients with AKI.[51] In addition to a higher baseline CVD burden, the observed difference in AKI prevalence at index hospitalization may have negatively influenced cardiovascular outcomes in the CKD-T2DM cohort during FU. Additionally, readmission numbers for hyperkalaemia were significantly higher in the T2DM cohort. The increased risk for hyperkalaemia in patients with CKD is evident[52] and exacerbated in the presence of DKD.[53,54] From a pathophysiological perspective, diabetes leads to hyporeninemic hypoaldosteronism resulting in lower aldosterone levels, reduced potassium excretion and type IV renal tubular acidosis.[53–57] Patients presenting with the triad of diabetes, CKD and CVD, especially those with heart failure, must be considered a high-risk population for the development of hyperkalaemia as guideline-recommended medical therapy in these cohorts, such as inhibitors of the renin-angiotensin-aldosterone system or potassium-sparing diuretics, may cause additional increases in serum potassium levels.[53] Potassium-lowering agents might present an option for these patients in order to continue guideline-directed medical therapy up to the maximum tolerated dose.[52,53] The influence of hyperkalaemia in our CKD-T2DM cohort on the increased risk of cardiovascular events and mortality during FU should be noted, as previous studies have already provided evidence in this regard.[58–60]

Limitations

We acknowledge several limitations in connection with this study. First, this study was an observational cohort study using retrospective data only. Retrospective data are generally considered to be of inferior quality compared to prospective data.[61] However, a major advantage of retrospective data analysis is the ability to examine large nationwide datasets and provide a population-based overview on characteristics of specific patient cohorts, as our study has shown. Observational studies, however, only allow to describe associations and no cause-and-effect relationship. Hence, no hypothesis testing was performed.

Administrative data in general come with limitations as the data quality depends on correct coding and the data are stored not for research but remuneration reasons.[62] For CKD, this is especially important as the CaReMe global trial highlighted a discrepancy between eGFR-measured and diagnosed CKD.[2] A recent study by Bothe et al reported an acceptable sensitivity of ICD-10-GM codes to identify CKD, however, with limited discrimination between CKD stages.[63] Due to the unavailability of laboratory values, only patients with an ICD-10-GM-encoded CKD diagnosis (according to the definition described above)

were analysed. Therefore, the number of CKD cases (including "measured" CKD) during the observation period is likely to be higher and it can be expected that a significant number of patients with CKD could not be identified in our data set.

In our study, there was a marked discrepancy between encoded CKD stage 5 diagnoses (ICD-10-GM code N18.5) and kidney failure (as defined by N18.5 or ICD-10-GM/OPS codes indicating dialysis), suggesting a significant proportion of patients requiring dialysis but without a code for CKD stage 5 (see "Results" section). It is possible that some patients in the kidney failure cohort required only time-limited dialysis in an acute setting. However, OPS codes describing continuous methods for haemodialysis or haemofiltration, which are predominantly used to treat acute renal failure, were not included in our definitions (Supplemental Table 1). Nonetheless, incorrect coding cannot be ruled out in this context.

Furthermore, CKD definitions vary between studies. Most investigators use eGFR-based definitions,[13,37,39] which could not be applied in our claims data-based cohort as laboratory values were unavailable. This may hinder comparability between studies. However, we believe that our multimodal definition using ICD-10-GM and OPS codes helped establish a well-selected cohort of hospitalised patients with CKD.

Due to data structure and data protection regulations, linking patient data between hospitals was not possible, potentially leading to double counting of patients treated in different hospitals (fulfilling the above mentioned CKD definition), therefore affecting the cohort composition. Additionally, an underestimation of readmission numbers is likely, which is especially important in the light of Cox regression analyses. Lastly, we acknowledge that patient tracking during FU was only possible using in-hospital data from the Helios hospital network (no outpatient data or hospital data outside of Helios), potentially underestimating FU mortality and rehospitalization prevalence.

Conclusion

In this cohort of inpatients with CKD from a large-scale German hospital network, T2DM was present in nearly half of the patients. Hospitalised CKD patients are at a high risk for adverse outcomes. Patients with both CKD and T2DM have an increased prevalence of CVD and are prone to higher in-hospital mortality and rehospitalization rates. However, hospitalized CKD patients without T2DM had more advanced underlying renal disease. Future prospective studies including also outpatient data are required to understand the characteristics and outcomes of CKD patients with and without T2DM in Germany. The data derived from the CaReMe trial add to the body of evidence focusing on these specific patient cohorts in the hospital setting and highlight the need for close monitoring of patients with CKD to prevent adverse outcomes in the inpatient and outpatient sectors in Germany.

Abbreviations

AKI, acute kidney injury; CI, confidence interval; CKDopps, Chronic Kidney Disease Outcomes and Practice Patterns Study; CVD, cardiovascular diseases; DKD, diabetic kidney disease; GCKD, German Chronic Kidney Disease study; eGFR, estimated glomerular filtration rate; FU, follow-up; ICD-10-GM, International Statistical Classification of Diseases and Related Health Problems Version 10, German Modification; NDKD, non-diabetic kidney disease; OPS, Operation and Procedure classification system; OR, odds ratio; T2DM, Type 2 diabetes mellitus.

Data Sharing Statement

Statement of Ethics

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Author Contributions

All named authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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