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Associations between intercurrent events and cardiorenal clinical outcomes in non-diabetic chronic kidney disease: a real-world retrospective cohort study in the United States

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Abstract

Background Chronic kidney disease (CKD) is a global public health concern, with 50–70% of the burden attributed to non-diabetic aetiology. To expand CKD research, there is a need to identify novel surrogate endpoints preceding cardiorenal outcomes that are commonly used in CKD trials. This study explored and quantified associations between intercurrent events and clinical outcomes in patients with non-diabetic CKD to inform potential surrogate endpoints.

Methods In this retrospective observational cohort study, adults with non-diabetic, moderate-to-severe CKD (stage 3/4) were identified in the US Optum Clinformatics® Data Mart healthcare claims database. Key outcomes were hospitalization for heart failure, kidney failure/need for dialysis, and worsening of CKD stage from baseline. Intercurrent events were defined as events observed in patient medical or pharmacy claims after the cohort inclusion date that either precluded a clinical outcome of interest or were associated with a modified risk of the respective outcome. Intercurrent events were selected a priori or by a data-driven exploratory approach. Associations between intercurrent events and clinical outcomes were explored and quantified using a Cox proportional hazards regression model.

Results The study cohort included 504,924 patients. An outpatient heart failure diagnosis code was associated with an increased risk of consequent hospitalization for heart failure (hazard ratio [HR]: 12.92, 95% confidence interval [CI]: 12.67–13.17). CKD stage 4 diagnosis code was associated with an increased risk of kidney failure/need for dialysis (HR: 3.75, 95% CI: 3.69–3.81). Dispensation of potassium-removing resins and potassium-binding agents as an intercurrent event was associated with an increased risk of consequent worsening of CKD stage (HR: 4.83, 95% CI: 4.51–5.17). The estimated glomerular filtration rate decline in 295,174 patients with available laboratory data was associated with progressively increased risk of hospitalization for heart failure and kidney failure/need for dialysis.

Conclusions Associations between intercurrent events and clinical outcomes in patients with non-diabetic CKD were investigated, quantified, and ranked using a large set of routinely collected data from a US claims database. Our

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approach may help identify novel surrogate endpoints that occur earlier in the disease course and could be leveraged as indicators of clinical outcomes in CKD research.

Keywords Non-diabetic chronic kidney disease, End-stage kidney disease, Kidney failure, Cardiovascular, Heart failure hospitalization, Intercurrent event, Real-world evidence

Background

Chronic kidney disease (CKD) is a public health concern associated with a high burden of morbidity and mortality, affecting over 840 million people worldwide [1]. CKD-associated complications include anaemia, increased risk of acute kidney injury and kidney failure, and electrolyte abnormalities such as hyperkalaemia and hypocalcaemia/hyperphosphataemia, potentially leading to bone disorders and metabolic acidosis [2, 3]. CKD is also associated with a high risk of cardiovascular complications such as heart failure (HF) and cardiovascular events (i.e., myocardial infarction and stroke) [2, 4].

Although CKD is most often attributed to diabetes, non-diabetic aetiologies contribute to 50–70% of the global CKD burden [5, 6]. It is generally hypothesized that the pathophysiological events and treatment benefits observed in patients with diabetic CKD extend to patients with non-diabetic CKD aetiologies, and involve glomerular hyperfiltration, proteinuria, and interstitial inflammation, eventually leading to fibrosis [5, 7]. The Chronic Renal Insufficiency Cohort (CRIC) study involving over 3,000 adults with CKD in the United States found that diabetic and non-diabetic CKD share common risk factors for disease progression, such as non-Hispanic Black race, lower baseline estimated glomerular filtration rate (eGFR), higher levels of proteinuria, higher systolic blood pressure, and biomarkers including N-terminal pro–B-type natriuretic peptide and urinary neutrophil gelatinase-associated lipocalin [8]. Despite these similarities, the study also identified key differences between CKD aetiologies; plasma C-X-C motif chemokine ligand 12 was associated with an increased risk of diabetic CKD, while low serum bicarbonate and higher high-sensitivity troponin T levels were risk factors observed only among patients with non-diabetic CKD [8]. These differences indicate potential aetiology-specific pathways of CKD progression.

Current therapies for CKD include renin-angiotensin system inhibitors (RASis), as well as sodium-glucose co-transporter-2 inhibitors (SGLT-2is) and mineralocorticoid receptor antagonists (MRAs) on top of RAS inhibition. Their use is based on evidence derived mainly from global clinical trials in patients with CKD and diabetes (for RASi and MRAs), or patients with CKD with and without diabetes (for SGLT-2is) [7, 9–11]. Finerenone, a non-steroidal MRA approved for treatment of patients with CKD and type 2 diabetes on top of RASi, is also currently being investigated in patients with CKD of non-diabetic aetiology, who are at risk of progression [7, 12, 13]. Further research on disease mechanisms, potential risk factors, clinical endpoints, and patient outcomes is needed to gain a better understanding of non-diabetic CKD and its progression, and to further define pharmacological management strategies for patients with CKD of various aetiologies.

Clinical trials in CKD traditionally use clinical endpoints such as kidney failure, doubling of serum creatinine, or substantial percentage decline in eGFR, which are events that occur late in CKD progression [14, 15]. However, some interventions may have a greater effect when administered earlier in the disease course, emphasizing the need to identify alternative endpoints that occur in earlier stages of CKD [15]. This need prompts a growing interest in selecting biomarkers, surrogate endpoints, and overall clinical events that predict commonly used clinical endpoints in CKD studies [14]. Understanding clinical events with implications for patient risk of a clinical outcome downstream may help to identify surrogate endpoints that both occur earlier in the course of the disease and may be subsequently leveraged as indicators of the clinical outcome [16].

In clinical trials, intercurrent events are defined as events that occur after treatment initiation and may either affect the ability to measure the intervention being studied or its interpretation [17]. Examples of intercurrent events include treatment discontinuation, additional medication use, switching treatment arms, or terminal events such as death [18]. In 2017, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) released an addendum to the E9 guideline (ICH E9 R1) to provide statistical principles for handling intercurrent events in clinical studies [18, 19]. While the randomization procedure within a randomized clinical trial aims to evenly distribute all known and unknown confounding factors between the treatment and the control groups, intercurrent events may break this balance and therefore impose great uncertainty into the interpretation of treatment effect estimates. As such, understanding the impact of intercurrent events as early markers of disease progression is important to improve certainty in treatment effects studied in clinical trials.

Within the context of retrospective observational studies, evaluating intercurrent events may be of value to gain an understanding of the progression of disease and the factors associated with clinical endpoints using large volumes of individual patient-level data collected in routine clinical practice. These associations can be investigated and quantified at scale using data-driven techniques.

The retrospective, observational Exploratory analysis oF LongItudinal patiEnt level Data for non-diabEtic chRonic kidney disease (FLIEDER) study investigated a cohort of patients with non-diabetic CKD using routinely collected patient data from the Optum Clinformatics® Data Mart (CDM), a US healthcare claims database. This study demonstrated that patients with non-diabetic CKD are at high risk of severe clinical outcomes such as hospitalization for HF (HHF) and kidney failure [20]. The purpose of the current analysis was to investigate, quantify, and rank associations between intercurrent events and clinical outcomes in patients with non-diabetic CKD. Our approach may help to identify novel surrogate endpoints that occur earlier in the disease course and may serve as indicators of clinical outcomes in future CKD research.

Methods

Study design

The study design and details of the patient selection criteria, including characterization of index event and outcomes, have been published in detail previously [20]. The Optum CDM healthcare claims database is representative of the insured US population with respect to age, gender, and region, and is composed of the commercial health plan and Medicare Advantage data sets. This database was used to retrospectively identify adults (≥18 years at index) with non-diabetic, moderate-to-severe CKD (stages 3/4), as defined by International Classification of Diseases (ICD)-9/10 codes or laboratory values (eGFR 15–59 mL/min/1.73 m^2) confirmed by a second ICD code or eGFR value between 90 and 365 days apart. If both ICD code and eGFR value were recorded on the same day, eGFR value was given priority. The date of the confirmed CKD diagnosis was defined as cohort inclusion date or index date. In addition, included patients had to have ≥365 days of continuous insurance coverage prior to the index event (baseline period). Individuals were excluded for having a diagnosis or procedure code for CKD stage 5, end-stage kidney disease, unspecified or acute kidney failure, or kidney transplant prior to index; or for receiving dialysis as per a diagnosis or procedure code in the baseline period. Patient baseline characteristics such as age, sex, comorbidities, and use of co-medications were assessed at the index date or from the last recorded value within the baseline period. Additional details on the data available from the Optum CDM database are provided in the Supplementary Methods section of Supplementary Material 1.

Clinical outcomes

Patients were followed from 1 day after the index event until insurance disenrollment, the end of data availability, death, or the end of the analysis period, whichever occurred first. This defined the follow-up period for each patient. The clinical outcomes of the study were evaluated previously, and in the intercurrent event analysis presented here: 1) HHF; 2) a composite of kidney failure/need for dialysis; and 3) worsening of CKD stage from baseline [20]. The composite outcome of kidney failure/need for dialysis included diagnosis codes for CKD stage 5, end-stage kidney disease, and unspecified or acute kidney failure. The term *kidney failure* is used here to address all the listed conditions based on guideline recommendations [21]; however, this does not include dialysis. A list of diagnosis and procedure codes has been published previously [20].

Intercurrent event definition and selection

In this study, an intercurrent event was defined as an event observed in patient medical or pharmacy claims after the index date (confirmed CKD diagnosis) that either precluded a clinical outcome of interest or was associated with a modified risk of the respective outcome. An estimation of the effect of intercurrent events on the hazard rate of the clinical outcomes was performed. The analysis focused on formal quantification of association between an intercurrent event and a clinical outcome.

Intercurrent events were either selected a priori based on subject-matter expertise or were investigated in a data-driven exploratory manner with an exhaustive search through all possible clinical events recorded in patient medical and pharmacy claims. In the former case, a knowledge-driven approach was used to investigate and quantify the association between eGFR decline (≥30%, ≥40%, and ≥57%) post CKD diagnosis and the clinical outcomes of HHF and kidney failure/need for dialysis. In the latter case, the data-driven exploratory analysis was performed to measure associations between non-prespecified intercurrent events and 3 study outcomes of HHF, kidney failure/need for dialysis, and worsening of CKD stage from baseline in non-diabetic CKD. All data in patient medical and pharmacy claims in the Optum CDM database representing variables that could serve as intercurrent events and could have an association with clinical outcomes were initially included. Variables with a frequency of appearance in < 0.1% of patients in the study cohort were not considered for the analysis

of intercurrent events. Additional details on the knowledge-driven and data-driven approaches are provided in the Supplementary Methods section of Supplementary Material 1.

Statistical analysis

Analysis of association between intercurrent events and clinical outcomes was performed using a Cox proportional hazards regression model as per R package "rms" version 5.1–4 for the following derived time-to-event dataset consisting of two subsets: 1) 'Control' subset: all cohort patients from the start of the follow-up period until the clinical outcome, the intercurrent event, or the end of the follow-up period, whichever came first; 2) 'Exposed' subset: all cohort patients with an intercurrent event from the first intercurrent event until the clinical outcome or the end of the follow-up period. Further occurrences of the respective intercurrent event were ignored. For patients with an intercurrent event, the patient was retained in both the 'Control' and the 'Exposed' subsets. Hazard ratios (HRs) and 95% confidence intervals (CIs) for a given clinical outcome were calculated comparing patients with and without an intercurrent event (shown in Fig. 1). The HR was interpreted as a weighted average of the ratio of time-varying hazard rates of the 'Control' and the 'Exposed' subsets over the entire follow-up period [22]. Volcano plots were generated to depict HRs and the respective *p*-values for each intercurrent event and associated clinical outcome. The strength of the association between an intercurrent event and a clinical outcome was ranked by ascending *p*-values first, followed by descending absolute *log*(HR) values. To verify the suitability of the Cox proportional hazards regression model approach in assessing the association between intercurrent events and clinical outcomes, sensitivity analyses were conducted as detailed in the Supplementary Methods section of Supplementary Material 1.

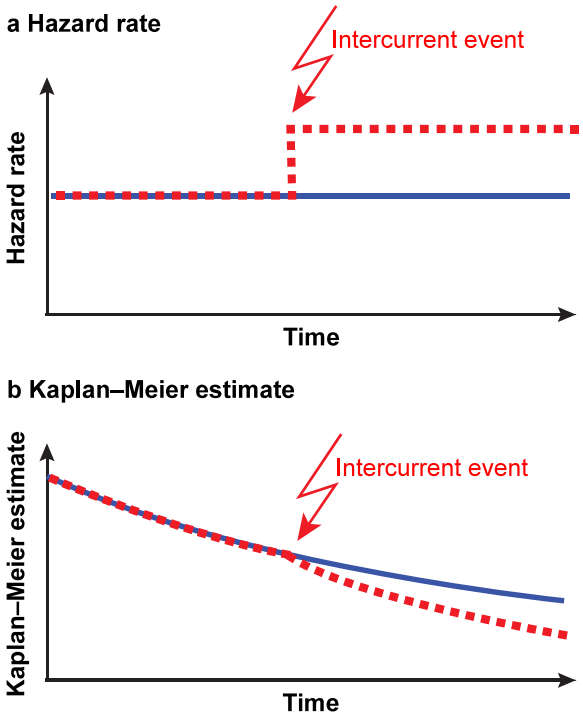

Fig. 1 Illustration of the risk of clinical outcome after an intercurrent event. **a** Hazard rate; **b** Kaplan–Meier estimate

Results

Patient cohort

Of approximately 64 million patients in the database, 1.41 million adults (aged ≥ 18 years) were classified as having CKD stage 3 or 4. There were 504,924 patients in the final study cohort with diagnosis for non-diabetic, moderate-to-severe CKD who met all the eligibility criteria of the study (Fig. 2) [20]. Among these patients, 56% were included based on a CKD diagnosis code at index, and 44% were included based on the available eGFR measurements. Patient baseline characteristics and clinical outcomes have been reported previously [20]. Briefly, median age was 75.0 years, and most patients were female (60.5%) and White (62.5%) and had CKD stage 3 at index (94.7%), with a median eGFR at baseline of 53.0 mL/min/1.73 m^2. The median follow-up period was 744 (interquartile range 328–1,432) days. The incidence rates of the clinical outcomes were 4.0 events/100 patient-years (PY) for HHF, 10.3 events/100 PY for the composite outcome of kidney failure/need for dialysis, and 4.4 events/100 PY for worsening of CKD stage from baseline. The number of patients with ≥ 1 baseline eGFR value and a non-zero follow-up time was 295,174. This group of patients was investigated in the intercurrent event analysis of association between the eGFR decline and the clinical outcomes of HHF and kidney failure/need for dialysis. Of the 504,924 patients from the main study cohort, 504,869 were included in the data-driven exploratory intercurrent event analysis (55 patients excluded because of database inconsistencies and 182 patients excluded because of 0 days follow-up).

eGFR decline as intercurrent event for HHF and kidney failure/need for dialysis

Among 295,174 patients with a baseline eGFR value and a non-zero follow-up time, 13,798 (4.7%), 6,670 (2.3%), and 2,076 (0.7%) had an intercurrent event of eGFR decline ≥ 30%, ≥ 40%, and ≥ 57%, respectively, prior to the HHF outcome [20]. Each of these intercurrent events was associated with an increased risk of HHF among patients with ≥ 30% eGFR decline (HR: 3.6, 95%

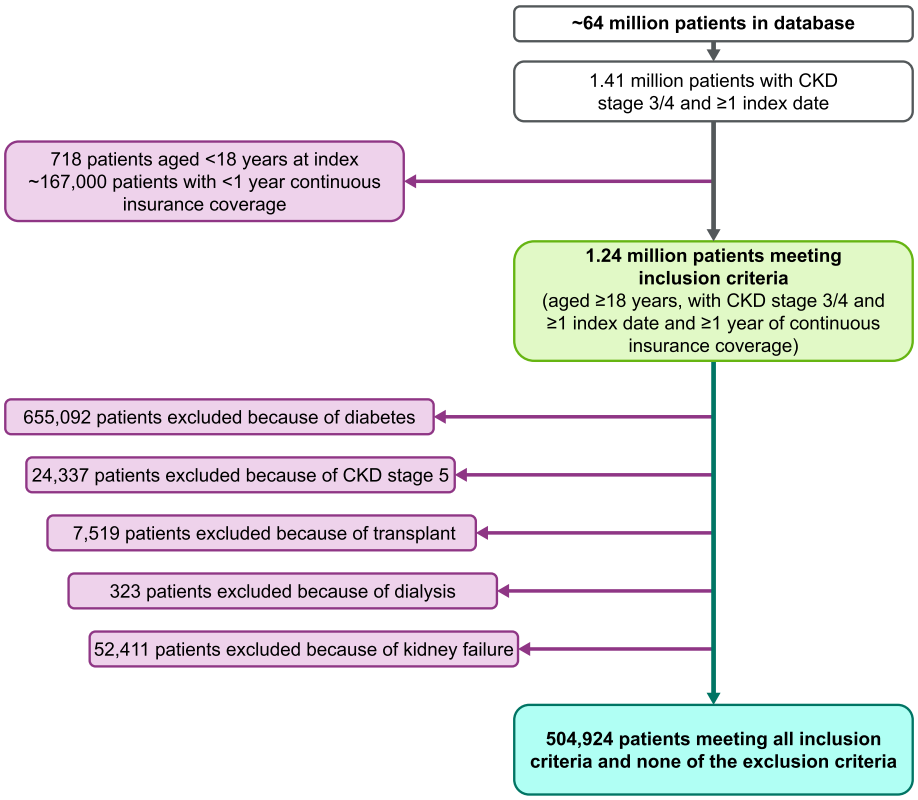

Fig. 2 Patient flowchart. CKD, chronic kidney disease

CI: 3.5–3.8), ≥ 40% eGFR decline (HR: 4.0, 95% CI: 3.7–4.2), and ≥ 57% eGFR decline (HR: 4.4, 95% CI: 3.9–4.9) compared with patients without such an event (Fig. 3a). Among patients with kidney failure/need for dialysis outcome, 9,786 (3.3%), 4,093 (1.4%), and 841 (0.3%) had an intercurrent event of eGFR decline ≥ 30%, ≥ 40%, and ≥ 57%, respectively [20], each of which was associated with an increased risk of the kidney outcome (≥ 30% eGFR decline: HR: 6.4, 95% CI: 6.2–6.6; ≥ 40% eGFR decline: HR: 9.2, 95% CI: 8.7–9.7; ≥ 57% eGFR decline: HR: 20.2, 95% CI: 17.3–23.6; Fig. 3b).

Data-driven exploratory approach

From the initial set of more than 540,000 variables, including diagnosis, medical procedure, and drug codes, 3,801 variables with a frequency of appearance in ≥ 0.1% of patients in the study cohort defined a set of intercurrent events. This set included 3,419 diagnosis-based variables, 214 procedure-based variables, and 168 medication-based variables (Supplementary Material 2).

Intercurrent events for HHF

In the overall cohort, the results of the data-driven exploratory intercurrent event analysis for the clinical outcome of HHF showed that HF (HR: 12.92, 95% CI: 12.67–13.17) defined by a broad list of ICD-9/10 codes found on the outpatient claims, and a diagnosis code "heart failure, unspecified" (HR: 10.06, 95% CI: 9.87–10.25) defined by a narrow list of ICD-9/10 codes found on the outpatient claims, were the intercurrent events most strongly associated with the subsequent HHF (shown in Fig. 4a and Table S1 in Supplementary Material 1, which also contains the diagnosis codes). Pulmonary-/respiratory-related diagnoses, such as pleural effusion (HR: 8.84, 95% CI: 8.57–9.11), acute pulmonary oedema (HR: 8.54, 95% CI: 7.99–9.12), and acute/chronic respiratory failure with hypoxia (HR: 8.16, 95% CI: 7.73–8.63), were also associated with high risk of HHF (shown in Fig. 4a and Table S1 in Supplementary Material 1). Dispensation of loop diuretics as an intercurrent event was strongly associated with the subsequent HHF compared with patients without dispensation of loop diuretics (HR: 5.29, 95% CI: 5.20–5.39). Dispensations of other medications, such as cardiac glycosides, antiarrhythmic agents, and oral anticoagulants, were top-ranked, therapeutic class-related intercurrent events associated with HHF (Supplementary Material 2). Medical procedures such as routine chest X-rays, respiratory intubation, incision of pleura, and haemodialysis were top-ranked, procedure-related intercurrent events associated with

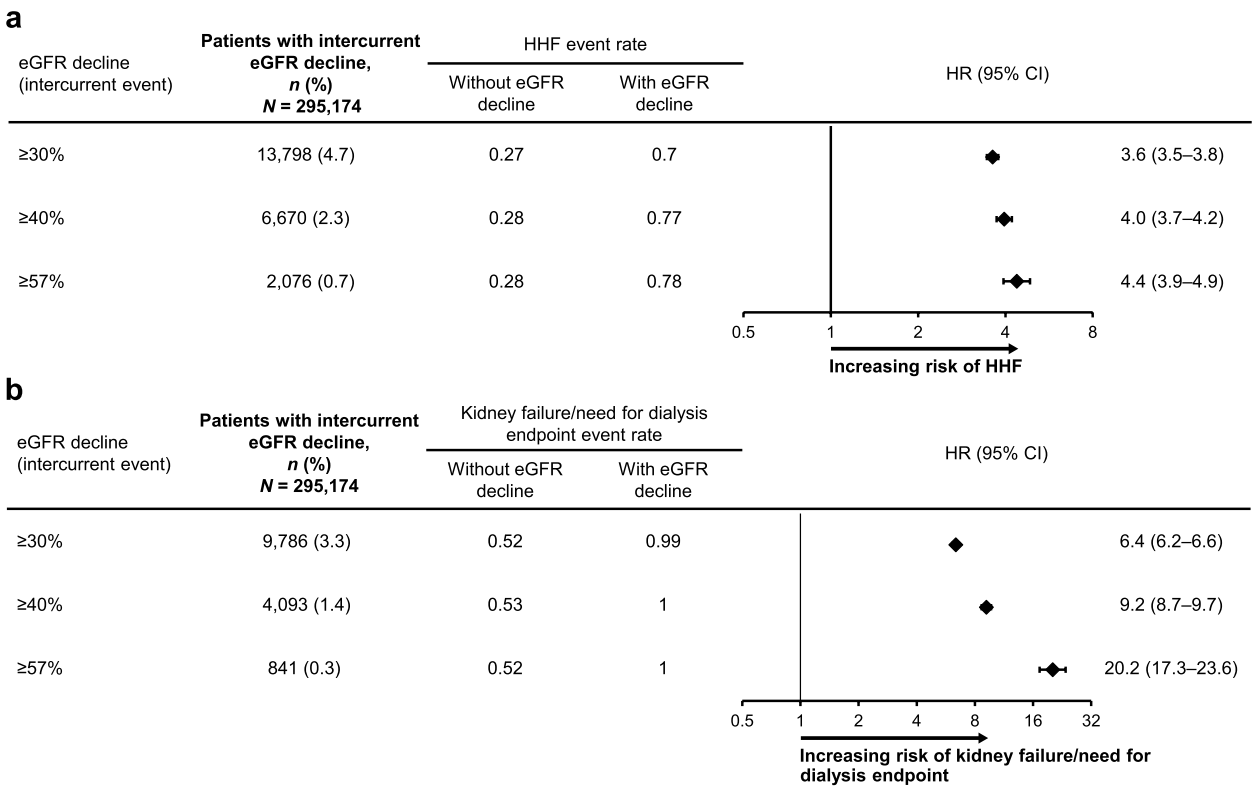

Fig. 3 eGFR decline as an intercurrent event. **a** HHF; **b** Composite outcome of kidney failure/need for dialysis. CI, confidence interval; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio

the subsequent HHF (Supplementary Material 2). Intercurrent events that were most strongly associated with a reduced risk (HR < 1) of subsequent HHF included encounters for routine gynaecological examination, mammography, and screening for malignant neoplasms (Fig. 4a and Table S1 in Supplementary Material 1).

Intercurrent events for kidney failure/need for dialysis

In the overall cohort, the data-driven exploratory analysis of intercurrent events for the composite kidney outcome demonstrated that CKD stage 4 defined by the ICD-9/10 code (HR: 3.75, 95% CI: 3.69–3.81) was the intercurrent event most strongly associated with the subsequent kidney failure/need for dialysis (shown in Fig. 4b and Table S2 in Supplementary Material 1). Diagnoses of acute/chronic respiratory failure with hypoxia (HR: 3.65, 95% CI: 3.43–3.88), pleural effusion (HR: 3.51, 95% CI: 3.41–3.62), ascites (HR: 3.10, 95% CI: 2.95–3.27), and acidosis (HR: 3.05, 95% CI: 2.94–3.17) were also associated with a high risk of the subsequent kidney failure/need for dialysis. Dispensation of potassium-removing resins and potassium-binding agents (HR: 3.20, 95% CI: 3.02–3.39) as recorded on patient pharmacy claims showed strong association with the composite kidney outcome (Table S2 in Supplementary Material 1), followed by loop diuretics and antiarrhythmic agents (Supplementary Material 2). Medical procedures such as blood transfusion, routine chest X-rays, home health services, and vascular catheterization were top-ranked, procedure-related intercurrent events associated with a high risk of subsequent kidney failure/need for dialysis (Supplementary Material 2). Intercurrent events with the strongest association with a reduced risk (HR: < 1) of kidney failure/need for dialysis included encounters for screening for malignant neoplasms, including mammograms, routine gynaecological examinations, and general medical examinations (Fig. 4b and Table S2 in Supplementary Material 1).

Intercurrent events for worsening of CKD stage

The data-driven exploratory analysis on the main study cohort discovered that the intercurrent event most strongly associated with the subsequent worsening of CKD stage was dispensation of potassium-removing resins and potassium-binding agents (HR: 4.83, 95% CI: 4.51–5.17) (shown in Fig. 4c and Table S3 in Supplementary Material 1). Other intercurrent events strongly associated with worsening of CKD stage outcome included polycystic kidney disease (HR: 4.56, 95% CI: 4.25–4.90), anaemia in CKD (HR: 4.36, 95% CI: 4.26–4.47), acidosis

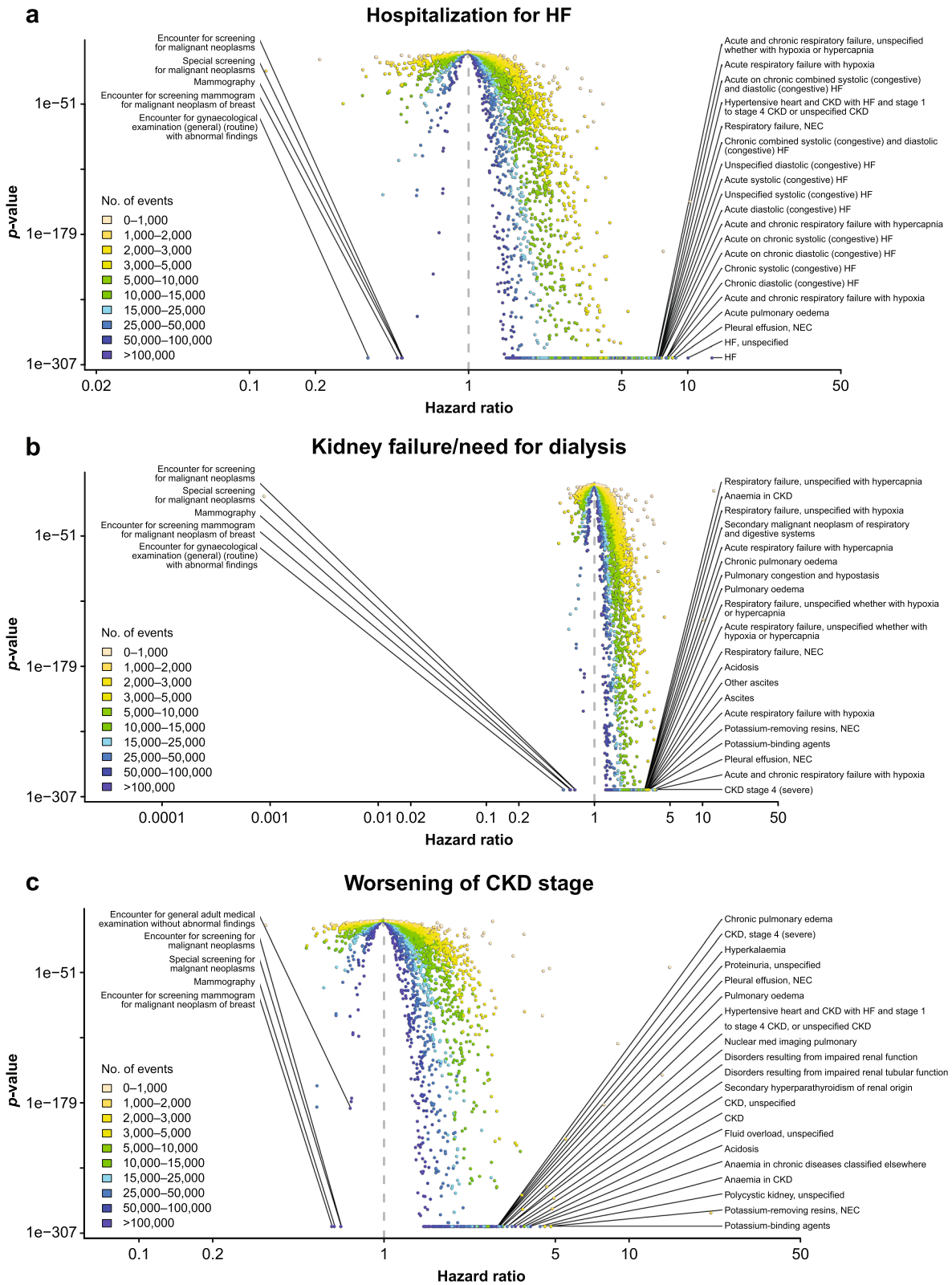

Fig. 4 Volcano plots. **a** Hospitalization for HF; **b** Kidney failure/need for dialysis; **c** Worsening of CKD stage. CKD, chronic kidney disease; HF, heart failure; NEC, not elsewhere classified

(HR: 3.90, 95% CI: 3.76–4.04), and fluid overload (HR: 3.76, 95% CI: 3.54–3.99; Table S3 in Supplementary Material 1). Dispensations of loop diuretics, vitamin D, hypotensive agents, and antigout agents were further top-ranked, therapeutic class-related intercurrent events associated with worsening of CKD outcome (Supplementary Material 2). Medical procedures such as pulmonary imaging, blood transfusion, ultrasounds of the abdomen or heart, vascular catheterization, and routine chest X-rays were among those with the top increased risk (HR > 1) of worsening of CKD stage (Supplementary Material 2). Intercurrent events with the strongest association with a reduced risk (HR < 1) of worsening of CKD stage included encounters for screening for malignant neoplasms, including mammograms, general medical examinations, and routine gynaecological examinations (Fig. 4c and Table S3 in Supplementary Material 1), similar to the two outcomes above.

Sensitivity analyses

As detailed in the Supplementary Results section and Table S4 in Supplementary Material 1, the results of the sensitivity analyses using a bootstrapping approach and log-rank test were consistent with those obtained in the main Cox regression analysis.

Discussion

The current study aimed to explore and quantify associations between intercurrent events and selected cardiorenal clinical outcomes in patients with non-diabetic CKD treated in routine clinical practice in the United States. The results obtained may be of value to understand the impact of intercurrent events that may serve as surrogate markers or early risk factors associated with the consequent clinical outcomes. The generated real-world evidence can be useful to develop statistical testing strategies and to select intercurrent events for future clinical trials in non-diabetic CKD, as well as for assessing individual risks of the clinical outcomes [17, 23–25].

The results of the knowledge-driven analysis not only confirmed but also quantified the association between eGFR decline and selected cardiorenal outcomes in patients with non-diabetic CKD, with larger decreases in eGFR resulting in a progressively stronger association with the risk of the analysed outcomes. This is in line with expectations and with previous evidence showing that CKD progression and eGFR decline are associated with higher risks of HHF, kidney failure, and death in diabetic and non-diabetic CKD [3, 20, 26, 27]. An observational study in patients with CKD and type 2 diabetes also identified that cardiovascular intercurrent events were associated with kidney failure, further demonstrating the relationship between kidney and cardiovascular diseases [28]. An eGFR decline of ≥ 40% has been accepted by the US Food and Drug Administration and European Medicines Agency as a surrogate kidney endpoint in CKD trials; however, in its analysis of clinical trial populations, approximately 40% of included patients had diabetic CKD [29]. Our findings may add to the pool of evidence on eGFR decline as a surrogate endpoint among patients with a non-diabetic CKD aetiology.

Results from the data-driven exploratory analyses indicated that pulmonary and respiratory dysfunction diagnoses as intercurrent events were associated with all three investigated cardiorenal outcomes; for instance, a diagnosis of pulmonary oedema was associated with an increased risk (HR ≥ 3.0) for all three outcomes. This is likely because of the pathophysiologic interplay between the respiratory, cardiovascular, and renal systems in CKD, with the presence of inflammation, endothelial damage and dysfunction, altered haemodynamic regulation, and uremic toxins in CKD contributing to further pulmonary dysfunction and remodelling [30]. Furthermore, a meta-analysis of observational studies has shown that pulmonary hypertension was associated with an increased risk of cardiovascular events in patients with CKD [31]. Nevertheless, it is worth nothing that, like the current study, this meta-analysis did not identify a causal relationship, but associations, between variables and the risk of a certain outcome.

The data-driven exploratory analyses results also showed that, as would be expected, an HF diagnosis in an outpatient setting was the intercurrent event that was most strongly associated with subsequent HHF. Dispensation of loop diuretics was also associated with an increased risk of HHF. Diuretics, including loop diuretics, are indicated for treatment of congestion among patients with HF [32]. The association found in this study is supported by findings from an observational cohort study involving patients with suspected or confirmed HF, which showed that the use of loop diuretics to treat congestion was associated with adverse outcomes, including HHF [33].

This study also revealed a strong association between a diagnosis of CKD stage 4 and kidney failure/need for dialysis. This is consistent with the findings of a meta-analysis involving participants from the multinational CKD Prognosis Consortium, which showed that a diagnosis of CKD stage 4 (eGFR 15–29 ml/min/1.73 m^2) was strongly associated (HR > 280) with kidney failure requiring kidney replacement therapy among patients with or without albuminuria [34]. Additionally, the dispensation of potassium-removing resins and potassium-binding agents was associated with both the kidney failure/need for dialysis and worsening of CKD stage outcomes. CKD is associated with dysregulation of serum potassium [35, 36], with

an increased risk of hyperkalaemia with decreasing eGFR [35–37]. Moreover, some CKD therapies increase the risk of hyperkalaemia [38, 39]. The increased frequency of dispensation of potassium-removing resins and potassium-binding agents is, therefore, likely to be expected as patients' CKD progresses.

Furthermore, the data-driven analyses results showed that routine medical procedures, such as screening for malignant neoplasms, gynaecological examinations, and general medical examinations, were found to be associated with a lower risk of the subsequent cardiorenal clinical outcomes. These findings can possibly be explained by the fact that patients who make use of preventive care and who are carefully monitored can receive early diagnosis and appropriate treatment, and hence may be better protected against severe clinical outcomes [40].

In this analysis of real-world data from the FLIEDER study, we presented an approach on how to identify and measure the effect of intercurrent events associated with subsequent clinical outcomes in a retrospective, observational setting. We have demonstrated how subject-matter expertise and data-driven "unsupervised" approaches can be instrumental for quantification and discovery of new associations between sequential clinical events in non-diabetic CKD.

For both the knowledge-driven and data-driven analyses, a univariate Cox proportional hazards regression model was used, although it was expected that the HR might vary over the follow-up period. The HR was interpreted as a weighted average of the ratio of time-varying hazard rates of the two groups over the entire follow-up period [22]. A sensitivity analysis conducted in the knowledge-driven analysis showed that similar results were obtained using Cox regression and a bootstrapping method. In the data-driven exploratory analyses, it was not feasible to apply the bootstrapping method in all runs due to the large number of intercurrent events to be investigated and the respective computational demand. However, a sensitivity analysis with a log-rank test was conducted that demonstrated highly significant *p*-values for all top results reported in this study. Together, the results of these additional analyses support the appropriateness of the method employed for assessing and ranking intercurrent events in the current study.

In future clinical trials, a better understanding of the association between intercurrent events and clinical outcomes in patients with non-diabetic CKD will enable researchers to identify relevant events and design trials with appropriate strategies to account for their impact on clinical endpoints in this population. The findings of the current study contribute to this understanding. Moreover, the results reported herein may be used to guide future research on selected intercurrent events of interest.

Limitations

Although this analysis was conducted on a robust and diverse sample of patients with non-diabetic CKD, there are some limitations to be acknowledged. Firstly, because of the nature of claims data that are collected for administrative and not research purposes, some missing data, including laboratory results or over-the-counter medications, as well as mis- or underreported data, are expected and cannot be ruled out. Furthermore, the mean follow-up period of 744 days is relatively short for investigation of progressive CKD. Together, this may result in underestimation of the impact of intercurrent events on clinical outcomes. Secondly, the effect of recurrent intercurrent events on clinical outcomes was not investigated; however, the frequency of such events may modify the risk of the consequent events substantially. This is subject to future investigations. Thirdly, the presented analysis did not address competing risks because of the complexity of statistical methods required to adjust for those risks. The findings of the study shall be interpreted as associations between clinical events that do not inform causality. Lastly, although the approach described in this paper can be applied to other therapeutic areas, the results obtained here can be used only for intercurrent events analysis of selected cardiorenal outcomes in patients with stage 3/4 non-diabetic CKD. The results should not be projected to patient populations outside of the cohort herein described.

Conclusions

This analysis used a large sample of patients with non-diabetic CKD from a US healthcare claims database to identify and quantify association between a wide range of intercurrent events and clinical outcomes commonly measured in CKD. In line with the overall FLIEDER study objective to gain a better understanding of non-diabetic CKD, the presented findings also provide important insights that confirm and quantify associations between widely used surrogate endpoints based on eGFR and cardiorenal outcomes. Overall, the reported findings may contribute to a better understanding of the associations between a broad variety of intercurrent events and cardiorenal outcomes studied in clinical trials, allowing for adequate measures to adjust for such events. The results may inform further clinical and patient outcomes research of CKD.

Abbreviations

CKD	Chronic kidney disease
CDM	Optum Clinformatics® Data Mart database
CI	Confidence interval

FLIEDER	Exploratory analysis oF LongItudinal patiEnt level Data for non-diabEtic chRonic kidney disease
eGFR	Estimated glomerular filtration rate
HF	Heart failure
HHF	Hospitalization for heart failure
HR	Hazard ratio
ICD	International Classification of Diseases
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
PY	Patient-years

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04021-6.

Supplementary Material 1. Supplementary Methods, Results from intercurrent event analysis of HHF outcome, composite outcome of kidney failure/need for dialysis, and outcome of worsening CKD stage from baseline (top 40 results), and Results of the sensitivity analyses.

Supplementary Material 2. Results from intercurrent event analysis of HHF outcome, composite outcome of kidney failure/need for dialysis, and outcome of worsening CKD stage from baseline (full set of results, including codes used to define intercurrent events).

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Authors' contributions

CW was involved in the conceptualization and supervision of the manuscript. JS and CB were involved in the formal analysis and investigation and in preparation of the original draft of the manuscript. MB was involved in the conceptualization and preparation of the original draft of the manuscript. FK was involved in the conceptualization, formal analysis and investigation, preparation of the original draft, resources, and supervision of the manuscript. TV was involved in the conceptualization, preparation of the original draft, funding acquisition, resources, and supervision of this manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability

The data that support the findings of this study are available from Optum Insights Life Science, Inc under a license to Bayer AG for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Optum Insights Life Science, Inc and Bayer AG.

Declarations

Ethics approval and consent to participate

Data used in this study were obtained from Optum® under a license to Bayer AG and are not publicly available. Data included in the Optum CDM database are de-identified and are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 to preserve participant anonymity and confidentiality, and as such this study followed the principles of the declaration of Helsinki without the requirement for review from a formal ethics review committee. The use of the provided Optum® data was determined by the New England Institutional Review Board (IRB) to not constitute research involving human subjects and was therefore exempt from board oversight.

Consent for publication

Not applicable.

Competing interests

CW reports advisory board and lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GSK, MSD, and Novo Nordisk. JS and CB are employees of MicroDiscovery GmbH, Berlin, Germany. MB is an employee of Bayer AG, Wuppertal, Germany. FK is an employee of Bayer AG, Berlin, Germany. TV was an employee of Bayer AG, Berlin, Germany at the time the study was performed and owns shares in Bayer AG. TV is now an employee of Boehringer Ingelheim Pharma GmbH & Co KG.

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