STUDY REPORT SYNOPSIS

REVEAL-CKD: Prevalence and Consequences of Undiagnosed Chronic Kidney Disease

A multinational observational study to determine the prevalence and consequences of undiagnosed chronic kidney disease

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Milestones:

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Final Study Protocol	02 December 2020
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Background/Rationale

A diagnosis of chronic kidney disease (CKD) occurs predominantly during advanced disease (stages 4, 5) when there are few opportunities to delay further progression and avoid complications. Detection of CKD to optimise patient outcomes requires active screening and monitoring in the early stages, especially in at-risk asymptomatic patients, such as those with existing type 2 diabetes mellitus (T2DM) and treatment-resistant hypertension (TRH). Early disease interventions can slow CKD progression, which may ultimately translate into significant cost savings and, more importantly, reduce the risk of complications and the number of patients developing end-stage kidney failure. Low diagnosis rates of CKD at early stages have been reported in the United States (US), but this has not been broadly studied in other countries. Moreover, the demographic and clinical predictors of undiagnosed CKD remain undetermined.

Objectives

Primary Objectives

1. To estimate the prevalence of undiagnosed stage 3 CKD (proportion of patients with estimated glomerular filtration rate [eGFR] measurements indicating stage 3 CKD with no corresponding CKD diagnostic code before or up to six months after the second abnormal eGFR value).
2. To describe time to CKD diagnosis in patients with no prior CKD diagnosis code at index date (time of second qualifying eGFR), overall and by patient characteristics.

Secondary Objectives

1. To describe the prevalence of undiagnosed stage 3 CKD by calendar year.
2. To describe baseline characteristics (at index date) among those with undiagnosed versus diagnosed stage 3 CKD.
3. To assess CKD management and monitoring practices (post-index date) in patients with diagnosed versus undiagnosed stage 3 CKD.

Exploratory Objectives

1. To describe the risk of selected adverse clinical outcomes longitudinally among those with undiagnosed versus diagnosed stage 3 CKD.
2. To describe healthcare resource use (HCRU) associated with undiagnosed versus diagnosed stage 3 CKD.
3. To assess the association between the timing of the CKD diagnosis and the risk of selected adverse clinical outcomes and HCRU in patients with no CKD diagnosis code prior to the index date.
4. To describe the healthcare costs associated with undiagnosed versus diagnosed stage 3 CKD (for outcomes identified in exploratory objectives 1–2).
5. To describe eGFR and CKD stage among Black and non-Black patients when using:
    a. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with race modification.
    b. CKD-EPI equation without race modification.
    c. A recently developed eGFR equation that omits race entirely.

Methods

Study Design

A multinational, non-interventional, observational study was conducted using 13 databases across 11 countries, including the US (three databases), Italy, Japan, France, Germany, the United Kingdom (UK), Spain, Australia, Brazil, Canada and China. A series of cohort studies was conducted to assess the prevalence of undiagnosed stage 3 CKD using eGFR laboratory measurements and diagnostic codes. The study also assessed the current state of CKD management and the risk of selected adverse clinical outcomes and HCRU associated with undiagnosed stage 3 CKD.

Data Source

This study was conducted using claims data and electronic medical records (EMRs) across 11 countries in the following databases: TriNetX, Humana, and Limited IBM MarketScan Explorys Claims-EMR Data Set (LCED) in the US; IQVIA Longitudinal Patient Data (LPD) in Italy; Real-World Data (RWD) in Japan; Cegedim The Health Improvement Network (THIN) in France; Disease Analyzer in Germany; Clinical Practice Research Datalink (CPRD) Aurum in the UK; BIG-PAC in Spain; PenCS database in Australia; United States Pharmacopeia (USP) in Brazil; Canadian Primary Care Sentinel Surveillance Network (CPCSSN) in Canada; and the China Renal Data System (CRDS) database in China. These databases record outpatient and/or inpatient care data.

Study Population

This study included all patients ≥18 years old with two consecutive eGFR laboratory measurements indicating stage 3 CKD (eGFR ≥30 and <60 mL/min/1.73m^2 using CKD-EPI [preferred] or Modification of Diet in Renal Disease [MDRD] equation) recorded at least three months apart during the observation period (from 2015 onwards). The date of the second qualifying eGFR measure (i.e., meeting the criteria for stage 3 CKD definition) was considered the index date. A subset of the study population with no diagnosis code for CKD any time prior to the study index date was identified for assessing study primary objective 2. An additional subset of the study population for whom race data were available was identified for assessing study exploratory objective 5.

Inclusion Criteria

Patients were included if they met the following criteria:

1. At least two consecutive eGFR laboratory tests with values ≥30 and <60 mL/min/1.73m^2 (Stage 3A or 3B) that are >90 and ≤730 days apart (defining stage 3 CKD) from 2015 onwards.
2. At least 12 months of continuous presence in the database or registration in the data prior to the first qualifying eGFR measure defining stage 3 CKD.
3. Aged ≥18 years at index date.

Exclusion Criteria

Patients were excluded if they met the following criteria:

1. Solid organ transplant before the study index date.
2. Any evidence of advanced CKD (stages 4, 5) based on CKD diagnostic codes or renal replacement therapy before the index date.
3. No or <6 months of follow-up data after the second qualifying eGFR measure.

Statistical Methods

The prevalence of undiagnosed stage 3 CKD was calculated in each database over the available data period which varies according to database. The prevalence numerator included all patients who fulfilled the undiagnosed stage 3 CKD case definition at any time during the observation period available per database. Undiagnosed stage 3 CKD cases were defined as those with eGFR measurements indicating stage 3 CKD (i.e., at least two consecutive eGFR values ≥30 and <60 mL/min/1.73m^2 that are >90 and ≤730 days apart) with no corresponding CKD diagnostic code (e.g., based on International Classification of Diseases, Ninth or 10th Revision [ICD-9/10]) at any time during the ≥12-month look-back period before the first qualifying eGFR measurement and up to six months after index date. Those fulfilling this definition (i.e., with laboratory evidence of stage 3 CKD) with a documented diagnosis code of CKD during this time period were considered as diagnosed stage 3 CKD patients. The prevalence denominator included all individuals included in the study (i.e., who fulfilled the criteria for inclusion in the study; designate cohort 1). Prevalence was estimated by dividing the numerator by the denominator, and 95% confidence intervals (CIs) were estimated using a binomial distribution. Furthermore, annual prevalence of undiagnosed stage 3 CKD was assessed during the study observation period available in each database by calendar year of the index date. Prevalence was also calculated among subgroups of patients based on age, sex, and the presence of key baseline comorbidities. For those with no CKD diagnosis code on or before the index date (designate cohort 2), time to CKD diagnosis was assessed using a Kaplan-Meier (KM) curve. Furthermore, median and interquartile range (IQR) of the time to CKD diagnosis was computed among patients of this cohort 2 who were diagnosed after index date (non-KM analysis). This was a post-hoc analysis, given that the median time to CKD diagnosis estimates from the KM analysis was indeterminate in many databases due to more than 50% of the undiagnosed CKD patients at index date remaining clinically undiagnosed by the end of the study follow-up period. Unless otherwise specified, the non-KM analysis results are provided in this report. Baseline characteristics at index were described among undiagnosed versus diagnosed stage 3 CKD patients. The proportion of patients achieving each of the CKD management quality indicators (Qi); specified in the study statistical analysis plan (SAP) were described among undiagnosed and diagnosed stage 3 CKD patients, overall, and by comorbidities.

Exploratory objectives were initially assessed in the US, Japan, and Spain. Data analyses were performed using a stepwise approach, where the objectives pertinent to describing the undiagnosed stage 3 CKD cohort were performed first, and results were reviewed by the study team before the analysis on the rest of the objectives took place. Risk of selected adverse clinical outcomes and HCRU were described for patients with diagnosed and undiagnosed stage 3 CKD. For those with no CKD diagnosis code on or before the index date, associations between the timing of CKD diagnosis and adverse clinical outcomes were estimated from the index date using Cox regression analysis. Exploratory objective 5 was first assessed in the US TriNetX database where patients' race was recorded, and other countries and databases were considered

based on the availability of these data.

Results

In nearly all databases, a vast majority of cases with laboratory evidence of stage 3 CKD did not have a recorded diagnostic code for CKD. Prevalence estimates of undiagnosed stage 3 CKD over the observation period available in each database ranged from 32.1% to 97%. The estimated prevalence of undiagnosed stage 3 CKD was 61.6% and 64.2% in the US (LCED and TriNetX databases, respectively) to >80.0% in Germany (IQVIA's Disease Analyzer database, 84.2%), Spain (BIG-PAC database, 84.9%), Japan (Japan RWD, 92.0%), France (Cegedim THIN database, 95.5%), Australia (PenCS General Practitioner-EMR, 90.0%), Brazil (USP database, 97.1%), and Canada (CPCSSN database, 92.0%). In Italy, the estimated prevalence was 76.9%. In China (CRDS database) the estimated prevalence was 71.6%. In the UK (CPRD Aurum database) and the Humana database in the US, the estimated prevalence of undiagnosed stage 3 CKD was 56.8% and 32.1%, respectively. The lowest prevalence of undiagnosed stage 3 CKD observed in the Humana database could be explained at least in part by the specific population covered in this database, which included an elderly population (65+ years old) beneficiaries of Medicare Advantage Plans, and those having private insurance.

Table 11: Estimated prevalence of undiagnosed stage 3 CKD in the 12 databases from the 10 study participating countries between 2015-2022.

Country	Database	Prevalence of Undiagnosed Stage 3 CKD	95% CI
US	TriNetX (2015-2020)	64.28%	64.09%, 64.46%
	Humana (2017-2019)	32.10%	31.92%, 32.28%
	LCED (2015-2019)	61.62%	60.98%, 62.25%
Italy	IQVIA LPD (2015-2020)	76.96%	76.64%, 77.29%
Japan	Japan RWD (2015-2020)	92.07%	91.89%, 92.25%
France	THIN (2015-2020)	95.54%	95.26%, 95.83%
Germany	IQVIA Disease Analyzer (2019-2021)	84.27%	83.84%, 84.71%
UK	CPRD (2015-2020)	56.86%	56.61%, 57.11%
Spain	BIG-PAC (2015-2020)	84.90%	84.51%, 85.29%
Australia	PenCS GP-EMR (2016-2022)	90.03%	88.27%, 91.79%
Brazil	USP (2015-2022)	97.01%	96.68%, 97.31%
Canada	CPCSSN (2015-2021)	91.97%	91.72%, 92.21%
China	CRDS (2015-2020)	71.59%	71.12%, 72.07%

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CPCSSN = Canadian Primary Care Sentinel Surveillance Network; CPRD = Clinical Practice Research Datalink; CRDS = China Renal Data System; EMR = electronic medical record; GP = general practitioner; LCED = Limited IBM MarketScan Explorys Claims; EMR Data Set; LPD = Longitudinal Patient Data; RWD = real-world data; THIN = The Health Improvement Network; UK = United Kingdom; US = United States; USP = United States Pharmacopeia

Between 2015 and 2022, the estimated prevalence of undiagnosed stage 3 CKD per calendar year remained stable and consistent in each database/country with overlapping 95% CIs of the estimates across the years.

Stage 3 CKD appeared consistently more underdiagnosed in women than in men in all databases across countries and regions, with an estimated prevalence of undiagnosed stage 3 CKD among women ranging from more 60% in the US (TriNetX, and LCED databases) to more than 90% in Japan and France.

Older age was associated with higher prevalence of undiagnosed CKD (in all databases except Humana (US)) and more so among patients aged 75 years or older, who were found to be more likely to have undiagnosed stage 3 CKD compared with patients under the age of 45 years. Patients without a history of certain comorbidities, including T2DM, heart failure, and hypertension, were more likely to have stage 3 CKD undiagnosed than those with a history of these comorbidities. No association between a history of established CVD and undiagnosed stage 3 CKD was observed in this study.

The median time to CKD diagnosis among patients with undiagnosed stage 3 CKD at index date varied across databases and countries and ranged from hundred days (in IQVIA Diseases Analyzer (Germany), and CRPD (UK) to nearly 1,000 days in the USP database (Brazil). In addition, more than 50% of the patients with undiagnosed stage 3 CKD at index remained undiagnosed at the end of the study follow-up period in China, France, Germany, and in the US LCED databases.

The time to CKD diagnosis among patients with no prior CKD diagnosis code at index date appeared longer in women compared with men, in older/elderly compared with younger age groups, in patients with stage 3A compared to those with stage 3B, and in patients with no history of the common factors associated with higher risk of CKD diagnosis, including T2DM, hypertension, and heart failure, compared with those with these factors. The factors positively associated with earlier diagnosis of CKD across the study databases and countries included younger age, male sex (compared with female), CKD stage 3B (compared with stage 3A), and most common factors associated with higher risk of CKD diagnosis, including heart failure, T2DM, and hypertension (compared with those without a history of these comorbidities).

Assessment of CKD management and monitoring practices among patients with diagnosed and undiagnosed stage 3 CKD showed that the proportions of patients who had relevant lab test performed for the management or monitoring of CKD within the first 7–30 days, six months, or 18 months of follow-up from index date (depending on the lab test) appeared systematically lower in patients with undiagnosed stage 3 CKD than in patients with diagnosed stage 3 CKD at index date. Similarly, the proportions of patients who had recommended medication dispensations for controlling CKD comorbidities, including statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and sodium/glucose cotransporter-2 inhibitors, within one year of follow-up from index date, appeared systematically lower in patients with undiagnosed stage 3 CKD than in patients with diagnosed stage 3 CKD, at index date.

Conclusion

Patients with stage 3 CKD as demonstrated by lack of a recorded diagnosis code for CKD are common across countries and regions, with estimated prevalence of undiagnosed stage 3 CKD ranging from 32% to more than 90% depending on the database. This study shows that understanding the characteristics of the undiagnosed stage 3 CKD population and the factors associated with higher risk of undiagnosed stage 3 CKD, as well as improving screening in those

patient populations, in addition to the knowledge of at-risk populations, could increase early detection and improve earlier diagnosis of CKD. The early detection of CKD, combined with appropriate management, monitoring, and treatment, may slow disease progression and reduce end-stage CKD, along with the healthcare costs associated with CKD complications and end-stage disease management.