Different rates of progression and mortality in patients with chronic kidney disease at outpatient nephrology clinics across Europe

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The incidence of renal replacement therapy varies across countries. However, little is known about the epidemiology of chronic kidney disease (CKD) outcomes. Here we describe progression and mortality risk of patients with CKD but not on renal replacement therapy at outpatient nephrology clinics across Europe using individual data from nine CKD cohorts participating in the European CKD Burden Consortium. A joint model assessed the mean change in estimated glomerular filtration rate (eGFR) and mortality risk simultaneously, thereby accounting for mortality risk when estimating eGFR decline and vice versa, while also correcting for the measurement error in eGFR. Results were adjusted for important risk factors (baseline eGFR, age, sex, albuminuria, primary renal disease, diabetes, hypertension, obesity and smoking) in 27,771 patients from five countries. The adjusted mean annual eGFR decline varied from 0.77 (95% confidence interval 0.45, 1.08) ml/min/1.73m^2 in the Belgium cohort to 2.43 (2.11, 2.75) ml/min/1.73m^2 in the Spanish cohort. As compared to the Italian PIRP cohort, the adjusted mortality hazard ratio varied from 0.22 (0.11, 0.43) in the London LACKABO cohort to 1.30 (1.13, 1.49) in the English CRISIS cohort. These results suggest that the eGFR decline showed minor variation but mortality showed the most variation. Thus, different health care organization systems are potentially associated with differences in outcome of patients with CKD within Europe. These results can be used by policy makers to plan resources on a regional, national and European level.

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Chronic kidney disease (CKD) is one of the fastest growing causes of death worldwide.[1] In stark contrast is the lack of novel treatment options for the management of CKD.[2] Current predialysis care can slow the progression in patients with CKD and reduce mortality in ESRD patients.[3] In addition, national health care system characteristics may influence outcomes in patients with CKD.[4]

Describing outcomes in CKD patients across regions and countries may identify regions with overall slow CKD

progression and/or low rates of mortality. Such a comparison may help to identify health care system characteristics that are associated with improved population health. Moreover, information regarding the decline of mean estimated glomerular filtration rate (eGFR) over time can be used by policy makers to plan resources at the regional, national, and European level.

Up to the present, little is known about the epidemiology of CKD progression. Studies from individual countries describing CKD progression in referred CKD patients have reported declines in the rates of eGFR varying from 0.35 to 5.16 ml/min per 1.73 m^2 per year.[5,6] Next to differences in the way progression is being expressed, comparisons of these studies is complicated by differences in baseline eGFR, albuminuria, primary renal disease (PRD), and presence of comorbidities, all factors that independently may influence the rate of CKD progression.[7] Importantly, as the rate of change in eGFR influences mortality risk,[8] mortality risk needs to be taken into account when describing eGFR change in CKD patients.

A relatively new statistical method, which enables simultaneous analysis of longitudinal and survival data, is the joint model.[9,10] The main advantage of this model, in the context of CKD progression, is its ability to correct for the measurement error in repeated eGFRs.[10,11] Another advantage is that it accounts for mortality risk when estimating GFR decline.[9,12] Despite these clear advantages for studies investigating outcomes in CKD patients, joint models are currently underused within the nephrology research.[11,13]

The objective of this study was to describe CKD progression and mortality outcomes in patients attending outpatient nephrology clinics. We used individual patient data from 9 CKD cohorts in 5 European countries taking part in the European CKD Burden Consortium.[14,15] Using a joint model, we combined a linear mixed model to estimate mean annual eGFR changes and a Weibull survival model to estimate all-cause mortality risk. Additionally, we determined mean annual eGFR changes for subgroups based on age, sex, and the presence of diabetes mellitus.

RESULTS

Study characteristics

We obtained data from 9 cohort studies,[16–22] followed in 5 European countries, including a total of 27,771 CKD patients not on renal replacement therapy (RRT), of which 25,702 patients (93%) had a baseline eGFR below 60 ml/min per 1.73 m^2. Of these patients, 18,126 had at least 2 creatinine measurements and were included in the main analysis. Inclusion and exclusion criteria for the cohorts are listed in Table 1. One cohort (Complesso Integrato Columbus [CIC]) did not have any exclusion criteria, 3 cohorts (Prevention of Renal Insufficiency Progression [PIRP], Chronic Renal Insufficiency Standards Implementation Study [CRISIS], London Arterial Calcification, Kidney and Bone Outcomes [LACKABO]) solely excluded patients with acute kidney injury or with RRT at first presentation, and the remaining cohorts had additional exclusion criteria in place. Table 1 additionally shows the type of access to nephrology care by cohort. Four cohorts applied an open access system (i.e., patients could visit a nephrologist without a referral from their general practitioner). In the other 5 cohorts, patients required a referral from their general practitioner prior to visiting the nephrologist (i.e., gatekeeper system).

Data extraction

All cohorts provided data for serum creatinine concentration, age, and sex. Eight cohorts provided data for the presence of comorbidities, baseline albuminuria, and PRD. Of the patients included in the main analysis, 34% had data available for either albuminuria or proteinuria. Tables 2 and 3 show baseline characteristics, and the availability of follow-up measurements of patients included in the main analysis (i.e., CKD stages 3 to 5 and ≥2 creatinine measurements). Supplementary Table S1 shows the characteristics of all included patients compared to those with only 1 creatinine measurement. Eight studies (89% of included studies) used isotope dilution mass spectrometry (IDMS) standardized creatinine measurements, of which 1 study used IDMS standardized creatinine methods in 79% of included patients.

CKD outcomes

We assessed CKD progression by using a joint model, simultaneously analyzing repeated measures of eGFR and mortality risk. As such, mortality risk was taken into account for the calculation of the mean annual eGFR decline, and conversely, eGFR decline was taken into account for calculating the mortality risk. Both crude results and results adjusted for baseline eGFR, age, sex, PRD, diabetes mellitus, hypertension, obesity, and smoking are presented. Adjustment for the presence of albuminuria and angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi's) are presented in the Supplementary Tables S2, S3, S4, and S5.

Survival analysis

Figure 1 and Table 4 show the crude and adjusted mortality hazard ratios (HR) and their 95% confidence intervals (95% CI). The PIRP cohort served as the reference, based on population size. The crude HR varied from 0.08 (95% CI, 0.04 to 0.16) in the English LACKABO cohort to 1.0 in the reference population. The adjusted HR varied from 0.22 (95% CI, 0.11 to 0.43) in the LACKABO cohort to 1.30 (95% CI, 1.13 to 1.49) in the CRISIS cohort. Supplementary Table S2 presents the HR additionally adjusted for use of ACEi and ARB, indicating the impact of ACEi and ARB use in the causal pathway between cohort and CKD outcome. This HR ranged from 0.21 (95% CI, 0.11 to 0.41) in the LACKABO cohort to 1.11 (95% CI, 0.96 to 1.27) in the CRISIS cohort.

eGFR decline

Figure 1 and Table 5 show the crude and adjusted mean annual eGFR decline by study including the 95% CI. The crude mean eGFR decline varied from 0.30 (95% CI, +0.03 to 0.62 [+eGFR indicates increase instead of decline]) ml/min per 1.73 m^2 per year in the Italian CIC cohort to 2.36 (95%