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Original Research

Annual all-cause mortality rate for patients with diabetic kidney disease in Singapore

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ABSTRACT

Background: The prognosis of diabetic kidney disease is poor because epidemiological data have shown that all-cause mortality increases with declining renal function. This study aims to estimate the annual mortality rate of diabetic kidney disease stratified by chronic kidney disease (CKD) stages and to identify the predictors of mortality.

Methods: Patients with Stage 3–5 CKD (estimated glomerular filtration rate [eGFR] less than 60 mL/min per 1.73 m^2) with diabetic kidney disease from the National Healthcare Group CKD Registry from 1 January 2007 to 31 December 2007 were included in this study. The patients were followed up till 30 November 2013. Cox's proportional hazards regression modelling was used to assess the factors associated with all-cause mortality.

Results: Over a median follow up period of 6.0 years, 985 out of 3008 patients (32.8%) died. Of those who died, 363 (36.9%) died from cardiovascular causes. The annual mortality rate was 64.1 per 1000 individuals (95% confidence interval [CI] 60.2–68.3) and the mortality rate increased with severity of CKD [Stage 3A (37.0), Stage 3B (57.5), Stage 4 (98.3) and Stage 5 (198.5)]. Predictors of mortality were age, male gender, CKD stages, albuminuria, comorbid conditions such as peripheral vascular disease, neuropathy, retinopathy and the use of antiplatelet agents.

Conclusion: Our study estimated the annual all-cause mortality rate for Singaporean patients with diabetic kidney disease by CKD stages and identified predictors of all-cause mortality. This study has affirmed the poor prognosis of these patients and an urgency to intervene early so as to retard the progression to later stages of CKD.

Background

Chronic kidney disease (CKD) is defined as either functional or structural kidney damage or an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 for at least 3 months [1]. CKD has 5 stages (stage 1 to stage 5) with stage 3 being subdivided into stages 3A and 3B based on the eGFR.

Worldwide, the prevalence of CKD is estimated to be 7.2% in persons aged 30 years and above, with the prevalence varying from 23.4% to 35.8% in persons aged 64 years and above [2]. According to the 2010 Global Burden of Disease study CKD was ranked 18th in the list of causes of global deaths (annual death rate of 15.7 per 100,000) [3].

The prognosis of patients with CKD is poor [4] because lower eGFR and albuminuria are associated with incident cardiovascular disease and all-cause mortality [5,6]. A systematic review showed that the unadjusted relative risk for all-cause mortality in CKD patients compared with non-CKD patients ranged from 0.94 to 5.0 and was significantly higher (relative risk more than 1.0) in 93% of the cohorts included [7]. The corresponding unadjusted relative risk for cardiovascular mortality ranged from 1.4 to 3.7 [7]. In Singapore, a recent study showed that the risks of both cardiovascular deaths and all-cause mortality increase with decreasing estimated GFR and increasing albuminuria [5]. The association between estimated GFR <60 mL/min per 1.73 m^2 and all-cause mortality was even stronger among those with diabetes [5]. Furthermore, Singapore has the fifth highest incidence of end-stage renal failure in the world and the highest incidence of diabetic nephropathy causing end-stage renal failure compared to other countries [8]. A recent study has

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also found that the prevalence of diabetic nephropathy in a primary health cluster in Singapore is as high as 52.5% [9].

Therefore, it is important to be cognizant of the mortality rate in patients with chronic kidney disease for the purpose of health service provision planning. This study aims to quantify the mortality rate among diabetic CKD patients and to determine the predictors associated with all-cause mortality for these patients. The stage stratified mortality rates will provide a good estimate of the population heath while the predictors of mortality will help prognosticate patients for early and appropriate interventions to mitigate their risks of renal failure progression thereby reducing subsequent morbidity and mortality.

Methods

The National Healthcare Group (NHG) provides public healthcare services through an integrated network of primary healthcare polyclinics, acute care and tertiary hospitals, national specialty centres and business divisions [10]. Patients in the NHG CKD Registry were identified to have CKD if they were at least 16 years old and fulfilled any one of the following conditions:

1. Coded with CKD diagnosis [International classification of disease codes, ninth edition (585, 585.1, 585.2, 585,3, 585.4, 585.5, 585.6, 585.9)];
2. Two eGFR <60 mL/min/1.73 m^2 90 days apart;
3. Two urine albumin creatinine ratio (ACR) ≥2.5 mg/mmol (male) for males or ≥3.5 mg/mmol for females, or >30 mg/g taken 90 days apart
4. Two urine protein creatinine ratio (PCR) ≥20 mg/mmol or >0.2 mg/mg 90 days apart;
5. Two urine protein ≥0.2 g/day 90 days apart.

All patients who fulfilled the above criteria will be automatically included in the CKD registry. In addition, the CKD Registry contains administrative, clinical and pharmacy information of these patients, which would be extracted for the purpose of this study.

This is a retrospective cohort study of Type 2 diabetes patients with CKD stage 3A and above (estimated glomerular filtration rate <60 mL/min per 1.73 m^2) from the Registry from 1 January 2007 to 31 December 2007. Patients with CKD stages 1–2 or unknown CKD stage status were excluded from the study.

To ensure comprehensive capture of all diabetes patients into the registry, the following rules, ranked in descending order, were used:

(i) Rule 1, patients from existing standalone diabetes registries;
(ii) Rule 2, patients with diagnosis code of §250 (§250.0–§250.9) under the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9CM), coded as either the primary or secondary diagnosis;
(iii) Rule 3, patients on anti-diabetes medication; and
(iv) Rule 4, patients with 2-hour blood sugar level of ≥11.1 mmol/L on oral glucose tolerance test (OGTT), or a random blood sugar level of ≥11.1 mmol/L on 2 occasions within 2 years, or fasting plasma glucose ≥7.0 on 2 occasions within 2 years, or random blood sugar level of ≥11.1 mmol/L and fasting plasma glucose ≥7.0 within 2 years [11].

Variables extracted from the CKD Registry for the study included demographic data (age, gender and ethnicity), diabetes onset age, duration of diabetes, comorbidities (hypertension, dyslipidaemia, ischaemic heart disease, cerebrovascular disease, retinopathy, peripheral vascular disease and neuropathy), use of medications [angiotensin converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB), statins, oral hypoglycaemic agents and/or insulin and antiplatelet agents] and laboratory results (glycated haemoglobulin [HBA1c], serum creatinine, eGFR and albuminuria). Serum creatinine was measured using an Isotope Dilution Mass Spectrometry (IDMS) traceable standard and eGFR was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation. Microalbuminuria was defined as urine ACR 2.5–30 mg/mmol for males, urine ACR 3.5–30 mg/mmol for females, or urine PCR 20–50 mg/mmol or total urinary protein 0.2–0.5 g/day. Macroalbuminuria was defined as urine ACR >30 mg/mmol or urine PCR >50 mg/mmol or total urinary protein >0.5 g/day.

Mortality data were obtained from the relevant local death registry. Patients were followed up until 30 November 2013 where the outcomes of interest were deaths from all causes. In Singapore, the law requires all deaths occurring in Singapore to be registered within 24 hours of occurrence and a certificate of cause of death issued by doctors or authorized medical practitioners is required. Deaths were considered to be from cardiovascular causes if they were due to ischaemic heart diseases (ICD10: I20–I25), cerebrovascular diseases (ICD 10:I60–69), hypertensive diseases (ICD10: I10–I15) and other heart diseases (ICD10:I00–I09, I26–I51).

Statistical analysis

Characteristics of the study population are described for categorical variables by n (%) and for continuous variable as the mean ± SD. The unadjusted overall time to death was described using the Kaplan–Meier survival curve. Five year survival estimates (by CKD stage) were obtained via life tables. Univariate Cox's proportional hazards regression was used to assess associations, measured as hazard ratios (HR), between variables and all-cause deaths, followed by multivariate Cox's proportional hazards regression. The level of significance was set at $p \leq 0.20$ for consideration to be used in multivariate regression using backward elimination of non-significant variables with $p = 0.05$ for the final model. All analyses were conducted using STATA (StataCorp, College Station, TX, USA) statistical software, version 12.0. The study was approved by the NHG's Domain-specific Ethics Review Board which is an independent committee constituting of medical, scientific and non-scientific members.

Results

Description

There were a total of 3008 Type 2 diabetes patients in 2007 who met the study criteria, i.e. stages 3A and above, and were followed up until 30 November 2013 (Table 1). A total of 19 patients were excluded from the survival analysis as they died at the start of the study. The mean age of the study cohort was 70.0 (standard deviation: 10.4) years. Majority (72.5%) of patients belonged to CKD stages 3A and 3B and had hypertension (95.8%) and dyslipidaemia (97.6%). At least 84.6% of patients were on ACEi, ARB or both.

Mortality rate

The median follow-up period was 6.0 years (range 0– 6.9 years). During the study period, 985 (32.8%) participants died, of whom majority (363, 36.9%) died from cardiovascular causes (Table 2). The annual all-cause mortality rate over the study period was 64.1 per 1000 individuals (95% CI 60.2–68.3) per year and that of cardiovascular mortality was 23.8 per 1000 individuals (95% CI 21.5–26.4) per year (Fig. 1). There was a progressive increase in annual mortality rate with advancing CKD stages from 37.0 per 1000 individuals (95% CI 32.5–42.3) among patients with stage 3A to 57.5