Creating a 13-year National Longitudinal Cohort of veterans with chronic kidney disease

Mukoso N. Ozieh, Mulugeta Gebregziabher, Ralph C. Ward, David J. Taber and Leonard E. Egede

Abstract

Background: The development of large-scale chronic kidney disease (CKD) cohorts within the Veterans Affairs (VA) system has been limited by several factors, including the high proportion of missing race data etc. The goal of this study is to address the limitations of prior studies by creating a large cohort utilizing robust KDIGO recommendations for identifying and staging CKD.

Methods: Multiple patient and administrative files from the Veterans Health Administration (VHA) National Patient Care were linked to create a national cohort of Veterans with chronic kidney disease (CKD) between January 2000 – December 2012; patients identified during this period were followed until 2015. CKD was defined for stages 1 through 5 if markers of kidney damage, specifically proteinuria, were present for at least 3 months. Estimated glomerular filtration rate (eGFR) values were calculated based on serum creatinine levels and the patient's age, gender, and race using both the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas.

Results: About 50 million observations were collected that supported a CKD diagnosis during the study period; these observations corresponded to 3,051,001 unique veterans; 80.9% were non-Hispanic white (NHW), 13.4% were non-Hispanic black (NHB), 3.6% were Hispanic, and 2.0% were in other groups. The mean age 76.7, about 97% were male and 50.2% died prior to January 2016. Among those with stage 3, 12.3% progressed to stage 4, 21.6% of those with stage 4 progressed to stage 5. We found that eGFR values calculated from serum creatinine levels identified about 98% of all patients, while about 11.4% of patients could be identified through ICD-9 codes; only 6.4% could be identified through both sources.

Conclusion: This 13-year national cohort provides an important resource for answering numerous research questions in the future such as racial/ethnic disparities questions, tracking health service utilization, medication adherence, cost and health outcomes in veterans with CKD.

Keywords: Veterans, CKD, Kidney disease

Background

Chronic kidney disease (CKD) is defined as structural or functional abnormalities of the kidney, with either presence of markers of kidney damage and or decreased glomerular filtration rate (GFR) for > 3 months [1]. CKD is a public health burden [2, 3] and imposes a huge economic burden on individuals affected, their families and the country at large [4–6]. Thirty million US adults are estimated to have CKD and it was ranked the 9th leading cause of death in the US in 2015 [7]. Veterans have approximately 34% higher CKD prevalence than the general population [8], which has been attributed to the significant multi-morbidity and higher mean age in this group. The Veterans Administration health system – the largest U.S. integrated health care system - provides a unique setting to study and monitor progress towards improving the health of people with CKD.
Previous studies have used several CKD definitions to form cohorts [9–12], and these all differed from the current guidelines for disease classification contained in the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [1]. In some cases, studies relied on the Modification of Diet in Renal Disease (MDRD) equation [13] rather than the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14]. One evaluated normal kidney function using estimated glomerular filtration rate (eGFR) values alone without considering albuminuria; another included a definition for CKD based on International Classification of Diseases (ICD) diagnostic codes.

The development of large-scale CKD cohorts within the Veterans Affairs (VA) system has been limited by several factors, including the high proportion of missing race data, short cohort entry windows, exclusion of Hispanics or women and failure to include markers of kidney damage for early stage kidney disease as recommended by the KDIGO 2012 guidelines [1]. The goal of this study is to address the limitations of prior studies by creating a large cohort utilizing robust KDIGO recommendations for identifying and staging CKD.

**Methods**

**Source of Data**

Multiple patient and administrative files from the Veterans Health Administration (VHA) National Patient Care were linked [15] to create a national cohort of Veterans with chronic kidney disease (CKD) from January 2000 – December 2012; patients identified during this period were followed until 2015. Figure 1 provides an overview of cohort formation, which closely follows the KDIGO 2012 definition [1]. CKD was defined for stages 1 through 5 when the following conditions were present for at least 3 months: Stage 1: an estimated glomerular filtration rate (eGFR) $\geq 90$ ml/min per 1.73 m$^2$ with urine albumin creatinine ratio $> 30$ mg/g or presence of positive urine protein on dipstick (with negative WBCs or leukocyte esterase) or presence of microalbuminuria; Stage 2: eGFR $= 60$ and $< 90$ ml/min per 1.73 m$^2$ with urine albumin creatinine ratio $> 30$ mg/g or presence of positive urine protein on dipstick (with negative WBCs or leukocyte esterase) or presence of microalbuminuria; Stage 3: eGFR $= 45$ and $< 60$ ml/min per 1.73 m$^2$; Stage 4: eGFR $= 15$ and $< 30$ ml/min per 1.73 m$^2$; Stage 5: eGFR $< 15$ ml/min per 1.73 m$^2$. In addition, patients who had two or more International Classification of Diseases,
ninth revision (ICD-9-CM) codes for CKD stages 1 through 5 (codes 585.1 through 585.6) within a 24-month window were included, excluding the 24 months prior to initiation of the cohort. Patients under age 18 or with heart, liver or lung transplants were excluded. Estimated GFR values were calculated based on serum creatinine levels and the patient’s age, gender, and race using both the Modification of Diet in Renal Disease (MDRD) equation [13] - GFR (mL/min/1.73 m²) = 175 × (Scr)−1.154 × (Age)−0.203 × (0.742 if female) × (1.212 if African American) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14] - GFR = \frac{141 \times \min (\text{Scr}/\kappa, 1) \times \max (\text{Scr}/\kappa, 1)-1.209 \times 0.993\text{Age} \times 1.018}{\text{[if female]} \times 1.159 \text{[if black]}} equations to support future comparisons of the two methods.

Since CKD disproportionately affects certain racial and ethnic minority groups [16], we took steps to minimize the fraction of missing race/ethnicity values. We developed an optimized algorithm based on the full information maximum likelihood approach [17], and used multiple VHA Corporate Date Warehouse (CDW) and Medicare sources to reduce the fraction of missing race data to less than 1%.

We collected each patient’s ICD-9 codes over the entire study period, and determined the 31 Elixhauser comorbidities as enhanced by Quan [18].

Our Institutional Review Board (IRB) and local VA Research and Development committee approved the study. Waiver of patient consent was obtained from our institutional IRB, since the study was based on existing data.

**Study population**
Cohort entry was from January 2000 – December 2012; patients identified during this period were followed until loss to follow-up, death, or December 2015.

**Outcome measure**
The primary outcome was the proportion of patients that died and the proportion that progressed across the CKD stages within the study’s time frame. Patients who were alive on 31 December 2015 were censored.

**Demographic variables**
This included: 1) Age treated as continuous; 2) Gender treated as nominal; 3) Marital status classified as divorced, single, widowed, or married. 4) Race or ethnicity categorized as Non Hispanic White (NHW), Non Hispanic Black (NHB), Hispanic, and ‘Other’ categories. 5) Veterans Administration geographic regions [1 through 5]. 6) Location of residence (Urban, Rural, Highly Rural) was based on Rural Urban Commuting Area (RUCA) codes which were derived from patient-level, residential zip code information. 7) Percent of service-connected disability, representing the degree of disability due to illness or injury that was aggravated by or incurred in military service, was dichotomized (< 50% = 0; ≥50% = 1).

**Medical comorbidity measure**
Medical comorbidities were defined based on the Quan enhanced ICD-9-CM version of the Elixhauser Comorbidity Index [18]. Each was determined based on each patient’s unique ICD-9 codes recorded during the study’s timeframe. The total number of comorbidities was then categorized as 3 or less, 4–5, 6–7, and 8 or more. The Elixhauser comorbidity for renal failure was excluded to avoid collinearity.

**Statistical analysis**
Descriptive statistics (means for continuous and proportions for categorical variables) were computed. We estimated progression through the various CKD stages using proportions and calculated median follow up in each stage as well as proportion that died across each stage using descriptive statistics. All analyses were performed in SAS 9.4 (SAS Institute, Inc., Cary NC).

**Results**
About 50 million observations were collected that supported a CKD diagnosis during the study period; these observations corresponded to 3,051,001 unique patients. Table 1 provides a summary of the demographic characteristics and important comorbidities for the population, of which 80.9% were non-Hispanic white (NHW), 13.4% were non-Hispanic black (NHB), 3.6% were Hispanic, and 2.0% were in other groups. About 97% was male; the mean age 76.7, and 50.2% died prior to January 2016. Table 2 provides a distribution of patients by their median CKD stage in the last observed year; mortality rates varied between 29 to 81% for stages 1 through 5, respectively. The median follow-time was 104 months overall, or 8.7 years. Table 3 summarizes progression from a given CKD stage to a higher stage with 4.2, 3.5 and 3.1% of patients with CKD stage 1, 2 and 3 respectively at baseline progressing CKD stage 5. While 12.3% of those with stage 3 progressed to stage 4, 21.6% of those with stage 4 progressed to stage 5.

We found that eGFR values calculated from serum creatinine levels identified about 98% of all patients with CKD, while about 11.4% of patients could be identified through ICD-9 codes; only 6.4% could be identified through both sources. For patients with CKD stages 1 and 2, less than 1% could be identified through both sources.

**Discussion**
This 13-year CKD cohort of Veterans overcomes the limitations of previous cohorts by utilizing the most recent KDIGO guidelines and by including patients at all stages of disease regardless of race or gender. Because it...
captures a large group over a long period, patient trajectories from early to late stage disease can be analyzed. This work will enable numerous follow-on studies concerning health disparities and treatment effects especially in older people with CKD.

The importance of utilizing the most recent KDIGO guidelines in CKD staging cannot be overemphasized. Studies show that the degree of proteinuria and CKD stage impact cardiovascular and overall health outcomes [19–21]. Yet, there is no CKD cohort for Veterans that utilizes the KDIGO recommendations for CKD staging. Our study cohort demonstrates the importance and impact of CKD staging on health outcomes. For example, the overall mortality rate in our CKD cohort was 50%, but at stages 4 and 5, significantly higher mortality rates were observed (81%). Studies have also shown that older people with CKD are at a higher risk of CKD complications as opposed to CKD progression [22]. This could explain why a low percentage of patients in our study with CKD stage 1, 2 or 3 at baseline progressed to CKD stage 5 during the last observed year.

By including several factors not included in the KDIGO 2012 definitions, we will be able to examine their performance in future studies. For example, the KDIGO definitions generally recommend use of the CKD-EPI equation to calculation eGFR; we also included calculations based on the MDRD equation. Though not mentioned in the KDIGO guidelines, we also used ICD-9 codes to identify patients since this was a commonly-used method in numerous previous studies. We showed here that ICD-9 codes identified far fewer patients compared with calculated eGFR values. This may indicate that patients with CKD could have other conditions that were the primary reason for visits, and thus CKD-related codes were less likely to appear in their records.

### Table 1 Baseline Characteristics of Cohort

| Sample size (n) | 3,051,001 |
|----------------|-----------|
| Mean age (std. dev.) | 76.7 (11.0) |
| Married (%) | 57.8 |
| Gender (% female) | 3.7 |
| Race (%) | Non-Hispanic black 13.4, Hispanic 3.6, Other 2.0, Non-Hispanic white 80.9 |
| VA Region (%) | 1 Atlantic 23.2, 2 Southeast 20.5, 3 Upper Midwest 25.8, 4 Central West 15.6, 5 Southwest 14.9 |
| Rural-Urban (%) | Urban 71.0, Rural 28.0, Insular Islands 1.0 |
| *Service-related disability (> 50%) | 22.7 |
| Mortality (%) (prior to 1/1/2016) | 50.2 |
| Comorbidities | Hypertension, uncomplicated (%) 90.3, Diabetes with complications (%) 27.1, Diabetes, uncomplicated (%) 48.7, Peripheral vascular disorders (%) 29.0, Chronic pulmonary disease (%) 42.6, Congestive heart failure (%) 27.7, Hypertension, complications (%) 21.2, Kidney transplant (%) 0.5 |
| Medical Comorbidities (%) | 3 or less 24.0, 4-5 25.8, 6-7 20.9, 8 or more 29.4 |

*Percent of service-connected disability represents the degree of disability due to illness or injury that was aggravated by or incurred in military service

### Table 2 Distribution of patients by median CKD stage in last observed year

| Stage | 1 | 2 | 3 | 4 | 5 | Total |
|-------|---|---|---|---|---|-------|
| Alive | 97,923 | 203,317 | 1,172,346 | 31,692 | 13,699 | 1,518,977 |
| Dead  | 40,388 | 105,338 | 1,188,259 | 136,324 | 61,715 | 1,532,024 |
| Total | 138,311 | 308,655 | 2,360,605 | 168,016 | 75,414 | 3,051,001 |
| Mortality (%) | 29.2 | 34.1 | 50.3 | 81.1 | 81.3 | 50.2 |
| Median follow time (months) | 85 | 98 | 109 | 84 | 80 | 104 |

### Table 3 CKD progression during the study period (2000–2012)

| Stage | Percentage who eventually reached CKD stage: |
|-------|--------------------------------------------|
| For those in | 2 | 3 | 4 | 5 |
| 1 | 74.9 | 32.1 | 8.0 | 4.2 |
| 2 | 59.1 | 10.3 | 3.5 |
| 3 | 12.3 | 3.1 |
| 4 | 21.6 |
Conclusion
In summary, this is the first large-scale CKD Veteran cohort based on the most recent KDIGO guidelines. It captures 13 years of patient history and provides an important resource for answering numerous research questions in the future such as racial/ethnic disparities questions, tracking health service utilization, medication adherence, cost and health outcomes in veterans with CKD.

Abbreviations
CKD: Chronic Kidney Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: Estimated Glomerular Filtration Rate; ICD-9: International Classification of Diseases, Ninth Revision; Clinical Modification; IRB: Institutional Review Board; KDIGO: Kidney Disease: Improving Global Outcomes; MDRD: Modification of Diet in Renal Disease; NHB: Non Hispanic Black; NHW: Non Hispanic White; RUCA: Rural Urban Commuting Area; VA: Veterans Affairs; VAMC: Veterans Affairs Medical Center; VHA: Veterans Health Administration

Acknowledgements
None.

Funding
This study was supported by Grant K24DK093699 from The National Institute of Diabetes and Digestive and Kidney Disease (PI: Leonard Egede). The funding body supported the study by protecting the time spent in designing study, analysis interpretation and writing of the manuscript.

Authors’ contributions
LEE obtained funding for the study. LEE and MNO designed the study. RW, MG, LEE acquired and analyzed the data. LEE, MG, RW, DJT, MNO developed the analysis, contributed to interpretation and critically revised the manuscript for important intellectual content. All authors approved the final manuscript. LEE and MNO are the guarantors of the study and take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Availability of data and materials
The data that support the findings of this study are available from VAMC but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the VAMC.

Ethics approval and consent to participate
This study was approved by Medical University of South Carolina Institutional Review Board (IRB) and Research and Development committee of Ralph H. Johnson Veterans Affairs Medical Center. Waiver of patient consent was obtained from our institutional IRB, since the study was based on existing data.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Division of Nephrology, Medical College of Wisconsin, Milwaukee, WI, USA. 2Center for Advancing Population Science (CAPS), Medical College of Wisconsin, Milwaukee, WI, USA. 3Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, WI, USA. 4Ralph H. Johnson Department of Veterans Affairs Medical Center, Health Equity and Rural Outreach Innovation Center, Charleston, SC, USA. 5Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA. 6Department of Surgery, Medical University of South Carolina (MUSC), Charleston, SC, USA. 7Division of General Internal Medicine, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226-3596, USA.
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