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Predictive Risk Models to Identify Patients at High-Risk for Severe Clinical Outcomes With Chronic Kidney Disease and Type 2 Diabetes

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Abstract

Introduction/Objective: Predictive risk models identifying patients at high risk for specific outcomes may provide valuable insights to providers and payers regarding points of intervention and modifiable factors. The goal of our study was to build predictive risk models to identify patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) at high risk for progression to end stage kidney disease (ESKD), mortality, and hospitalization for cardiovascular disease (CVD), cerebrovascular disease (CeVD), and heart failure (HF). **Methods:** This was a retrospective observational cohort study utilizing administrative claims data in patients with CKD (stage 3-4) and T2D aged 65 to 89 years enrolled in a Medicare Advantage Drug Prescription plan offered by Humana Inc. between 1/1/2012 and 12/31/2017. Patients were enrolled ≥1 year pre-index and followed for outcomes, including hospitalization for CVD, CeVD and HF, ESKD, and mortality, 2 years post-index. Pre-index characteristics comprising demographic, comorbidities, laboratory values, and treatment (T2D and cardiovascular) were evaluated and included in the models. LASSO technique was used to identify predictors to be retained in the final models followed by logistic regression to generate parameter estimates and model performance statistics. Inverse probability censoring weighting was used to account for varying follow-up time. **Results:** We identified 169 876 patients for inclusion. Declining estimated glomerular filtration rate (eGFR) increased the risk of hospitalization for CVD (38.6%-61.8%) and HF (2-3 times) for patients with eGFR 15 to 29 mL/min/1.73 m^2 compared to patients with eGFR 50 to 59 mL/min/1.73 m^2. Patients with urine albumin-to-creatinine ratio (UACR) ≥300 mg/g had greater chance for hospitalization for CVD (2.0 times) and HF (4.9 times), progression to ESKD (2.9 times) and all-cause mortality (2.4 times) than patients with UACR <30 mg/g. Elevated hemoglobin A1c (≥8%) increased the chances for hospitalization for CVD (21.3%), CeVD (45.4%), and death (20.6%). Among comorbidities, history of HF increased the risk for ESKD, mortality, and hospitalization for CVD, CeVD, and HF. **Conclusions:** The predictive models developed in this study could potentially be used as decision support tools for physicians and payers, and the risk scores from these models can be applied to future outcomes studies focused on patients with T2D and CKD.

Keywords

T2D, CKD, predictive risk model, CVD, ESKD

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Introduction

Chronic Kidney Disease (CKD) is a complex condition that affects 1 in 7 adults in the United States.[1] The prevalence is noted to be much higher (38%) among individuals ≥65 years of age. Progression of CKD is not only associated with advancing to end stage kidney disease (ESKD) and dialysis, but also an elevated cardiovascular (CV) risk manifesting

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as coronary artery disease, heart failure, arrhythmias, and sudden cardiac death.[2-4] Cardiovascular disease (CVD) has been reported in up to 50% of patients with CKD stages 3 to 5.[5] Furthermore, CVD-related mortality accounted for 40% to 50% of the deaths among patients with CKD stages 4 to 5 compared to 26% of the deaths in patients with normal kidney function.[6,7]

CKD is also a common comorbidity observed among individuals with type 2 diabetes (T2D). Based on the 1999-2012 National Health and Nutrition Examination Surveys (NHANES), among individuals with T2D, the prevalence of CKD was 22% overall and 43% among individuals ≥65 years.[8] The authors reported coronary heart disease (12.5% overall, 19.9% among ≥65 years) myocardial infarction (MI 12.0% overall, 18.2% among ≥65 years) and congestive heart failure (CHF 10.6% overall, 16.9% among ≥65 years) among the most common comorbidities observed in these patients with T2D and CKD.

Individuals with T2D have a twofold increased risk for CVD (MI, stroke, peripheral vascular disease), and CVD is the primary cause of death in these patients,[9] which has been demonstrated in several prospective trials.[10,11] Presence of diabetes mellitus has a pervasive impact on vasculature and hence increasing risk of CVD.[12] Adding presence of CKD in patients with T2D has a significant impact on health and increases the risk of CVD, cerebrovascular diseases (CeVD), and heart failure (HF).[13-15] Keith et al[13] reported that patients with CKD were more likely to die due to CVD than ESKD. Progression to ESKD has been reported to be driven by various factors including but not limited to age, onset of diabetes, glycemic levels, and albuminuria.[16,17] The clinical complexities associated with CKD and T2D provide challenges to providers and healthcare systems regarding prioritized management of risk factors. Predictive models can serve as tools to identify patients based on collective and competing risks to determine those patients who might benefit the most from particular interventions with the goal of reducing negative clinical outcomes.

Several risk predictive models have been developed using various methodologies and data sources in patients with CKD, with most focused on modeling progression of CKD to ESKD[18-21] and mortality.[22,23] In general, few studies have focused on the progression of CKD to ESKD in a T2D population.[19,21] While there are studies reporting predictive models and risk scores for CVD, CeVD, and HF in the general population,[24,25] to our knowledge, there is no published literature on predictive risk models for the same outcomes in patients with T2D and CKD. Predictive risk models identifying patients at high risk for specific outcomes may provide valuable insights to providers and payers regarding points of intervention and modifiable factors to help develop potential interventions and disease management programs utilizing technology (digital devices) and to avoid or delay unwanted outcomes. The goal of our study was to develop models to predict patients with T2D and CKD at high risk for progression to ESKD, mortality, and hospitalization for CVD, CeVD, and HF.

Methods

This was a retrospective observational cohort study utilizing administrative claims data for patients with CKD and T2D enrolled in Medicare Advantage and Prescription Drug (MAPD) plans offered by Humana Inc with representation across the United States. Within the Humana system, a unique identifier links each patient enrollment data with their medical and pharmacy claims. The medical claims data include information related to facility (inpatient) and provider (outpatient) claims, service date, diagnosis codes, procedure codes, and place of treatment. Pharmacy claims data contain outpatient pharmacy claims for medications with prescription fill date, and days' supply. Laboratory results data for HbA1c testing were available for 88% of patients; UACR for 45%.

We identified individuals 65 to 89 years of age with an estimated glomerular filtration rate (eGFR) measure of 15 to 59 mL/min/1.73 m^2 or urine albumin-to-creatinine ratio (UACR) ≥30 mg/g between January 1, 2012 and December 31, 2017. The second or confirmatory eGFR 15 to 59 mL/min/1.73 m^2 or UACR ≥30 mg/g within 90 to 365 days of the first value was identified and set as the index date (Figure 1).

Individuals had to be diagnosed with T2D prior to the index date and enrolled in a MAPD plan for at least 12 months. We excluded all individuals with claims for stage V CKD/kidney failure (diagnosis or eGFR <15 mL/min/1.73 m^2), ESKD based on diagnosis, dialysis or renal transplant, or type 1 diabetes during the pre-index period. Follow-up was up to 24 months or until end of enrollment or death, whichever came first. Definitions for all inclusion and exclusion criteria are listed in the Supplemental Tables A and B.

Outcomes and Covariates

The outcomes measured during the 24 months post-index included hospitalization for CVD, CeVD, or HF, progression to ESKD and all-cause mortality. Using the principal hospital diagnosis, we identified individuals hospitalized for CVD (myocardial infarction, unstable angina, atrial fibrillation, peripheral arterial disease, or revascularization [percutaneous coronary intervention, coronary artery bypass graft]), CeVD (ischemic stroke, trans-ischemic attack), and HF. Progression to ESKD during the follow-up period was identified based on diagnosis codes for ESKD, stage V or kidney failure, dialysis or renal transplant, or sustained eGFR <15 mL/min/1.73 m^2(>1 eGFR value on different dates) during the post-index period (definitions

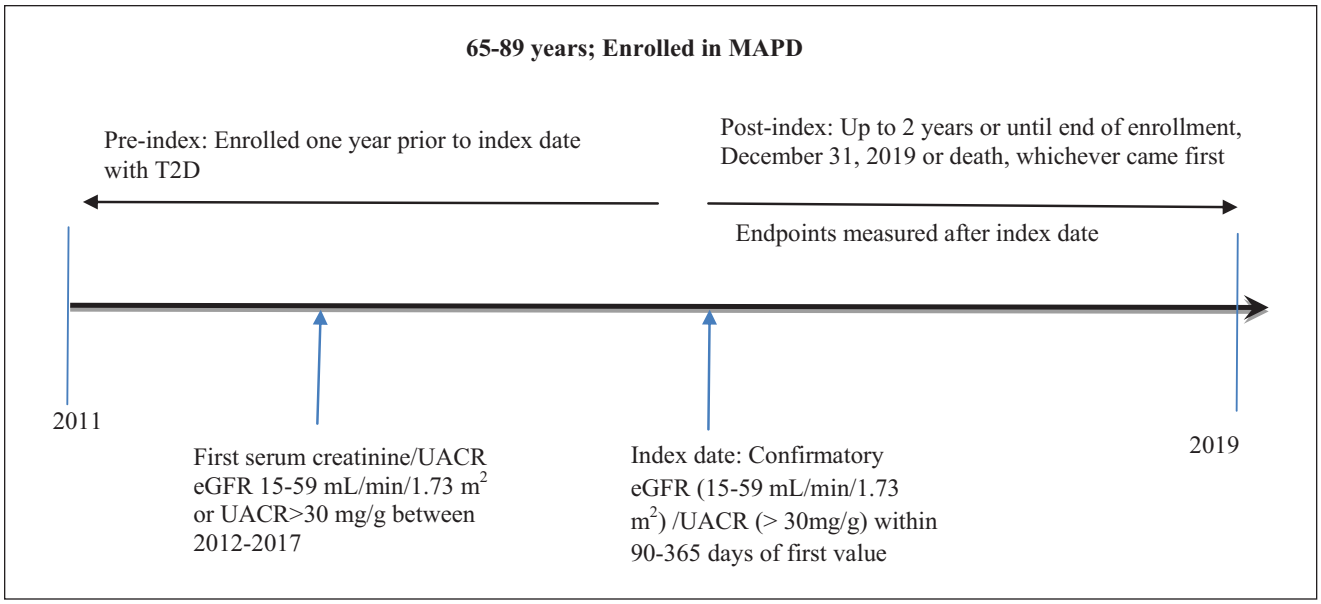

Figure 1. Study design.
Abbreviations: eGFR, estimated glomerular filtration rate; MAPD, Medicare Advantage and Prescription Drug; T2D, type 2 diabetes; UACR, urine albumin creatinine ratio.

available in Supplemental Tables A and B). All-cause mortality data was obtained from Centers for Medicare & Medicaid Services Social Security Administration records.

Demographic characteristics included age as of index date, sex, race/ethnicity, low income subsidy (income below 150% of poverty level and limited resources enable individuals to be eligible for additional premium and cost-share assistance for prescription drugs under the Medicare Part D program) or dual eligibility (Medicare and Medicaid). All baseline clinical measures were assessed over the 12 months pre-index period. Comorbidity indices including Elixhauser comorbidity index[26,27] and Diabetes Complication and Severity Index (DCSI)[28] were calculated. Additional comorbidities based on diagnosis codes (anemia, retinopathy, dyslipidemia, microalbuminuria/macroalbuminuria) and hospitalizations based on principal diagnosis code (pneumonia, dehydration, urinary tract infection, hypertension, chronic obstructive pulmonary disease COPD, short- and long-term complications of diabetes mellitus, uncontrolled diabetes, lower extremity amputation, and hypoglycemia) were flagged.

In addition to the previously mentioned eGFR and UACR values, other baseline available laboratory values including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and hemoglobin A1c (HbA1c) along with the number of tests conducted (serum creatinine, HbA1c, and UACR) were reported. Pre-index use of CV-related medications, glucose-lowering medication use and adherence measured as proportion of days covered (oral, glucagon-like peptide-1 receptor agonist [GLP-1 RA] and insulins), and healthcare resource use (physician encounters, hospitalizations, and emergency department [ED] visits) were identified.

Analyses

Central tendency measures and proportions were used to describe the demographic and pre-index clinical characteristics for the study cohort and for patients with and without each of the specific endpoints or outcomes. We identified >150 000 patients for the study and observed most outcomes in <10% of the sample during the initial descriptive analyses. Given the large sample size, the models would yield statistically significant regression coefficients for many variables which may or may not be clinically relevant.[29] Additionally, patients with these outcomes would be underrepresented in the dataset used to develop the models. Hence, for model development, controls were randomly sampled 1 case (patient with the outcome) for each control (patient without the outcome). Shrinkage and the variable selection method LASSO technique[30] was used to identify predictors to be retained in the final models followed by logistic regression to generate parameter estimates and model performance statistics. Additionally, we used inverse probability censoring weighting (IPCW)[31] to account for the varying follow-up time.

All baseline demographic, clinical, and utilization characteristics were considered for model input. The sample was randomly split into a training data set (70%) and a testing data set (30%). The training data set was used to fit and

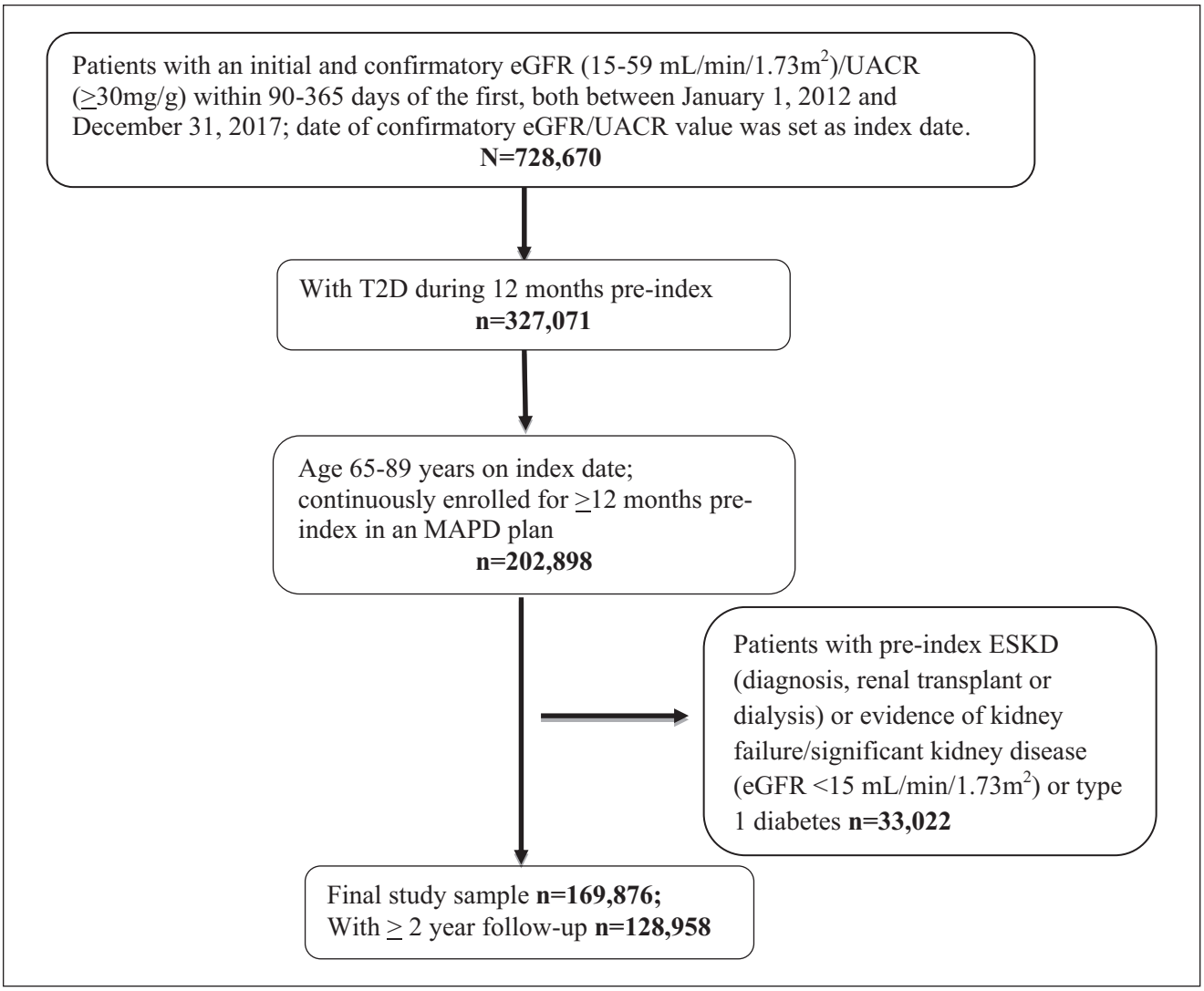

Figure 2. Sample selection.
Abbreviations: eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; MAPD, Medicare Advantage and Prescription Drug plan; T2D, type 2 diabetes; UACR, urine albumin creatinine ratio.

tune the predictive risk models for each of the specified endpoints and the testing data set was used to assess the performance of the models. Quality receiver operating characteristic (QROC) statistics and C-statistics (area under the curve) were reported to determine the extent of misclassification error and overall model performance. As a sensitivity analysis, we ran logistic regression models for each of the 5 outcome variables using backward elimination and a retention value of $P = .01$ without LASSO.

Results

On applying all inclusion and exclusion criteria, we identified a sample of 169 876 patients, of which 128 958 patients with T2D and Stage 3 to 4 CKD based on eGFR/UACR levels (Figure 2) had ≥2 years follow-up. The average age of the overall sample was 75.2 years (standard deviation [SD] 6.1), 76.3% were white and 17.4% were black, with 11.9% low-income subsidy and/or dual eligible (Supplemental Table C). In general, for each of the outcomes assessed, the mean Elixhauser comorbidity index and prevalence of each of the comorbidities was higher among those with the outcomes than those without (Supplemental Table C). While 20.5% of the patients had UACR <30 mg/g, 19.7% and 4.8% of the patients had UACR 30 to 299 mg/g and ≥300 mg/g, respectively, about 55% of the patients had no UACR values reported. The mean confirmatory eGFR for the overall sample was 47.9 mL/min/1.73 m^2 (SD 9.7) and in general was lower for patients with the outcomes assessed compared to the patients without the outcome.

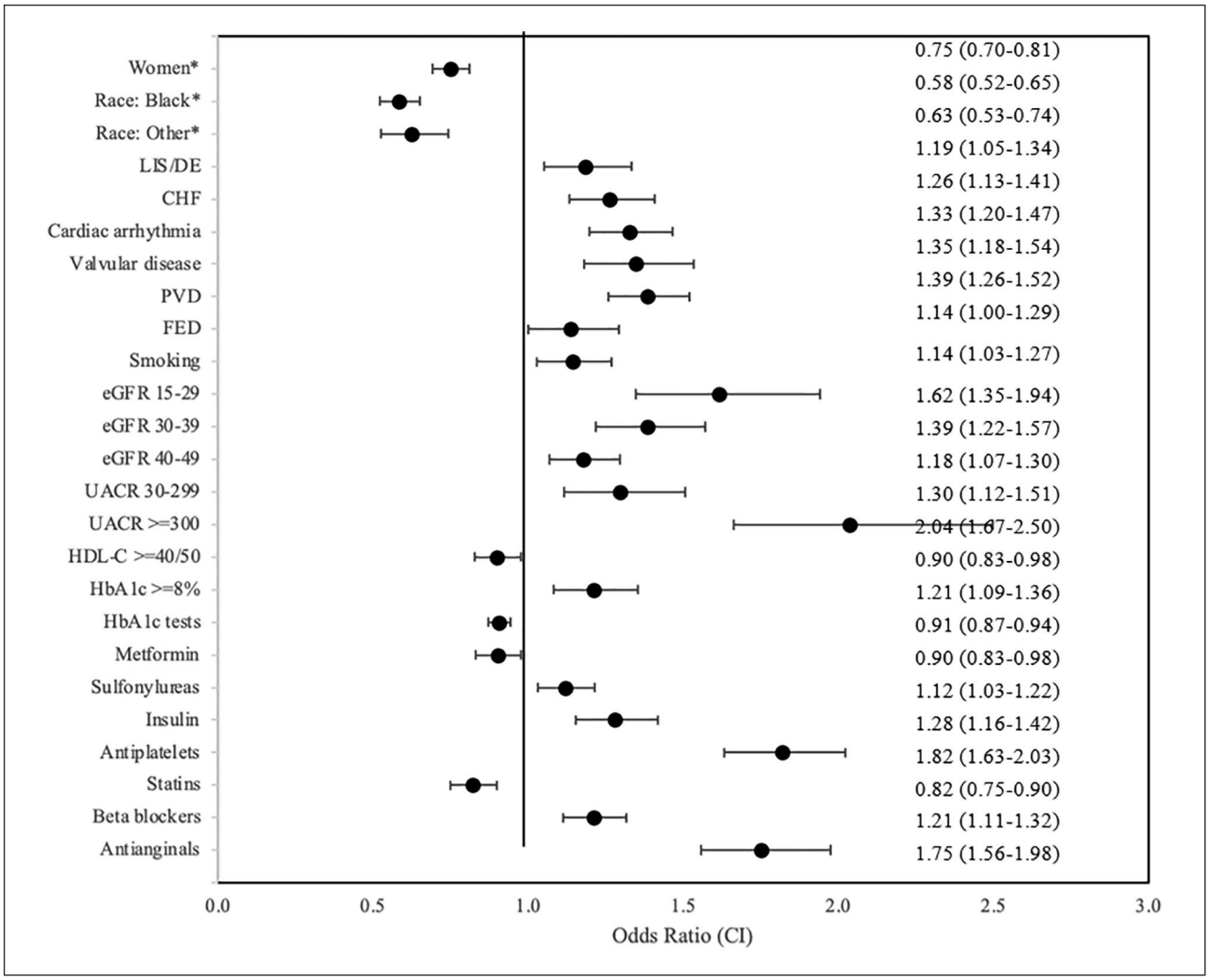

Figure 3. Factors associated with hospitalization for cardiovascular disease in patients with chronic kidney disease and type 2 diabetes.

Abbreviations: CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; FED, fluid electrolyte disorders; HbA1c, Hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; LIS/DE, low-income subsidy/dual eligible; PVD, peripheral vascular disease; UACR, urine albumin creatinine ratio.

Other race includes all races not including patients of white or black race; HDL-C ≥40/50 indicates ≥40 mg/dL for men and ≥50 mg/dL for women.

*Reference groups: Men; white; eGFR 50-59 mL/min/1.73 m^2; UACR <30 mg/g; HDL-C <40 mg/dL for men and <50 mg/dL for women; HbA1c <8%.

Figures 3 to 5 report the factors associated with hospitalization for CVD, CeVD, and HF, respectively. Figures 6 and 7 report the factors associated with progression to ESKD and all-cause mortality. Model performances (Supplemental Table D) along with the parameter estimates are reported in the Supplemental Tables E to I. Women had lower risk of progression to ESKD (34.8%), mortality (31.0%), and hospitalization for CVD (25.0%) and HF (18.8%), than men. For the race/ethnicity variable, compared to patients of white race, patients of black and other race had greater risk for progression to ESKD (35.9% and 33.6%, respectively) but lower risk of hospitalization for CVD (41.6% and 37.4%, respectively) and death (17.4% and 27.9%, respectively).

Among lab values, eGFR, UACR, and HbA1c were associated with almost all outcomes assessed. Decreasing eGFR levels was associated with increased the risk of hospitalization for CVD (38.6%-61.8%) and HF (2-3 times) for patients with eGFR 15 to 39 mL/min/1.73 m^2 compared to patients with eGFR 50 to 59 mL/min/1.73 m^2. Patients with index eGFR 15 to 29 mL/min/1.73 m^2 had over twice the risk of death compared to patients with eGFR 50 to 59 mL/min/1.73 m^2. Patients with UACR ≥300 mg/g had greater chance for hospitalization for CVD (2.0 times) and HF (4.9

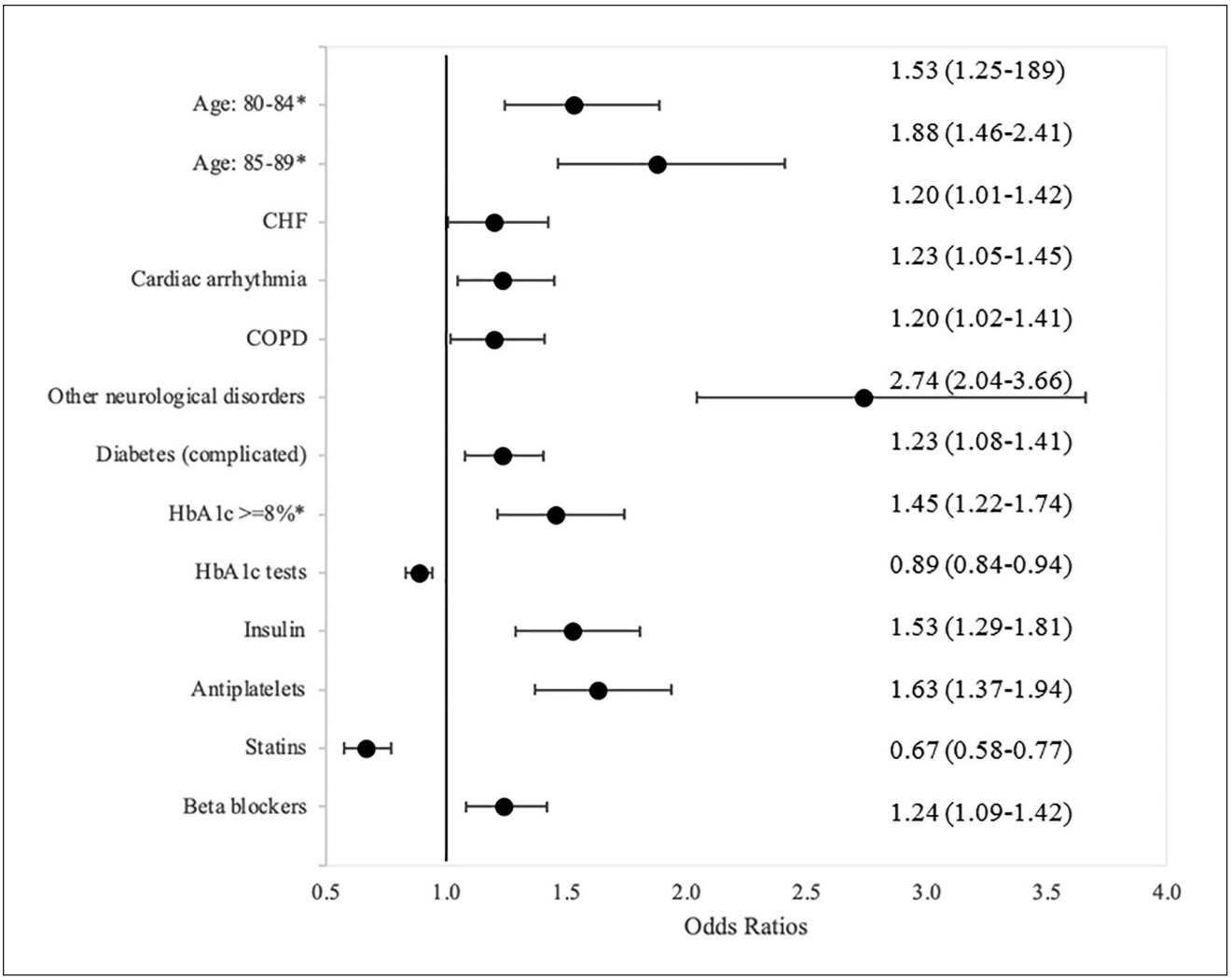

Figure 4. Factors associated with hospitalization for cerebrovascular disease in patients with chronic kidney disease and type 2 diabetes.

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HbA1c, Hemoglobin A1c.

*Reference group: Age 65-69 years; HbA1c <8% (Other neurological disorders include Parkinson's disease, choreas, unspecified extrapyramidal diseases and abnormal movement disorders, spinocerebellar disease, anterior horn cell disease, subacute combined degeneration of spinal cord in diseases, multiple sclerosis, other demyelinating disease of the central nervous system, hemiplegia, hemiparesis, anoxic brain damage, encephalopathy, convulsions, aphasia).

times), progression to ESKD (2.9 times) and all-cause mortality (2.4 times) than patients with UACR <30 mg/g. Elevated levels of HbA1c (≥8%) increased the chances for hospitalization for CVD (21.3%), CeVD (45.4%), and death (20.6%). However, increased testing for HbA1c lowered the risk of all outcomes including hospitalization for CVD (9.3%), CeVD (11.4%), and HF (10.4%), progression to ESKD (8.7%) and death (9.6%).

Among comorbidities, history of CHF increased the risk for all outcomes including hospitalization for CVD (26.4%), CeVD (19.7%), and HF (three times), progression to ESKD (35.7%) and death (55.9%). Similarly, prevalence of cardiac arrhythmia increased the risk of hospitalization for CVD (32.7%), CeVD (23.3%), and HF (61.0%), and death (19.7%).

The use of statins consistently decreased the risk for all outcomes including hospitalization for CVD (17.9%), CeVD (33.2%), and HF (25.6%), progression to ESKD (11.9%) and mortality (21.7%). However, history of use of insulin increased the risk for all outcomes including hospitalization or CVD (28.0%), CeVD (52.5%), and HF (48.0%), progression to ESKD (26.6%) and death (37.6%). Use of ACE inhibitors/ARBs was associated with lower risk of hospitalization for HF (12.1%) and death (8.6%).

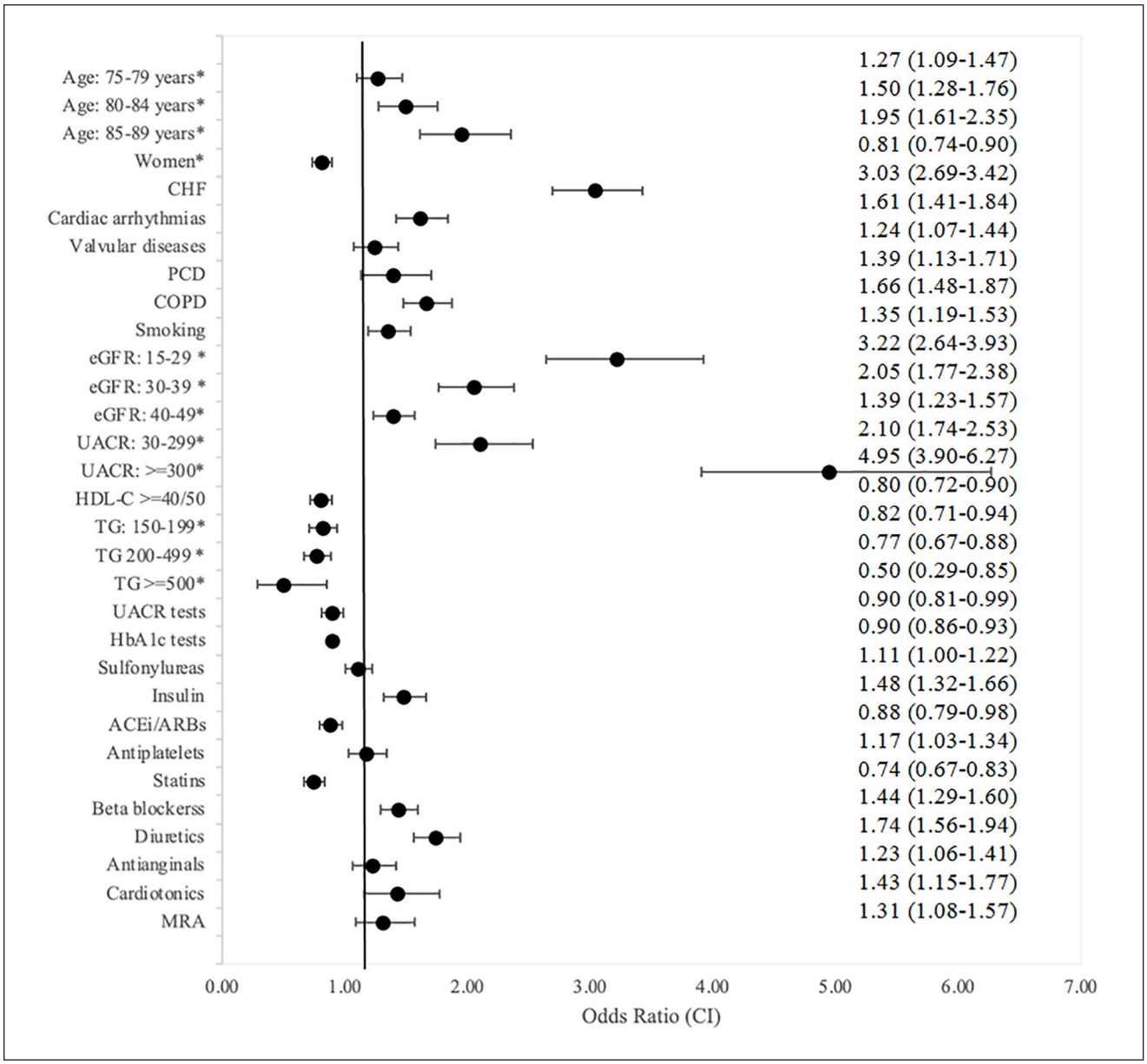

Figure 5. Factors associated with hospitalization for heart failure in patients with chronic kidney disease and type 2 diabetes.
Abbreviations: ACEi/ARBs, Angiotensin Converting Enzyme Inhibitors (ACE), Angiotensin II Receptor Blockers (ARB); CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; MRAs, mineralocorticoid receptor antagonists; PCD, pulmonary circulatory disorder; TG, triglycerides; UACR, urine albumin-creatinine ratio.
HDL-C ≥40/50 indicates ≥40 mg/dL for men and ≥50 mg/dL for women.
*Reference groups: Age 65-69 years; Men; eGFR 50-59 mL/min/1.73 m^2; UACR <30 mg/g; HDL-C <40 mg/dL for men/50 mg/dL for women; Triglycerides <150 mg/dL.

The predictive models in the training and validation datasets performed very well, with C-statistics (area under the curve) exceeding 0.70 in 4 of the 5 models, and in the case of hospitalization for HF, exceeding 0.80. As a sensitivity analysis, we also ran logistic regression models using backward selection and a retention value of $P = .01$, without employing the LASSO technique (Supplemental Tables E-I), which yielded mostly similar results and comparable model performance (Supplemental Table D).

Discussion

Among patients with T2D and CKD (stage 3-4), those with a history of CVD (cardiac arrhythmias, peripheral vascular disease), CHF, COPD, and fluid electrolyte disorders should

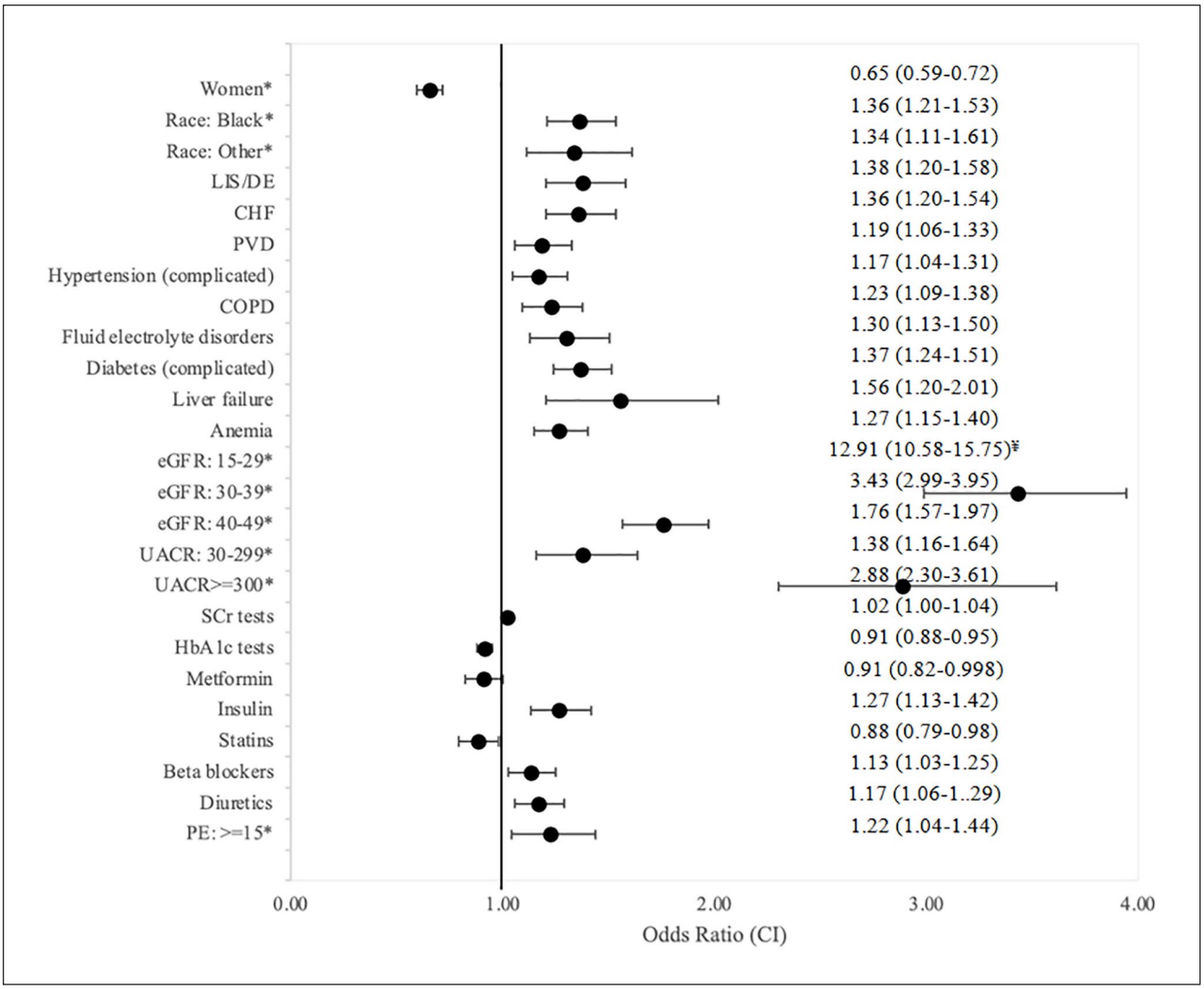

Figure 6. Factors associated with progression to end stage kidney disease in patients with chronic kidney disease and type 2 diabetes.

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FED, fluid electrolyte disorder; HbA1c, Hemoglobin A1c; LIS, low-income subsidy; PE, physician encounter; PVD, peripheral vascular disease; SCr, serum creatinine; UACR, urine albumin-creatinine ratio.

Other race includes all races not including patients of white or black race.

*Reference groups: Men; eGFR 50-59 mL/min/1.73 m^2; UACR $<$30 mg/g; Physician encounters $<$5.

¥Results not displayed on chart for eGFR 15-29 mL/min/1.73 m^2 (Odds ratio 12.91, 95% confidence interval 10.58-15.75).

be closely monitored since these comorbidities were predictive of multiple outcomes. Effective management of comorbidities, slowing down the decline in eGFR, managing albuminuria, increasing monitoring of HbA1c, glycemic control (HbA1c $<$8%), and use of statins may have the potential to avoid unwanted consequences.

In general, few studies have focused on the progression of CKD to ESKD in the T2D population.[19,21] While there are studies reporting predictive models and risk scores for CVD, CeVD, and HF,[24,25] to our knowledge, there is no published literature on predictive models for CVD, CeVD, and HF in patients with T2D and CKD. This study identified some key comorbidities and disease monitoring laboratory tests (eGFR, UACR, HbA1c) that can help identify patients with T2D and CKD at high-risk for clinical outcomes including progression to ESKD, mortality, and hospitalization for CVD, CeVD, and HF.

The C-statistics for the predictive models in the current study exceeded 0.70 in 4 of the 5 models, indicating that the models performed very well. The C-statistic (area under the curve) is the proportion of occurrences where a patient who had the outcome of interest had a higher

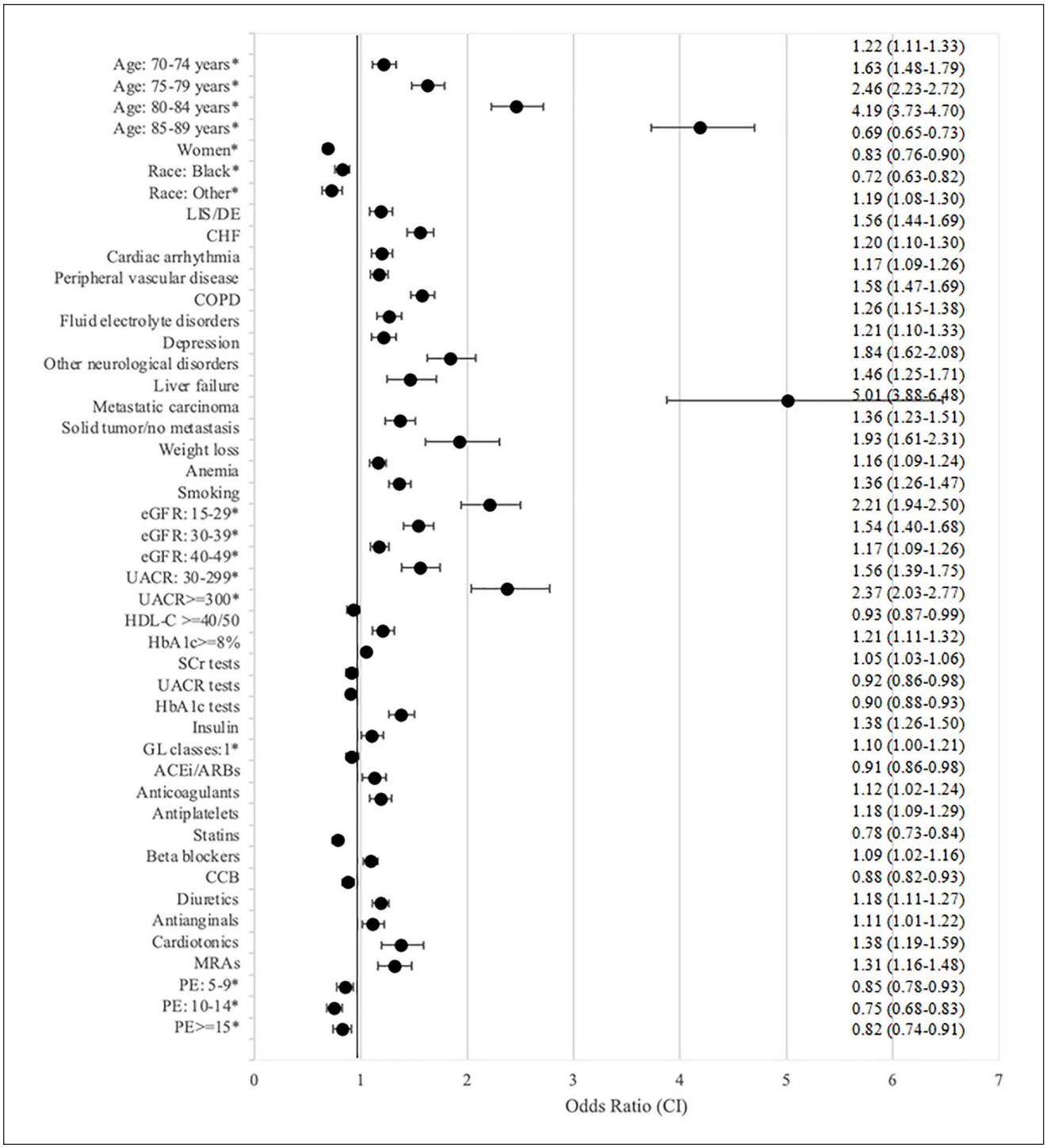

Figure 7. Factors associated with all-cause mortality in patients with chronic kidney disease type 2 diabetes.

Abbreviations: ACEi/ARBs, Angiotensin Converting Enzyme Inhibitors (ACEi), Angiotensin II Receptor Blockers (ARB); CCB, calcium channel blockers; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FED, fluid electrolyte disorder; GL, glucose-lowering; HbA1c, Hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LIS/DE, low income subsidy/dual eligible; MRAs, mineralocorticoid receptor antagonists; PE, physician encounters; PVD, peripheral vascular disease; SCr, serum creatinine; UACR, urine albumin-creatinine ratio.

Solid tumor category includes "no metastasis"; other race includes all races not including patients of white or black race.

*Reference groups: Age 65-69 years; Race White; Men; eGFR 50-59 mL/min/1.73 m^2; UACR $<$30 mg/g; HDL-C $<$40 mg/dL for men/50 mg/dL for women; Number of glucose-lowering medications—0; Physician encounters $<$5.

HDL-C $\geq$40/50 indicates $\geq$40 mg/dL for men and $\geq$50 mg/dL for women.

predicted probability than a patient who did not have the outcome. Models are typically considered effective when the C-statistic is greater than 0.7 and strong when it exceeds 0.8.[32,33] The models in the current study were based exclusively on claims data and included demographic and clinical characteristics along with laboratory values and healthcare resource use, making these models uniquely applicable for use by payers who may need to make decisions without having electronic health records readily available to them.

While patients of black and other race had lower risk for hospitalization for CVD and all-cause mortality compared to white patients, they had a high risk for progression to ESKD. Studies have reported the lower risk for CVD and mortality in patients of minority race compared to the white race,[34] but higher risk for ESKD[35-37] especially for black patients. Women had 19% to 31% lower chance of hospitalization for CVD and HF, progression to ESKD and all-cause mortality compared to men. Similar to the current study, Young et al[25] reported lower risk for women for cardiovascular events (CVD, CeVD, HF) and death than men in patients with T2D. However, published literature also notes that while the incidence of CVD is low among women compared to men, the associated morbidity and all-cause mortality is higher among women.[38,39] While none of these demographic characteristics are modifiable, understanding who is at highest risk for specific outcomes according to age, sex, and race can enable physicians and payers to customize treatment, disease management programs, and other interventions.

Young et al[25] developed models predicting the risk of cardiovascular risk events (CVD, CeVD, HF, and death) among patients with T2D but included patients with and without CKD. Similar to the current study, some of the comorbidities associated with risk of cardiovascular events reported by Young et al. included COPD, fluid electrolyte disorders, pulmonary circulatory disorders, cancers and history of CVD, CeVD, and HF. Identifying patients with these specific comorbidities that increase risk for specific negative outcomes can also help providers to focus on these patients in the management of T2D and CKD.

Decreasing eGFR levels (15-49 mL/min/1.73 m^2) were associated with increased risk for all outcomes, except hospitalization for CeVD. Wang et al[41] evaluated the association of coronary heart disease and eGFR by race and reported that lower levels of eGFR were associated with increased risk for coronary artery disease among both whites and African Americans. Low eGFR levels have been reported to increase risk for HF[42] and mortality.[42-45] While the published literature reports an increased risk of stroke with decreasing levels of eGFR,[41,46] we did not find this in the current study. In patients with low index eGFR levels, especially 15 to 29 mL/min/1.73 m^2, even a small change in eGFR can lead to ESKD. These declining eGFR levels and their association with the unwanted outcomes may simply be indicative of the progression and severity of CKD.

With the exception of hospitalization for CeVD, patients with UACR 30 to 299 mg/g and ≥300 mg/g increased the risk for hospitalization for CVD (29.9% and 2.0 times) and HF (2.1 and 4.9 times), progression to ESKD (1.4 and 2.9 times) and all-cause mortality (1.6 and 2.4 times) compared to those without albuminuria. The relationships between elevated UACR levels or albuminuria with renal function,[47-49] CVD,[50-52] HF,[52] and mortality,[44,51,52] have been reported previously. However, 55% to 65% of the overall sample and patients with the pre-specified outcomes did not have any UACR values and >50% of the patients had no indication in the claims data that an UACR test was performed. While this is consistent with literature,[53] it warrants further evaluation to identify the reasons for the low number of UACR tests documented.

Poor glycemic control not only has detrimental effects on the management of DM but also increases the risk of development of microvascular complications and mortality.[54-56] In the current study, patients with HbA1c ≥8% had a greater risk for hospitalization for CVD, CeVD, and death. Among patients with HbA1c values, only 16% to 23% of patients with these outcomes (hospitalization for CVD, CeVD, and death) and had HbA1c ≥8%. However, they are in alignment with the statistics reported by population-based studies.[57] In other population-based studies, elevated HbA1c has been reported to be an independent predictor of all-cause and CVD-related mortality.[58] Furthermore, every 1% increase in HbA1c in patients with DM was associated with a 30% increase in CVD-related mortality.[59] In the current study, we also observed that increased number of HbA1c tests was associated with lower risk of all outcomes. Monitoring eGFR, UACR and HbA1c can play a crucial role in preventing or delaying some of these negative outcomes. These tests signal the decline of kidney function and difficulty in managing the chronic conditions and can enable providers and payers to identify these high-risk patients for interventions designed to help manage their condition.

As expected, the use of statins during pre-index decreased the risk of all outcomes. While dyslipidemia has been noted to be a risk factor for heart diseases, the benefits of statin use in decreasing mortality, CVD, CeVD, and HF have been well documented in the literature, especially for primary prevention.[60,61] Statin use is also an indicator that these patients are more likely to engage in health-promoting behaviors.[62]

The cardiovascular and renal systems are interconnected and disorders affecting one system often adversely affects the other.[63] As both diseases progress through a chain of continuous events in the cardiorenal continuum due to certain risk factors, it can lead to subclinical disease and events and ultimately negative outcomes such as hospitalization for CVD, CeVD, HF, progression to ESKD, and death. Focusing on key factors, such as managing albuminuria, slowing decline of kidney function, and management of diabetes, that could reduce negative outcomes in patients

with CKD and T2D, can serve as strategic areas of focus for multiple stakeholders. Healthcare providers could utilize these findings to create awareness with their patients regarding these risk factors and communicate the urgency of taking action to avoid consequences of inadequate management. Through shared decision making, patients and providers can align on specific goals to manage these aspects in order to improve future outcomes. To support providers, payers may consider programs to proactively identify at-risk patients who may be appropriate for further clinical management programs or other novel interventions, such as remote UACR monitoring with digital devices, to avoid adverse outcomes. The results of this study can be immediately leveraged by stakeholders; however, future work could focus on further validation in other populations in addition to development of a risk-scoring algorithm that could increase the real-world clinical utility for providers.

Limitations

As with all studies utilizing administrative claims data, common limitations such as potential errors in coding, omissions in claims data, and unmeasured clinical, economic, or behavioral factors may affect results. Since this study focused on an MAPD population within in a large national health plan, the results may not be generalizable to a younger population enrolled in commercial plans. Future studies should be conducted in a different population to validate these results.

No causal inference can be ascertained from the results since this was a non-randomized study using data observed in a non-interventional setting. Additionally, a lack of medical records makes it difficult to understand their impact on diagnosis, treatment, and outcomes. Furthermore, laboratory values (eGFR, UACR, and HbA1c) were available only for a subset of patients. The characteristics and outcomes for patients with laboratory values and that were included in the study may differ from those who did not have any values. Evidence of smoking was based on diagnosis codes and certain counseling codes and hence may be underreported.

Patients were enrolled a year prior to index date and followed until end of enrollment or death, whichever came first. Since not all patients had full 2 years of post-index enrollment, we used inverse probability censoring weighting to account for the varying follow-up time.

Conclusion

The predictive risk models developed in this study could immediately serve as a valuable decision support tools for physicians to identify patients with CKD and T2D eligible for further intervention. Payers can use these models to develop interventions and identify appropriate patients who may benefit from them and support healthcare providers in developing tools for clinical management. Moreover, the risk scores from these models can be applied to future outcomes studies focused in CKD and T2D (eg, for confounder adjustment). Further validation of the models is needed prior to extrapolating to other populations and to help providers and payers to apply these in real-world clinical practice.

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Author Contributions

All authors actively collaborated on the study design and interpretation of results; contributed in writing this paper; and have provided final approval of the submitted version.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: RS and RN are employees of Humana Healthcare Research, Inc. MP was an employee of Humana Healthcare Research at the time of the study. MC is an employee of Humana Inc. The following authors are employees of Bayer AG at the time of the study: TE, AG, RS, and NS.

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Supplemental Material

Supplemental material for this article is available online.

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