DEVELOPMENT AND PREDICTIVE UTILITY OF A COMPREHENSIVE GERIATRIC ASSESSMENT FOR OLDER ADULTS WITH CHRONIC KIDNEY DISEASE

by
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Abstract

Background: Older adults with chronic kidney disease (CKD) are at high risk of developing geriatric conditions in multiple domains, resulting in adverse health outcomes. A comprehensive geriatric assessment (CGA) tailored to the CKD population would yield a more targeted approach to assessment and care. The aims of this study were to 1) identify domains of a CKD-specific CGA (CKD-CGA), 2) characterize patterns of these domains in older adults with CKD, and 3) test the predictive utility of the CKD-CGA on adverse health outcomes.

Methods: We used data from 868 participants enrolled in the Chronic Renal Insufficiency Cohort who were 55 years or older and not on dialysis (median age=67). Constituents of the CKD-CGA were selected a priori. Latent class analysis was conducted to inform the development of the CKD-CGA and to identify patterns of geriatric conditions in the participants. We examined the predictive utility of the CKD-CGA on mortality (Cox regression), dialysis initiation (Cox regression), and hospitalization (logistic regression), adjusting for age, sex, race, eGFR, smoking status, and BMI. Model discrimination was assessed with C-statistics.

Results: The CKD-CGA included 16 domains: cardiovascular disease, diabetes, five frailty phenotype components, depression, cognition, five kidney disease quality of life components, health literacy, and medication use. A two-class model fit the data best, with 34.9% and 65.1% in the high and low burden of geriatric conditions class, respectively. Compared to participants in the low burden of geriatric conditions class, those in the high burden of geriatric conditions class were at higher risk of mortality (aHR=2.10; 95% CI: 1.55, 2.85), dialysis initiation

(aHR=1.74; 95% CI: 1.13, 2.68), and hospitalization (aOR=1.98; 95% CI: 1.37, 2.84). Model discrimination was the strongest for dialysis initiation (C-statistics=0.86), and moderate for mortality and hospitalization (C-statistics= 0.70 and 0.66, respectively).

Conclusions: We derived a CKD-CGA for older adults using psychometric methods and identified a class of participants with a high burden of geriatric conditions who were at risk of adverse health outcomes. The CKD-CGA has the potential to be used in nephrology practice for assessing and managing geriatric conditions in older adults with CKD.

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1. Introduction

Chronic kidney disease (CKD) is prevalent among older adults, affecting over 38% of those 65 years and older[1]. This group of individuals is at high risk of co-morbidities and declines in various domains, such as frailty[2,3], cognitive impairment[3-5], and poor quality of life[6]. These medical, social, and functional conditions may independently or interactively result in downstream adverse health outcomes, including progression to end-stage kidney disease and mortality[7-9]. Clarifying the milieu of geriatric conditions commonly experienced by older patients with CKD, and optimizing targeted assessment for these conditions could lead to timely management of health issues and improve health outcomes.

A comprehensive geriatric assessment (CGA) can be used for identifying multidimensional needs unique to older patients and helps inform multidisciplinary, coordinated care plans to improve outcomes[10-13]. The implementations of CGAs in older CKD patients have been found to help guide care processes, improve treatment satisfaction, and decrease distress[14-16]. Previous studies have applied generic CGAs to patients with CKD[17,18]. However, generic CGAs are designed for older patients without CKD and, thus, may be less practical and have flooring or ceiling effects in older patients with CKD. Moreover, generic CGAs often do not include geriatric conditions that frequently coexist with CKD. For example, frailty can develop at younger ages (i.e., ≤65)[19], and is more common among older adults with CKD than those with normal kidney function[2]. Similarly, kidney disease-specific quality of life domains are important patient-reported domains predictive of adverse health outcomes but would not be included in generic

CGAs[20,21]. Given the nuances of aging with CKD, finding the right elements of a CKD-specific CGA may yield a more practical and less resource-intensive approach to assessment and care[22].

In this study, we sought to develop a CKD-specific CGA (CKD-CGA) leveraging the rich data from the Chronic Renal Insufficiency Cohort (CRIC). Using 868 community-dwelling older participants (55 years and older) representing all stages of CKD, we 1) identified domains of a CKD-CGA, 2) characterized patterns of these domains in older adults with CKD, and 3) tested the predictive utility of the CKD-CGA on adverse health outcomes.

2. Methods

2.1 Study design

The Chronic Renal Insufficiency Cohort (CRIC) is an ongoing, multicenter prospective cohort study for examining risk factors, etiology, diagnosis, and outcomes of adults with CKD. Between 2003 and 2008, 3,939 participants between 21 and 74 years old with mild to moderate chronic kidney disease (age-specific estimated glomerular filtration rate [eGFR] rate ranging 20-70 ml/min/1.73m^2) were recruited at seven clinical centers in the United States. Participants had annual in-person follow-up visits. Follow-up data were available through December 2018. The design and methods of the study have been extensively described elsewhere[23,24].

We selected participants enrolled in the Physical Performance ancillary study. The cross-sectional ancillary study was conducted in four of the seven centers from April 2008 to February 2010 (University of Pennsylvania, Johns Hopkins University, University of Michigan, and Kaiser

Permanente of Northern California). The ancillary study visit serves as the baseline visit for the current study. A total of 1,156 participants were enrolled in the Physical Performance Ancillary Study. We excluded 253 individuals younger than 55 years old and 35 individuals who had initiated dialysis. The study protocol was approved by the institutional review boards at each participating site. All participants provided written informed consent.

2.2 Potential domains in the CKD-CGA

Potential domains to include in the CKD-CGA were selected *a priori* based on clinical expertise, literature, and the availability of measures in CRIC. A total of 17 domains were considered: cardiovascular disease, hypertension, diabetes, five physical frailty phenotypes (Fried's physical frailty phenotypes[25]: weakness, exhaustion, slowness, low physical activity, and weight loss), depression (Becks Depression Inventory [BDI][26]), cognition (Modified Mini-Mental State [3MS][27]), five kidney disease quality of life components (Kidney Disease Quality of Life-36 [KDQOL-36][28]: burden, effects, and symptoms of kidney disease, and physical and mental component summaries), health literacy (Short Test of Functional Health Literacy in Adults [S-TOFHLA][29]), and medication use (potentially inappropriate medication identified according to 2015 American Geriatric Society Beers Criteria[30]). Each domain was categorized into a binary indicator. The cut-offs for having a geriatric condition were derived from clinically recognized cut-offs. If no clinically recognized cut-offs exist, we used the 20th percentile, in line with Fried's precedent of choosing cut-offs for frailty phenotypes derived from continuous measures[25]. We used data collected at the baseline of the ancillary study to assess each geriatric domain. The only exception was health literacy, which was measured at the baseline of the parent study,

and values were assumed to be constant throughout follow-ups. Table 1 presents details on the considered domains, the timing of data collection, the description of instruments used, and the chosen cut-offs for having a geriatric condition.

2.3 Outcomes

The primary outcome of interest, for the purpose of evaluating the predictive utility of the derived CKD-CGA, was all-cause mortality. Death was ascertained using linkage with the Social Security Death Master File, retrieval of death certificates or obituaries, review of hospital records, or reports from next-of-kin. Participants were censored at death, loss to follow-up, or administratively in December 2018. Time to mortality was measured in years from baseline of the ancillary study.

Our secondary outcomes of interest were dialysis initiation and all-cause hospitalization. Initiation of dialysis was determined by self-report, records from local clinical centers, or linkage with the United States Renal Data System (USRDS) at each annual visit. Participants were censored at the first initiation of dialysis, death (a competing event), loss to follow-up, or administratively in December 2018. Time to dialysis initiation was measured in years from baseline of the ancillary study. The number of hospitalizations in the last 12 months was ascertained at each annual visit. We used data obtained the year after the baseline visit to predict the risk of hospitalization within 12 months of applying the comprehensive geriatric assessment. Hospitalization was treated as a binary variable; participants either had or did not have any hospitalization (1 or 0, respectively).

2.4 Covariates

Sociodemographic characteristics, including sex, race (white, black, and other), marital status (married and not married), education (less than high school, high school graduate, some college, and college graduate or higher), and household income ($20,000 or under, $20,001-$50,000, $50,001-$100,000, more than $100,000, and do not wish to answer) were measured at baseline of the parent study. Age, smoking status (current and non-current smokers), body mass index (BMI; weight in kilograms divided by height in meters squared), and eGFR were updated annually; values at baseline of the ancillary study were used. We determined eGFR, expressed in mL/min/1.73m^2, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[31].

2.5 Statistical analysis

Descriptive statistics, overall and stratified by age groups (55-64 versus 65 and above), were used to describe the study population at baseline. Categorical variables were reported in counts and proportion; comparisons between groups were conducted using chi-square tests. Continuous variables were reported in means and standard deviation; comparisons between groups were made using Students' t-tests.

2.5.1 Latent class analysis

Latent class analysis (LCA) is a parametric approach used to empirically identify underlying, distinct subgroups (or classes) based on patterns of binary indicators. LCA was applied to the 17

binary indicators of potential geriatric domains. We fit a series of 1- to 5-class models to identify the solution that provided the best fit to the data. For each class, the prevalence of class membership was estimated, as was the prevalence of each indicator conditioned on class membership (i.e., conditional probabilities). To evaluate the optimal number of latent classes, we compared models based on four fit indices: Akaike Information Criterion (AIC)[32], Bayesian Information Criterion (BIC)[33], Lo-Mendell-Rubin adjusted likelihood ratio test (LMR LRT)[34], and bootstrapped likelihood ratio test (BLRT)[35]. For AIC and BIC, lower values indicate better fit. However, these indices tend to decrease with additional parameters (i.e., additional classes) and may be poor indicators of parsimony. LMR LRT and BLRT compare the fit of a model (k-class) to a smaller model (k-1 class); a non-significant chi-square test ($p>0.05$) suggests a comparable fit between the two models. Entropy was estimated to evaluate classification error[36]. The index ranges from 0 to 1, with higher entropy suggesting less error in classifying individuals. Findings of more than one latent class, in which the conditional probabilities of the indicators are homogeneous in each class but show separation between classes, would be consistent with evidence for a syndromic nature of CKD-related geriatric conditions[37]

LCA aided the final selection of domains in the CKD-CGA. Comparisons of the difference in conditional probabilities of each geriatric condition across classes were done using Cohen's *d*, an effect size measure of the difference between two groups[38]. Effect sizes were categorized as trivial ($d < 0.2$), small-to-medium ($0.2 \leq d < 0.5$), medium-to-large ($0.5 \leq d < 0.8$), or large ($d > 0.8$). Hypertension had the smallest effect size relative to the other geriatric conditions ($d = 0.29$), suggesting that the domain did not discriminate as well between classes. Therefore, it

was removed from the final list of domains to include in the CKD-CGA. LCA was re-applied to the remaining 16 domains.

LCA assumes conditional independence; the indicators are independent of one another because any relationships are fully explained by latent class membership. We assessed this assumption by scrutinizing standardized bivariate residuals. If the Z-scores of the bivariate residuals exceed an absolute value of 1.96, that would suggest a potential violation of the local independence assumption and that the model may not be explaining the relationship between the variables well[39].

2.5.2 Outcome prediction

Cox proportional hazard models were conducted to examine time to mortality and dialysis initiation. Violation of the proportional hazard assumption was tested for all Cox proportional hazard models. Logistic regression models were conducted to examine hospitalization. For latent class regression (LCR; using latent class membership as the predictor in a regression analysis), we manually conducted Vermunt's three-step approach to account for classification error and to prevent the outcome from influencing class membership[40,41]. We evaluated model discrimination, the ability of the models to assign a higher probability of outcomes to participants who have the outcome, using concordance statistics (C-statistics)[42,43]. C-statistics range from 0.5 to 1, with 0.5 indicating model prediction is no better than chance and 1 indicating perfect prediction. C-statistics were calculated from Cox proportional hazard and logistic regression models that used the most-likely posterior class membership – the class

individuals have the highest probability to be in given their pattern of geriatric conditions – as the exposure variable[44]. All models were adjusted for age, sex, race, BMI, eGFR, and smoking status.

Missing data management

There was a high proportion of missing values for depressive symptoms (53.3%) and cognition (38.2%) at baseline because these measures were collected biannually. Given the longitudinal nature of the CRIC study, we conducted linear interpolation imputation[45], wherein missing values were imputed by averaging the values from the visit before and after the baseline visit. Domains other than depression and cognition had missingness at baseline ranging from 0% to 7%; this missingness was assumed missing at random conditional on other variables in the model. Full informational maximum likelihood (FIML) estimator accounted for missing values in LCA and LCR. Multiple imputation was implemented using chained equations (MICE) for multivariable models used to calculate C-statistics[46,47].

2.5.3 Sensitivity analysis

A total of 36 individuals were missing hospitalization data the year after baseline due to loss to follow-up. LCR in the main analysis accounted for missing values. However, the C-statistic calculation from the multivariable logistic regression model using most-likely posterior class membership as the exposure variable was conducted without these participants. As a sensitivity analysis, we included participants who were previously excluded by using their hospitalization data from the previous year.

To further test the predictive utility of the CKD-CGA, we created an index score for each participant by summing their 16 indicators of geriatric conditions. The continuous score, as well as quartiles of the scores were used as the exposure variables in the multivariable models for predicting adverse health outcomes.

LCA and LCR were conducted using Mplus 8.6 (Los Angeles, CA, USA)[48]; all other analyses were conducted using Stata 16.1 (College Station, TX, USA)[49].

3. Results

3.1 Study population

A total of 868 participants were followed for up to 10.8 years. The median age was 67 and ranged from 55 to 80 years old. Thirty-nine percent were 55-64 years old and 61% were 65 and above. In our sample, 47.1% were women, 58.6% were White, 35.5% were Black, 63.1% were married, 49.3% graduated college, and 6.7% were current smokers (Table 2). In comparison to their younger counterparts (age 55-64), a higher proportion of participants 65 and older had lower household income and eGFR.

Given the high proportion of missing depression and cognition measures, we compared the characteristics of those missing and not missing the measures. All sociodemographic characteristics between the groups were similar ($p>0.05$). However, those missing cognition or depression measures tend to have higher BMI ($p=0.001$ for cognition and $p=0.01$ for

depression), and lower eGFR (p=0.001 for depression, and p=0.046 for cognition). After imputation, there were no significant differences in the proportion of participants with cognitive impairment or depression, comparing those who had and did not have missing measures (p=0.149 for cognition and p=0.449 for depression).

A total of 16 domain indicators were included in the CKD-CGA. The median number of geriatric conditions among the older adults was 3, with a range from 0 to 15. Chronic conditions were prevalent among the study participants; 44.4% had diabetes and 36.8% had at least one cardiovascular disease. The sample was largely cognitively normal, with only 1.4% meeting the definition of cognitive impairment. A total of 8.4% had depression and 6.6% had limited health literacy. The majority (57.1%) were using potentially inappropriate medication. Compared to participants 55-64 years old, a higher proportion of participants 65 and older have cardiovascular disease and the frailty phenotypes: weakness, slowness, and low physical activity.

3.2 Patterns of geriatric conditions in older adults with CKD

The model fit indices (Table 3) suggest that a 2-class model fit the data the best. AIC was the lowest in a 5-class model (11691.1) while BIC was the lowest in the 3-class model (12033.9). However, the largest drop in both AIC and BIC was from the 1-class to the 2-class model (from 12947.1 to 11900.9 for AIC and from 13023.3 to 12058.2 for BIC). The BLRT was less helpful in distinguishing the best-fitted model; it estimated that all k-class models fit significantly better than the k-1 class models ($p<0.001$). On the other hand, the LMR LRT suggested that the 2-class

model fit significantly better than the 1-class model ($p<0.001$) but that a 3-class model was no better than a 2-class model ($p=0.08$), a 4-class model was no better than a 3-class model ($p=0.34$), and a 5-class model was no better than a 4-class model ($p=0.07$). Lastly, the Entropy was the highest in the 2-class model (entropy=0.80), indicating the least error in classifying participants into latent classes compared to the other models.

Of the 480 standardized bivariate residuals, there were multiple extreme values between domains in all models (23, 15, 10, and 7 in a 2-, 3-, 4-, and 5-class model, respectively), suggesting local dependence may be violated. However, given the trade-off being local independence and class size[44], the relatively superior fit indices, and the interpretability and meaningfulness of the classes, we believe altering the 2-class model was not justified.

The first latent class comprised of 34.9% of the population (Figure 1). The conditional probabilities of having geriatric conditions in the class were moderate to high (ranging from 26% to 69% with a few exceptions; Table 4). We named this class the "high burden of geriatric conditions" class. The second class, labelled the "low burden of geriatric conditions" class, comprised the remaining 65.1% of the sample (Figure 1). The conditional probabilities of having geriatric conditions were low to moderate (ranging from 1% to 27% with a few exceptions; Table 4). Both classes (high and low burden of geriatric conditions, respectively) have a relatively low conditional probability for weight loss (11% versus 3%), cognitive impairment (7% versus 1%), and limited health literacy (13% versus 4%); and a relatively high conditional probability for the use of potentially inappropriate medication (69% versus 52%).

3.3 Association of the CKD-CGA with outcomes

The median number of years of follow-up was 9.7 years for mortality and 8.3 years for dialysis initiation. Out of 868 participants, there were 236 deaths (27.2%) and 136 dialysis initiations (15.7%) during follow-up. A total of 274 individuals (out of 832; 32.9%) were hospitalized at least once within 12 months after study enrollment.

The cumulative incidence of death in the high burden of geriatric conditions class was consistently higher than in the low burden of geriatric conditions class throughout follow-up (Figure 2). At 1-, 5-, and 10-years of follow-up, the unadjusted cumulative incidence of death was 3.0%, 19.5%, and 41.8% in the high burden of geriatric conditions class and 0.9%, 8.6%, and 21.8% in the low burden of geriatric conditions class, respectively (Table 5). The cumulative incidence of dialysis initiation followed a similar trend (Figure 2): 2.8%, 17.6%, and 32.4% in the high burden class and 1.2%, 7.2%, and 16.1% in the low burden class at 1-, 5-, and 10-year, respectively (Table 5).

After adjusting for age, sex, race, eGFR, BMI, and smoking status, the high burden of geriatric conditions class had a 2.10-fold increased hazard of death (95% CI: 1.55, 2.85, $p<0.001$), a 1.74-fold increased hazard of dialysis initiation (95% CI: 1.13, 2.68, $p=0.01$), and a 1.98-fold increased odds of being hospitalized within 12 months of geriatric assessment (95% CI: 1.37, 2.84, $p<0.001$) compared to the low burden of geriatric conditions class (Table 5). Model discrimination was excellent for time-to-dialysis initiation (C-statistics=0.86) and moderate for

time-to-mortality and hospitalization (C-statistics= 0.70 and 0.66, respectively). Predicting outcomes with latent class membership slightly increased discrimination compared to a base model – a model that only includes the adjusted covariates. However, including all 16 geriatric domains in a model, after adjustment, provided the largest increase in discriminatory power (Table 6).

3.4 Sensitivity analysis

Replacing missing values of hospitalization 12 months from baseline using hospitalization 12 months prior to baseline resulted in a similar association and inference as the main analysis. The association between the burden of geriatric conditions and hospitalization remained statistically significant (aOR=2.00, 95% CI: 1.47, 2.73, p<0.001). Model discrimination slightly improved (C-statistics=0.67).

The index score of geriatric conditions was predictive of adverse outcomes. After adjusting for confounders, for each additional geriatric condition, participants experienced a 1.18-fold increased hazard of mortality (95% CI: 1.13, 1.24, p<0.001), a 1.11-fold increased hazard of dialysis initiation (95% CI: 1.04, 1.18, p=0.001), and a 1.15-fold increased odds of hospitalization (95% CI: 1.08, 1.22, p<0.001) (Table 7). Model discrimination using continuous index scores as the exposure variable was high for dialysis initiation (C-statistics=0.86) and moderate for mortality and hospitalization (C=statistics= 0.72 and 0.67, respectively).

Quartiles of the index scores consisted of participants with 0-1, 2-3, 4-5, and 6-15 geriatric conditions. The unadjusted cumulative incidence of mortality and dialysis initiation increased with higher quartiles of index score (Figure 3). After adjusting for confounders, being in higher quartiles was associated with a higher risk of adverse outcomes (Table 7). Compared to participants in the first quartile of index score, participants in any higher quartiles had a significantly increased hazard of mortality (second quartile: aHR=1.74, 95% CI: 1.09, 2.79; third quartile: aHR=2.80, 95% CI: 1.73, 4.52; fourth quartile: aHR=4.33, 95% CI: 2.70, 6.93). Similarly, having scores in a higher quartile, in comparison to the first quartile, was associated with a higher hazard of dialysis initiation. However, the association was only significant for those in the third and fourth quartiles (third quartile: aHR=2.23, 95% CI: 1.16, 4.28; fourth quartile: aHR=2.79, 95% CI: 1.48, 5.25). Lastly, participants with scores in the fourth quartile were associated with higher odds of hospitalization within 12 months of the geriatric assessment (aOR=2.61, 95% CI: 1.63, 4.18). Model discrimination using quartiles of index scores as the exposure variables were 0.72, 0.86, and 0.68 for mortality, dialysis initiation, and hospitalization, respectively.

4. Discussions

Using data from CRIC, we developed a CKD-CGA with 16 domains of geriatric conditions for adults aged 55 and older with all stages of CKD. The LCA indicated that the clustering of these geriatric conditions was syndromic in nature, tending to manifest together. Thirty-five percent of the participants had a moderate to high burden of geriatric conditions. Participants who had a high burden of geriatric conditions were more likely to experience future adverse health

outcomes. After adjusting for confounders, participants with a high burden of geriatric conditions had a 2.10-fold (95% CI:1.55, 2.85) increased risk of experiencing death, a 1.74-fold (95% CI: 1.13, 2.68) increased risk of dialysis initiation, and a 1.98-fold (95% CI: 1.37, 2.84) increased odds of hospitalization within the next year compared to participants with a low burden of geriatric conditions. The CKD-CGA was good at predicting dialysis initiation (C-statistics=0.86) and fair at predicting mortality and hospitalization (C-statistics= 0.70 and 0.66, respectively).

The designs of CKD-specific CGAs across studies differ in the number of domains, the instruments used to measure the domains, and the cut-offs that define the geriatric conditions. Therefore, direct comparisons with other studies on included domains and the prevalence of geriatric conditions are limited. In general, previous studies found a high prevalence of geriatric conditions among older adults with CKD[14,50-52]. This is consistent with our study which found over a third of older participants experienced a high burden of geriatric conditions. Similar to many of the studies that designed a CKD-specific CGA, our CKD-CGA included domains on chronic conditions, cognition, depression, and frailty. Our CKD-CGA additionally included less commonly incorporated domains that may more broadly capture the nuances of aging with CKD, such as quality of life, health literacy, and medication use. Declines and problems in these domains have been associated with CKD and subsequent adverse health outcomes[53-58]. Including these additional domains may allow our CKD-CGA to provide a more holistic assessment of geriatric conditions in the older CKD population living in the community.

Currently, no other studies of CKD-specific CGA, of which we are aware, have taken the development of the assessment a step further and tested predictive utility. One study of a multidimensional prognostic index derived from a generic eight-domain CGA reported that increased index scores were associated with short-term (one- and two-year) all-cause mortality in hospitalized older patients with CKD[17,18]. In using the CKD-CGA, we found that having a high burden, as well as having a higher number of geriatric conditions is predictive of all-cause mortality and dialysis initiation up to 10 years, and hospitalization within one year after assessment. Our study extends upon the current literature in suggesting that there may be both short-term and long-term consequences of having multiple geriatric conditions in the CKD population. In addition, incorporating more geriatric domains would provide a stronger prediction of adverse health outcomes than individual domains alone. This supports the need for multi-dimensional assessment and multidisciplinary care for the older CKD-population.

Our CKD-CGA was applied to a slightly younger population (≥55), compared to existing CKD-specific CGAs which studied participants mainly ≥65 years old. However, we believe the inclusion of younger participants was justifiable. Firstly, the main beneficiaries of CGAs in acute care – the setting CGAs were initially developed for – were people ≥55 years of age[11]. Similarly, the CKD population ≥55 and living in the community may also benefit from multidimensional health assessments. Secondly, the results of our study suggest that those ≥55 have a high burden of geriatric conditions. Moreover, the CKD-CGA provides moderate to good prediction of adverse health outcomes. This reinforces the advantage of applying the CKD-CGA to older

adults, including individuals in the 55-65 age group, so that early assessment and care can be provided before progression to end-stage kidney disease, a need for acute care, or mortality.

Our study has several strengths. To our knowledge, this is the first study to empirically identify the domains of a CKD-CGA using psychometric methods in conjunction with *a priori* knowledge, in an attempt to minimize potential bias associated with the subjective selection of domains[59]. The CKD-CGA is designed to be used for older adults at all stages of CKD, improving upon existing CKD-specific CGAs which often only targeted patients in advanced stages of CKD[16,50,59]. Further, we leveraged long-term follow-up data up to 10.8 years to assess the predictive utility of the CKD-CGA. This study, however, is not without limitations. In our data, cognition and depression measures had a high proportion of missing values due to the study design. However, we conducted imputation and, additionally, participants with and without missing measures did not significantly differ in any sociodemographic characteristics. Another limitation is that the participants in the study may not represent a generalizable sample of the CKD population in the United States. The cross-sectional ancillary study from which we selected our study population recruited participants with varying follow-up lengths since enrollment into the parent study. Individuals who remained in the parent study and subsequently enrolled in the ancillary study may be healthier. However, given that our sample consists of younger and potentially healthier older adults, our results are likely an underestimation. That is, the risk of adverse health outcomes associated with the burden of geriatric conditions in community-dwelling older adults with CKD is likely much higher, further warranting the use of the CKD-CGA to improve assessment and care in this population.

The findings in our study have strong clinical implications for nephrology and geriatric practices. The association of the burden of geriatric conditions with adverse health outcomes provides evidence for the value of assessing for geriatric conditions in older adults at all stages of CKD. Early identification of geriatric conditions has the potential to help initiate discussion on and guide individualized care plans, delay or prevent CKD progression, and ensure maintenance of independence and quality of life[14,16,50]. One potential disadvantage in using the CKD-CGA is logistical difficulties. CGAs may be time and labor-intensive given the comprehensive and multidisciplinary approach to assessment and care. However, a recent qualitative study with 47 health care providers has suggested that patients predominantly view the time and content of assessment positively[15]. Providers, on the other hand, appreciate the multidimensional approach to care provision[15]. Nevertheless, future research should examine the feasibility of incorporating the CKD-CGA into nephrology practice, as well as the effectiveness and impact of its implementation. Further validation of the assessment would be crucial in confirming the utility and potential of the CKD-CGA in elevating CKD care in the older population.

5. Conclusions

We developed a CKD-CGA for older adults of all stages of CKD using psychometric analyses, and examined its predictive utility. We identified a class of participants with a relatively high probability of experiencing most geriatric conditions. These individuals are at a higher risk of mortality, dialysis initiation, and hospitalization. The CKD-CGA has the potential to be used in

nephrology practices for assessing geriatric conditions, informing decision-making, and improving health outcomes in older adults with CKD.

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Table 1. Instruments and cut-offs for measuring potential geriatric conditions

Potential domains	Timing of data collection	Instrument(s) and description	Cut-off for having the geriatric condition
Cardiovascular disease	Annual	Participants were asked to respond "yes", "no", or "don't know" to the question: "have you ever been diagnosed with or has a doctor or other health professional ever told you" for coronary artery disease, prior revascularization, heart failure, stroke, and peripheral vascular disease.	Responding "yes" to any one of five cardiovascular diseases or labelled as having any cardiovascular disease at a previous visit.
Hypertension	Annual	Systolic or diastolic blood pressure (in mmHg) or self-report.	Systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 90 mmHg, self-reported use of hypertension medication, or labelled as having hypertension at a previous visit.
Diabetes	Annual	Fasting plasma glucose (in mg/dL), non-fasting plasma glucose (in mg/dL), or self-report.	Fasting glucose ≥ 126 mg/dl, non-fasting glucose ≥ 200 mg/dl, self-reported use of insulin or diabetic medication, or labelled as having diabetes at a previous visit.
PFP: Weakness	At baseline	Average of three grip strength tests (in kilogram-force) using a Digital Grip Dynamometer (Creative Health Products, Ann Arbor, MI).	Average grip strength lower than pre-specific gender- and body mass index-specific cut-offs (lowest 20%)[25].
PFP: Exhaustion	At baseline	Center for Epidemiologic Studies Depression Scale (CES-D)[60]. Participants were asked to rate how often in the last week they felt: "everything I did was an effort" and "I could not get going". 0 = Rarely or none of the time, 1 = some or little of the time, 2 = a moderate amount of the time, 3 = most of the time.	Self-report rating of "2" or "3" to either of the questions[25].

PFP: Slowness	At baseline	Average time (in seconds) to walk 15-feet, out of two trials.	Average time longer than pre-specified gender- and height-specific cut-offs (slowest 20%)[25].
PFP: Low physical activity	At baseline	Multiethnic Study of Atherosclerosis Typical Week Physical Activity Survey (MESA TWPAS)[61]). The instrument quantifies the amount and intensity of physical activity experienced in a typical week into metabolic equivalent (MET)-hours per week.	Lowest 20% of total MET-hours per week[25].
PFP: Weight loss	At baseline	Weight (in kilogram) was measured at each annual visit. Participants were asked, "in the last year, did you try to lose weight through diet and exercise?".	Weight loss of ≥ 5% compared to the previous year and self-report of unintentional weight loss[25].
Depression	Biannually	Beck Depression Inventory (BDI)[26]. A total of 21 items measures participants' depressive symptoms in the last week. Each question is scored from 0 to 3; the total score ranges from 0 to 63, with higher scores indicating greater depressive symptoms.	Scores ≥ 11[62].
Cognition	Biannually	Modified Mini-Mental State (3MS)[27]. 3MS is a measure of global cognitive function, assessing orientation, concentration, language, praxis, and memory. There are a total of 15 items; scores range from 0 to 100, with higher scores indicating better cognition.	Scores < 80[63,64].
KDQOL: Burden	Annual	Kidney Disease Quality of Life-36 (KDQOL-36)[28]. The Burden of Kidney Disease subscale (4 items) measures the extent kidney disease interferes with the lives of the respondent and others during the last 30 days on a 5-point Likert scale. For all KDQOL subscales, scores were transformed to range from 0 to 100, with higher scores indicating better quality of life.	Lowest 20% of scores.
KDQOL: Effects	Annual	Kidney Disease Quality of Life-36 (KDQOL-36)[28]. The Effects of Kidney Disease subscale (12 items) measures	

		the extent of the restriction on daily life during the last 30 days on a 5-point Likert scale.	
KDQOL: Symptoms	Annual	Kidney Disease Quality of Life-36 (KDQOL-36)[28]. The Symptoms and Problems of Kidney Disease subscale (8 items) measures the extent of bother from kidney disease issues during the last 30 days on a 5-point Likert scale.	
KDQOL: Physical	Annual	Kidney Disease Quality of Life-36 (KDQOL-36)[28]. The Physical Component Summary (PCS) subscale is derived from the 12-item Short Form Survey (SF-12) and scored on a T-score metric (mean = 50, SD = 10, in the US general population). The PCS measures functional status.	
KDQOL: Mental	Annual	Kidney Disease Quality of Life-36 (KDQOL-36)[28]. The Mental Component Summary (MCS) subscale is derived from the 12-item Short Form Survey (SF-12) and scored on a T-score metric (mean = 50, SD = 10, in the US general population). The MCS measures emotional well-being.	
Health literacy	At baseline of the parent study	Short Test of Functional Health Literacy in Adults (S-TOFHLA)[29]. The S-TOFHLA assesses participants' ability to read and understand health-related information. There are a total of 36 items; scores range from 0 to 36, with higher scores indicating better health literacy. Scores 0-16 = inadequate health literacy, 17-22 = marginal literacy, and 23-36 = adequate literacy.	Scores ≥ 23[65].
Medication use	Annual	Potentially inappropriate medication used by participants was identified based on the 2015 American Geriatric Society Beers Criteria[30].	Use of any potentially inappropriate medication.

PFP: physical frailty phenotype; KDQOL: Kidney disease quality of life
Unless otherwise specified, baseline refers to the Physical Performance ancillary study visit.

Table 2. Sample characteristics of older adults with chronic kidney disease at baseline

n (%)	Overall n=868	Age categories 55-64 n=336	Age categories ≥ 65 n=532	p-value‡
Female	409 (47.1)	158 (47.0)	251 (47.2)	0.96
Race				
White	509 (58.6)	191 (56.9)	318 (59.8)	
Black	308 (35.5)	125 (37.2)	183 (34.4)	0.68
Other	51 (5.9)	20 (6.0)	31 (5.8)	
BMI				
Underweight (<18.5)	5 (0.6)	2 (0.6)	3 (0.6)	
Normal (18.5-24.9)	139 (16.0)	59 (17.6)	80 (15.1)	0.16
Overweight (25-29.9)	282 (32.5)	94 (28.0)	188 (35.5)	
Obese (30+)	437 (50.4)	179 (53.3)	258 (48.8)	
Married	548 (63.1)	213 (63.4)	335 (63.0)	0.90
Education				
Less than high school	66 (7.6)	24 (7.1)	42 (7.9)	
High school graduate	127 (14.6)	42 (12.5)	85 (16.0)	
Some college	247 (28.5)	94 (28.0)	153 (28.8)	0.40
College graduate or higher	428 (49.3)	176 (52.4)	252 (47.4)	
Household income				
$20,000 or under	114 (13.1)	37 (11.0)	77 (14.5)	
$20,001-$50,000	226 (26.0)	60 (17.9)	166 (31.2)	
$50,001-$100,000	242 (27.9)	105 (31.3)	137 (25.8)	<0.001
More than $100,000	165 (19.0)	86 (25.6)	79 (14.9)	
Do not wish to answer	121 (13.9)	48 (14.3)	73 (13.7)	
Current smoker	58 (6.7)	27 (8.0)	31 (5.8)	0.204
eGFR (ml/min/1.73m^2)				
≥60	131 (15.1)	79 (23.5)	52 (9.8)	
30-59	579 (66.7)	206 (61.3)	373 (70.1)	<0.001
15-29	133 (15.3)	36 (10.7)	97 (18.2)	
<15	16 (1.8)	9 (2.7)	7 (1.3)	
Geriatric conditions in the CKD-CGA				
Chronic condition				
Any CVD	319 (36.8)	97 (28.9)	222 (41.7)	<0.001
Diabetes	385 (44.4)	150 (44.6)	235 (44.2)	0.89
Frailty				
Weakness	275 (31.7)	75 (22.3)	200 (37.6)	<0.001
Exhaustion	176 (20.3)	68 (20.2)	108 (20.3)	0.99
Slowness	124 (14.3)	36 (10.7)	88 (16.5)	0.02
Low physical activity	170 (19.6)	50 (14.9)	120 (22.6)	0.007

Weight loss	51 (5.9)	16 (4.8)	35 (6.6)	0.27
Depression[†]	73 (8.4)	35 (10.4)	38 (7.1)	0.18
Cognitive impairment[†]	12 (1.4)	4 (1.2)	8 (1.5)	0.69
Low KDQOL				
Burden	148 (17.1)	66 (19.6)	82 (15.4)	0.12
Effects	145 (16.7)	59 (17.6)	86 (16.2)	0.63
Symptoms	161 (18.6)	60 (17.9)	101 (19.0)	0.65
Physical	171 (19.7)	59 (17.6)	112 (21.1)	0.19
Mental	171 (19.7)	73 (21.7)	98 (18.4)	0.25
Limited health literacy	57 (6.6)	20 (6.0)	37 (7.0)	0.51
Use of potentially inappropriate medication	496 (57.1)	190 (56.6)	306 (57.5)	0.80

BMI: body mass index; eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease; KDQOL: kidney disease quality of life.

[†] Measures were collected bi-annually, resulting in high proportions of missing values. Depression was missing 463 observations (53.3%) and cognition was missing 332 observations (38.2%).

[‡] p-values are from chi-square tests; all sample characteristics were categorical.

Table 3. Latent class analysis model fit indices and entropy

Number of classes	AIC	BIC	LMR LRT (*p*-value)	BLRT (*p*-value)	Entropy
1	12947.077	13023.336	-	-	-
2	11900.885	12058.170	<0.001	<0.001	0.802
3	11795.547	12033.856	0.082	<0.001	0.784
4	11726.194	12045.529	0.349	<0.001	0.789
5	11691.126	12091.486	0.070	<0.001	0.796

AIC: Akaike information criterion; BIC: Bayesian information criterion, LMR LRT: Lo-Mendell-Rubin adjusted likelihood ratio test; BLRT: bootstrapped likelihood ratio test.

Table 4. Conditional probabilities of geriatric conditions by latent class membership

	Geriatric Conditions	High burden class (n=297) Conditional probability (SD)	Low burden class (n=571) Conditional probability (SD)
	Chronic condition		
1	Cardiovascular disease	0.56 (0.03)	0.27 (0.02)
2	Diabetes	0.59 (0.03)	0.36 (0.02)
	Frailty phenotype		
3	Weakness	0.52 (0.03)	0.25 (0.02)
4	Exhaustion	0.48 (0.04)	0.05 (0.01)
5	Slowness	0.26 (0.03)	0.09 (0.01)
6	Low physical activity	0.32 (0.03)	0.14 (0.02)
7	Weight loss	0.11 (0.02)	0.03 (0.01)
8	Depression	0.42 (0.04)	0.04 (0.01)
9	Cognitive impairment	0.07 (0.02)	0.01 (0.01)
	Low kidney disease quality of life		
10	Burden	0.45 (0.04)	0.02 (0.01)
11	Effects	0.44 (0.04)	0.02 (0.01)
12	Symptoms	0.50 (0.04)	0.02 (0.01)
13	Physical	0.46 (0.04)	0.06 (0.01)
14	Mental	0.47 (0.04)	0.06 (0.01)
15	Limited health literacy	0.13 (0.02)	0.04 (0.01)
16	Potentially inappropriate medication	0.69 (0.03)	0.52 (0.02)

SD: standard deviation.

Conditional probability is the prevalence of an indicator conditioned on class membership. A 0.56 conditional probability can be interpreted as: 56% of the participants had cardiovascular disease given that they were in the high burden of geriatric conditions class.

Table 5. Cumulative incidence and predictive association of latent class membership

	1-year	5-year	10-year	Multivariable model	C-statistics[†]
	Cumulative incidence (%)			HR/OR (95% CI)	
Mortality					
High burden class	3.03	19.52	41.82	2.10 (1.55, 2.85)***	0.70
Low burden class	0.88	8.56	21.78	Reference	
Dialysis initiation					
High burden class	2.76	17.57	32.44	1.74 (1.13, 2.68)*	0.86
Low burden class	1.23	7.22	16.14	Reference	
Hospitalization					
High burden class	-	-	-	1.98 (1.37, 2.84)***	0.66
Low burden class	-	-	-	Reference	

High burden of geriatric conditions class (n=297); low burden of geriatric conditions class (n=571)
All multivariable models were adjusted for age, sex, race, eGFR, smoking status, and body mass index. Age, eGFR, and body mass index were continuous measures.
* p<0.05, ** p<0.01, *** p<0.001.
[†] C-statistics were calculated from models that used the most-likely posterior class membership as the exposure variable.

Table 6. Predictive association of geriatric conditions with outcomes

	Mortality		Dialysis initiation		Hospitalization†	
	HR (95% CI)	C-statistics	HR (95% CI)	C-statistics	HR (95% CI)	C-statistics
Base model†	-	0.68	-	0.85	-	0.64
Any CVD	2.17 (1.67, 2.82)***	0.70	1.20 (0.84, 1.71)	0.85	1.45 (10.6, 1.98)*	0.65
Diabetes	1.58 (1.19, 2.08)**	0.69	2.14 (1.44, 3.16)***	0.86	1.41 (1.03, 1.95)*	0.65
Frailty: weakness	1.95 (1.48, 2.56)***	0.70	1.42 (0.99, 2.05)	0.86	1.56 (1.13, 2.18)**	0.66
Frailty: exhaustion	1.12 (0.82, 1.52)	0.68	1.12 (0.75, 1.68)	0.85	1.17 (0.80, 1.69)	0.64
Frailty: slowness	2.55 (1.85, 3.53)***	0.70	1.31 (0.81, 2.11)	0.86	1.73 (1.12, 2.67)*	0.65
Frailty: low physical activity	1.37 (1.03, 1.84)*	0.69	1.35 (0.89, 2.03)	0.86	1.18 (0.81, 1.72)	0.64
Frailty: weight loss	2.27 (1.48, 3.48)***	0.68	1.47 (0.76, 2.85)	0.86	2.08 (1.11, 3.88)*	0.65
Depression	1.66 (1.22, 2.26)**	0.69	2.05 (1.37, 3.08)***	0.86	1.76 (1.20, 2.59)**	0.65
Cognition	0.72 (0.32, 1.64)	0.68	2.17 (0.98, 4.80)	0.86	1.35 (0.56, 3.26)	0.64
KDQOL: burden	1.80 (1.32, 2.44)***	0.69	1.68 (1.16, 2.44)**	0.86	1.04 (0.69, 1.56)	0.64
KDQOL: effects	1.79 (1.32, 2.41)***	0.69	0.95 (0.62, 1.44)	0.85	1.36 (0.92, 2.03)	0.65
KDQOL: symptoms	1.84 (1.38, 2.47)***	0.69	1.43 (0.94, 2.16)	0.86	1.98 (1.36, 2.88)***	0.66
KDQOL: physical	2.31 (1.73, 3.09)***	0.69	1.30 (0.85, 2.00)	0.85	1.57 (1.08, 2.29)*	0.65
KDQOL: mental	1.18 (0.86, 1.60)	0.68	0.82 (0.54, 1.25)	0.85	1.81 (1.26, 2.60)**	0.65
Health literacy	1.29 (0.82, 2.05)	0.68	0.95 (0.50, 1.79)	0.85	1.46 (0.83, 2.56)	0.64
Medication	1.21 (0.93, 1.58)	0.68	1.17 (0.82, 1.67)	0.86	1.20 (0.88, 1.62)	0.64
All geriatric conditions	-	0.75	-	0.88	-	0.69

CVD: cardiovascular disease; KDQOL: kidney disease quality of life.

Base model consists of variables age, sex, race, eGFR, smoking status, body mass index. All geriatric condition models are adjusted for base model variables. Age, eGFR, and body mass index were continuous measures.

† n=832.

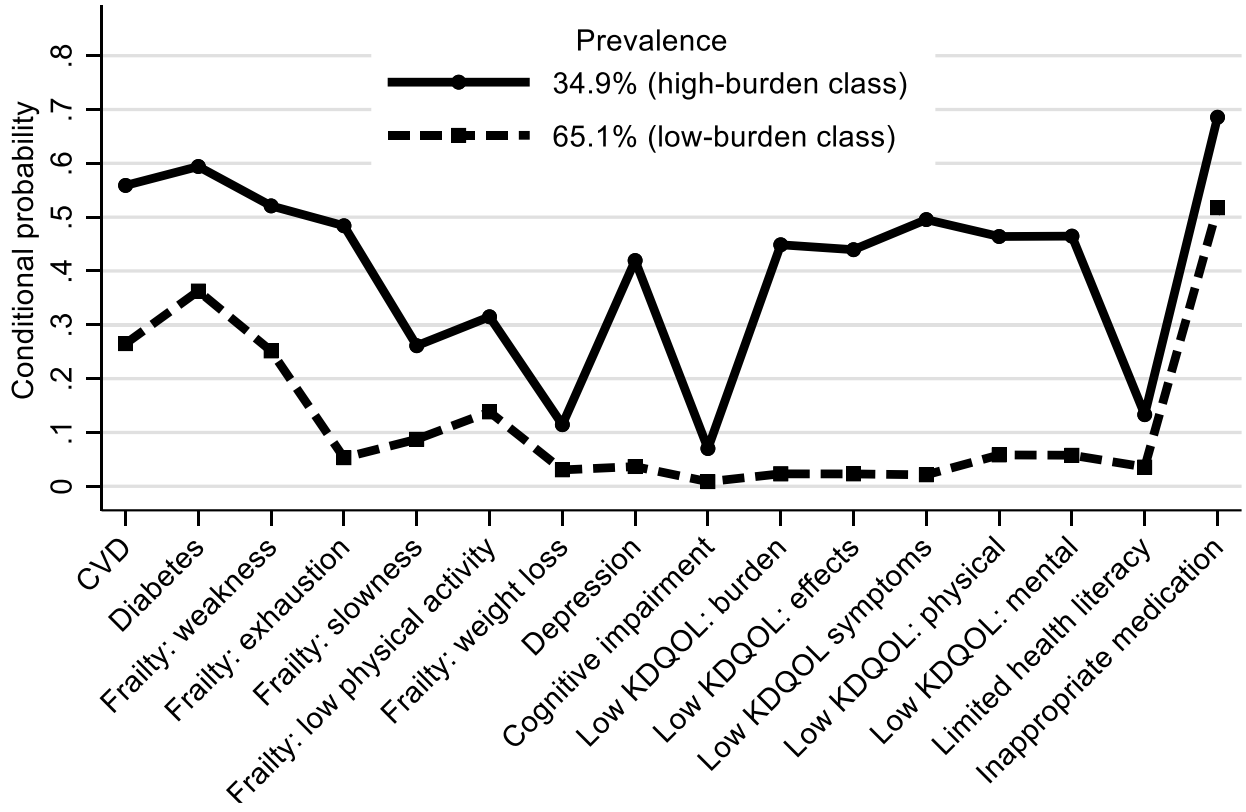
* p<0.05, ** p<0.01, *** p<0.001.

Table 7. Cumulative incidence and predictive association of index scores

		Mortality		n	Dialysis initiation		n	Hospitalization	
	n	HR (95% CI)	C-statistics		HR (95% CI)	C-statistics		OR (95% CI)	C-statistics
Score	868	1.18 (1.13, 1.24)***	0.72	868	1.11 (1.04, 1.18)**	0.86	832	1.15 (1.08, 1.22)***	0.67
Quartiles			0.72			0.86			0.68
Score 0-1	227	Reference		227	Reference		223	Reference	
Score 2-3	278	1.74 (1.09, 2.79)*		278	1.84 (0.99, 3.40)		269	0.97 (0.63, 1.49)	
Score 4-5	176	2.80 (1.73, 4.52)***		176	2.23 (1.16, 4.28)*		164	1.43 (0.90, 2.30)	
Score 6-15	187	4.33 (2.70, 6.93)***		187	2.79 (1.48, 5.25)**		176	2.61 (1.63, 4.18)***	

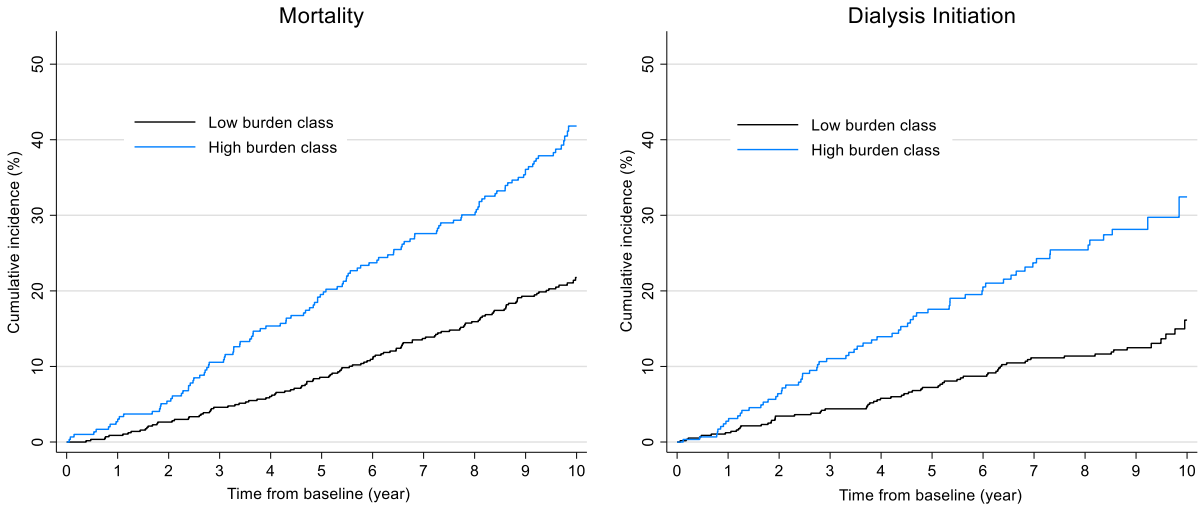
All multivariable models were adjusted for age, sex, race, eGFR, smoking status, and body mass index. Age, eGFR, and body mass index were continuous measures. * p<0.05, ** p<0.01, *** p<0.001.

Figure 1. Conditional probability of geriatric conditions by latent class membership



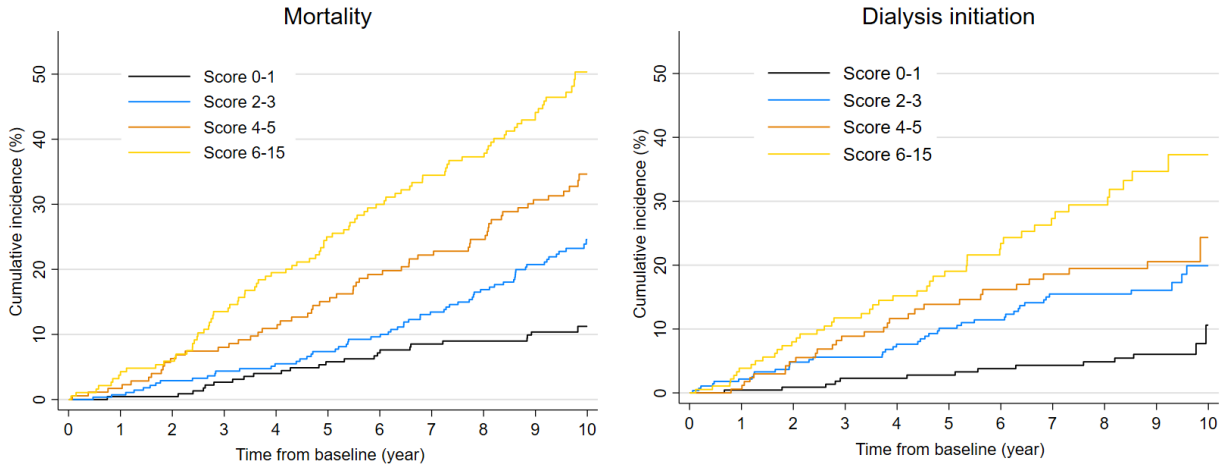
CVD: cardiovascular disease; KDQOL: kidney disease quality of life.

Figure 2. Cumulative incidence of mortality and dialysis initiation by latent class membership



The curves were truncated at year-10 due to the high loss to follow-up thereafter.

Figure 3. Cumulative incidence of mortality and dialysis initiation by quartiles of index score of geriatric conditions



The curves were truncated at year-10 due to the high loss to follow-up thereafter.