Predicting Death without Dialysis in Elderly Patients with CKD

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CKD is common and harmful, and its prevalence is rapidly rising in those aged >65 years (1). In these patients, CKD has been consistently associated with a range of adverse outcomes including cardiovascular disease, worsening frailty and disability, progression to ESRD, and early mortality (2–4). Models for risk stratification in elderly patients with CKD, for each of the individual adverse outcomes, can be difficult because of the multiple competing risks (5). In particular, clinical decision-making for elderly patients with CKD is more complex, because the majority of these patients die before developing kidney failure. As such, it may be harmful to treat the older patient with CKD with intensive medical and surgical interventions directed toward preparation for kidney failure, such as vascular access surgery or kidney transplantation (6). Models predicting all-cause mortality, combined with models that predict kidney failure, can help target health interventions more appropriately.

Despite potentially important applications for risk stratification in patients with CKD, risk prediction models are not routinely used for predicting mortality in this population. Three measures are important to establish before introducing a prediction model into a clinical setting: internal validity, external validity, and clinical usefulness (7,8). Internal validity refers to minimization of systematic bias/errors in model development and is reflected in the variable selection and modeling methods, as well as in performance measures such as discrimination, calibration, discrimination, and reclassification in the original development population (9). External validity refers to generalizability of the model and is necessary before models developed in a specific population can be applied to another. Ideally, a model should not exhibit a significant decline in predictive ability (especially discrimination) when applied to a new population. Clinical usefulness, which is more difficult to assess, may be evaluated by utility (the effect on a clinical decision linked to a risk category or threshold) and usability (the availability of a clinical decision aid, such as an online calculator or nomogram, that would allow risk prediction at the bedside) (9). An accurate model (good discrimination and calibration) should be externally validated and accompanied by a clinical decision tied to a risk threshold and a user-friendly aid, at the time of publication.

In this issue of CJASN, Bansal et al. present findings from an externally validated risk prediction model for all-cause mortality within 5 years before development of kidney failure or within 5 years without ESRD (10). The investigators used a development cohort from the Cardiovascular Health Study (CHS), which is a well-described multicenter, community-dwelling cohort study of persons aged ≥65 years (11). The study included 828 CHS participants with an eGFR < 60 ml/min per 1.73 m² (based on serum creatinine and the CKD Epidemiology Collaboration equation) (12). The investigators then externally validated the model in 789 elderly participants with an eGFR < 60 ml/min per 1.73 m² from the Health, Aging, and Body Composition (Health ABC) study.

The authors considered 16 candidate predictor variables regularly available in routine clinical settings. Candidate variables were associated with all-cause mortality first in univariate Cox proportional hazards models using bootstrap estimation and then all variables with \( P \leq 0.10 \) were included in a multivariate model. Bias-corrected coefficients and 95% confidence intervals (95% CIs) were obtained utilizing bootstrap estimation. The goodness of fit of the final 5-year risk mortality equation was evaluated by the Hosmer–Lemeshow chi-squared statistic. The investigators then measured the performance of the model utilizing the C-statistic and the slope of the linear predictor (10).

The final model included age, sex, race, eGFR, urinary albumin/creatinine ratio (UACR), diabetes, tobacco use, and history of heart failure or stroke. The nine-variable equation model had a reasonable C-statistic of 0.72 (95% CI, 0.68 to 0.74) with a calibration value of 7.80 (\( P = 0.50 \)) in internal validation. These variables were then included in a nomogram, in order to facilitate knowledge translation. Overall scores ranged from zero to 17, and mortality rates approximated 3.8% for lower scores and 93.7% in participants with ≥10 points. External validation of the model was then performed in the Health ABC cohort. Compared with CHS participants, the Health ABC cohort was younger and had lower proportions of whites and female participants, higher eGFR, lower UACR, and less prevalent cardiovascular disease. In the Health ABC cohort, the C-statistic was 0.69 (95% CI, 0.64 to 0.74), and calibration was preserved (Hosmer–Lemeshow chi-squared statistic, 3.96; \( P = 0.90 \)). In a separate analysis, change in eGFR over
4 years was examined as a candidate variable in the CHS cohort, but did not improve model performance. Both cohorts were also combined in a post hoc analysis to measure performance of the model predicting 2-year mortality. The C-statistic of this model was 0.77 (95% CI, 0.71 to 0.80) in internal validation (10).

Bansal et al. present a new prediction model for all-cause mortality in elderly patients with CKD, which is both internally and externally valid as well as clinically usable. The model achieved modest discrimination and was well calibrated in both internal and external validation. Ascertainment bias was low due to accurate follow-up of mortality in both cohorts and very few individuals lost to follow-up. The investigators also used a wide array of candidate variables, enabling other investigators to validate their findings in external populations. Compared with other models predicting mortality in patients with all causes of CKD, the current model had similar performance and may be clinically useful in older patients with earlier stages of CKD (9). There were, however, some limitations. Patients with advanced CKD (stages 4–5) were not well represented in both the CHS and Health ABC cohorts, and application of the model to these patients would require further validation. These patients are relatively more likely to survive to ESRD or have a greater risk of kidney failure, and a model that is accurate in this population may be more informative for dialysis planning. Furthermore, the exclusion of individuals not able to perform daily life functions in the Health ABC cohort also limited the generalizability of the model in the very frail elderly patients with CKD. Finally, important functional outcomes such as disposition to a nursing home, or meaningful declines in physical and cognitive function were not evaluated. These outcomes may be as, if not more, important as life expectancy in some older adults with kidney disease, and may also be tied to the clinical decision around choosing RRT (13).

The study by Bansal et al. (10) should prompt additional research. Findings from large cohort studies have identified biomarkers, such as troponin T, N-terminal probrain natriuretic peptide, and fibroblast growth factor 23, that can improve the risk prediction of mortality in CKD (14,15). Other studies have identified nondisease-specific problems, such as cognitive impairment, depression, and falls, that may be associated with mortality (16). Models with or without these biomarkers or functional variables should be carefully examined to evaluate the potential benefits from improved risk prediction versus the cost of the biomarker assays and the increased complexity of obtaining the functional measurement. In addition, all models for mortality in patients with CKD currently fail to address the key question of clinical utility. Models predicting cardiovascular disease in the general population have clinical decisions regarding statin use attached to an absolute risk threshold of 10% over 10 years (9). Similarly, models for kidney failure may be used to plan dialysis access at thresholds of 20% per year, or 40% over 2 years. Absolute risk thresholds for mortality in patients with CKD, and clinical decisions tied to these risks, need to be suggested and tested before clinical implementation (9). Nonetheless, the model created by Bansal et al. (10) is a useful incremental step in bringing risk-based care to nephrology. Evaluation of this tool, along with other externally validated tools for predicting mortality and facilitating clinical decision making for patients with CKD, deserves further study.

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References


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See related article, “Development and Validation of a Model to Predict 5-Year Risk of Death without ESRD among Older Adults with CKD,” on pages 363–371.