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In Focus

Optimally predicting mortality with kidney function markers is not the same as optimally determining how kidney function predicts mortality

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The relationships between the level of renal function at any given point in time or its change over an interval of time and all-cause mortality (ACM) or major cardiovascular (CV) events in the general population has attracted enormous interest, especially since the development of simple formulas to estimate renal function using serum biomarkers has stimulated extensive studies of such associations [1, 2]. A seminal observational study conducted by Go *et al.* [3] and published in 2004 served as a major stimulus. This study, carried out in an integrated system of health care and involving over 1 100 000 subjects, used serum creatinine as the biomarker transformed into estimated glomerular filtration rate (eGFR) by use of the abbreviated version of the Modification of Diet in Renal Disease (MDRD) Study equation, developed in 1999 [4], as the assessment of renal function. This formula, like many others that succeeded it, incorporates serum creatinine as the determinant variable and age, gender and ancestry as surrogates for creatinine formation, metabolism and excretion. In the primary analysis, a single value of serum creatinine was used for assessment of eGFR and mortality was analyzed according to categories advocated by the Kidney Disease Outcome Quality Outcomes Initiative in 2002 [5]. The absolute mortality rates (per 100 patient-years, standardized for age) were 0.70, 1.08, 4.76, 11.36 and 14.74 for eGFR categories of >60, 45–59, 30–44, 15–28 and <15 mL/min/1.73 m^2, respectively. The adjusted hazard ratio (HR) for death (fully adjusted for known comorbidities, including proteinuria; using an eGFR of >60 mL/min/1.73 m^2 as the reference value) were 1.2, 1.8, 3.2 and 5.9 for an eGFR of 45–59, 30–445, 15–29 and <15 mL/min/1.73 m^2, respectively. When more than one serum creatinine value was used to determine eGFR and to construct the HR, the value for HR declined to 1.0 for the group with an eGFR of 45–59 mL/min/1.73 m^2 [3]. Thus, the threshold for an increased risk of death in this population appeared to have an eGFR around 45 mL/min/1.73 m^2 or less.

Subsequently, many studies confirmed and extended the association between a decline in eGFR and mortality, most strikingly by the chronic kidney disease (CKD) Prognosis Consortium [6–8]. Age was also found to be a risk modifier for the impact of eGFR on mortality; reduced eGFR was associated with a 'greater' relative risk of mortality in younger patients [9], suggesting that thresholds for identifying the risk for mortality based on eGFR alone needed to be age-sensitive. For reasons of practicality, the vast majority of epidemiological studies linking renal function to mortality risk have been conducted using creatinine-based eGFR rather than directly measured GFR (mGFR), either by urinary clearance or plasma disappearance methods using an exogenous GFR biomarker (such as inulin, iohexol or iothalamate). More recently, serum cystatin C has been added to the surrogate biomarkers for eGFR formulas and incorporating combinations of serum creatinine and serum cystatin C provide a more accurate estimate of mGFR than either alone [10]. However, both eGFR-creatinine and eGFR-cystatin C suffer from physiological and pathological variation independent of mGFR [11–14]. These non-GFR determinants can give rise to discordance between the eGFR value and the corresponding mGFR value, even when these are measured simultaneously. For example, very low creatinine generation from age-related sarcopenia, chronic inflammation, muscle disorders and/or prolonged inactivity or strict vegetarian diets can reduce serum creatinine levels and spuriously elevate the calculated eGFR creatinine. Serum cystatin C levels may also be influenced by obesity, diabetes, thyroid disorders and chronic inflammation, some of which are in opposite directions to the serum creatinine. It has been argued that eGFR using both creatinine and cystatin C as the biomarker 'cancels out' the non-GFR-related determinants, but it is important to recognize that this is only partially true as the non-GFR determinants of creatinine are not the exact opposite of cystatin C [11–14]. Even more importantly, the equations using creatinine or cystatin C have

been optimized for prediction of mGFR not for prediction of mortality [15]. Several editorials have pointed out the fallacies of using the results of eGFR in which the variables of age, gender and race have been modified by coefficients optimized for assessment of mGFR, but then applied for the quite different purpose of predicting mortality, especially when non-GFR determinants of the equation variables can play such an important role in mortality risk [1, 15]. Proteinuria or albuminuria is frequently a missing element in epidemiological studies relating GFR to mortality, and it is very well known that the magnitude and duration of proteinuria (or albuminuria) linearly (without any threshold effect) associates strongly with an increased risk of mortality, independently of age or GFR [6, 8, 9, 16].

Against this background, Sundin *et al.* [17] carried out a prospective study to formally test the association of serum cystatin C and serum creatinine levels (or both combined) and mortality, and their independence from mGFR, in a cohort of 1157 Swedish subjects. The mGFR was assessed by plasma disappearance of iohexol, which although not a 'perfect' method for determining true mGFR gives values close to that of the 'gold-standard' inulin urinary clearance methods [18, 19]. After full adjustment of mGFR, 'higher' serum cystatin C values and 'lower' serum creatinine values were consistently associated with increased mortality. The combination of serum creatinine and serum cystatin C values predicted mortality with no added improvement in prediction with the further addition of mGFR as a predictor. It is worth noting that none of these analyses was performed using the derivative and calculated eGFR values, and thus the associations described obviated the confounding effects of age as a variable in the eGFR equations. A conclusion supported by this work is that neither serum creatinine nor serum cystatin C (and by inference the corresponding eGFR equation-derived values) are satisfactory biomarkers of the ACM risk that is predicted by kidney function alone (mGFR). Further, when the goal is to develop models that predict the risk of death, there is no added benefit for including a 'pure' measure of kidney function (mGFR). Serum creatinine and cystatin C cover the GFR contribution to predicting mortality and the non-GFR determinants of these markers further enhance the prediction of mortality.

It is also noteworthy that this study included a heterogeneous collection of subjects (arbitrary ratios of healthy kidney donors and patients with various risk factors and kidney diseases). Thus, the prediction of mortality by different mGFR, serum creatinine and cystatin C levels is difficult to meaningfully interpret. Nonetheless, evaluating the relative differences in risk prediction between mGFR, serum creatinine and cystatin C is still reasonable in this setting. Using a quantitative approach to characterize ACM risk by serum creatinine or cystatin C levels, the authors verified that each biomarker identifies elements of mortality risk not accounted for by the parameter they are designed to estimate, namely mGFR. Further, serum creatinine and cystatin C in combination best predicted mortality risk, with no added benefit of including mGFR to predicting mortality. While combinations of serum creatinine and cystatin C may be the most accurate in estimating mGFR [10, 20] and in estimating mortality risk [17], this should not be misinterpreted. In models that estimate mGFR, higher cystatin C and 'higher' serum creatinine (same direction) estimate a lower mGFR [10, 20], but in this model estimating mortality, higher cystatin C and 'lower' serum creatinine (opposite direction) indicated a higher mortality risk. Thus, the statistical model used to estimate GFR with serum creatinine and cystatin C is very different from the model used to predict mortality risk with serum creatinine and cystatin C.

Higher serum cystatin C levels, 'independent of mGFR', can be associated with heavy smoking, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, obesity and diabetes [11, 13, 14, 21–24]: all factors that contribute to a higher risk of CV disease and thereby to mortality. Some studies have also shown that a persistently elevated inflammatory state also can increase serum cystatin C levels, possibly due to increased production [11, 13, 14]. Cystatin C is an inhibitor of cysteine protease [25], a component of the inflammatory cascade, and levels of serum cystatin C can correlate directly with serum C-reactive protein levels, at least in some studies [14, 26]. The authors raise an intriguing alternative suggestion that reduced glomerular filtration of the larger cystatin C molecule (13.3 kDa) compared with creatinine (113 Da) (as illustrated by the serum cystatin C/creatinine concentration ratio) in states is characterized by microvascular (endothelial) injury and the 'shrunken pore syndrome' [26, 27]. Further studies are needed to confirm or deny this interesting hypothesis.

The study of Sundin *et al* is not without limitations and these have been largely acknowledged by the authors. The subjects had a relatively high risk of age-standardized mortality and were largely Caucasian, and are, therefore, not representative of the general population. The absence of proteinuria or albuminuria measurements is a further limitation rendering the application of the findings to the Kidney Disease: Improving Global Outcomes stratification of CKD problematical [28]. Overadjustment is a concern with the statistical modeling. Whether serum creatinine and cystatin C fully account for the mortality predicted by mGFR without adjusting for six other characteristics was not shown.

Nevertheless, the strengths of this study outweigh its weaknesses. First, it supports the notion that measuring GFR does not offer any material advantage over combined serum creatinine and cystatin C for determining the risk of mortality. In other words, if we just want to predict mortality, regardless of cause, mGFR is of no added benefit and is actually inferior to the much more easily determined serum creatinine and cystatin C. Second, serum creatinine and serum cystatin C, alone or in combination, have non-GFR determinants that affect the risk of mortality. Thus, if one wishes to know the contribution of kidney function alone for predicting mortality, mGFR is required as either serum creatinine or cystatin C will be inaccurate, due to the non-GFR-related factors on the values for these biomarkers.

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CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Sundin *et al.* Measured glomerular filtration rate does not improve prediction of mortality by cystatin C and creatinine. *Nephrol Dial Transplant* 2017; 32: 663–670)

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