Is Cystatin C an Important Prognostic Marker Independent of Renal Function?*

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Cystatin C (Cys-C) is a 122-amino acid, 13-kDa protein that is a member of a family of competitive inhibitors of cysteine proteases (1). Cys-C is produced by all human nucleated cells, and the human Cys-C gene is of the housekeeping type, which indicates a stable production rate of Cys-C by most nucleated cell types. Cys-C has several properties that make it a good candidate marker of glomerular filtration rate (GFR), including a constant production rate, free filtration at the glomerulus, complete reabsorption, and catabolism by the proximal tubules with no reabsorption into the bloodstream, and no renal tubular secretion (2). Serum Cys-C is a good marker of renal function and correlates better to direct measures of GFR more precisely than creatinine, because its serum concentrations are independent of muscle mass and do not seem to be affected by age or sex (3,4). The development of automated and rapid particle-enhanced immunoturbidimetric and immunonephelometric methods have allowed large-scale use of serum Cys-C as a clinically useful GFR marker. However, several factors have been reported to influence the production of Cys-C; large doses of glucocorticoids have been described to increase the production of Cys-C, whereas low and medium doses of glucocorticoids do not seem to alter the production of Cys-C (5). Thyroid dysfunction also has a major impact on Cys-C level. In contrast to creatinine concentrations, Cys-C levels are lower in the hypothyroid and higher in the hyperthyroid state as compared with the euthyroid state (1,6,7).

It has been well established that impaired renal function is associated with an increase in cardiovascular risk and mortality (8,9). Therefore, as Cys-C is a more accurate surrogate marker of renal function compared with plasma creatinine, it is not surprising that several cohort- and population-based studies have demonstrated that Cys-C is an important prognostic indicator of cardiovascular and overall mortality. Data from the Cardiovascular Health Study, a cohort study of elderly persons living in the community, demonstrated that Cys-C is a stronger predictor of the risk of death and cardiovascular events in elderly persons than is creatinine (10,11). The Heart and Soul Study reported an association of Cys-C with mortality, cardiovascular events, and incident heart failure among persons with coronary heart disease (12). Cys-C has also been proven to be a good predictor of outcome in suspected or confirmed non–ST-segment elevation acute coronary syndrome and acute heart failure (13). Finally, Maahs et al. (14), reported that serum Cys-C predicts progression of subclinical coronary atherosclerosis in individuals with type 1 diabetes.

In this issue of the Journal, Wu et al. (15) reported that Cys-C is prognostic of long-term mortality in the subjects with relatively normal renal function determined by creatinine-based estimated glomerular filtration rate (eGFR). The authors measured Cys-C in 2,990 subjects over 40 years old with normal eGFR who participated in the Third National Health and Nutrition Examination Survey (NHANES III). Normal eGFR was defined by ≥60 ml/min/1.73 m², as determined by the Modification of Diet in Renal Disease (MDRD) equation. When the first and last deciles of Cys-C were compared, the relative risks of all-cause, cardiovascular, cancer, and noncardiovascular mortalities were all increased statistically. Hazard ratios all moderated to lower values when the comparisons were expanded to include the upper and lower thirds. Similar associations were still present when Cys-C was modeled on a continuous scale, suggesting a linear relationship between Cys-C and mortality outcomes. The current study confirms that indeed, Cys-C has added prognostic value to conventional estimates of GFR based on serum creatinine measurement. This is consistent with the previous findings of Shlipak et al. (16), who reported, using the Cardiovascular Health Study, that among elderly persons without chronic kidney disease, Cys-C is a prognostic biomarker of risk for death and cardiovascular disease. Importantly, the current study also included younger patients up to 40 years of age.

Does Cys-C have prognostic value independent of renal function or is it a better marker for preclinical or mild renal dysfunction as compared to creatinine-based estimate of renal function?

An important limitation of the study by Wu et al. (15) is the lack of direct measurement of GFR. Hence, we cannot determine the extent to which Cys-C concentration reflects kidney function. It has been well established that estimation...
of GFR using plasma creatinine either by the MDRD or the Cockcroft-Gault (C-G) formula has its limitations (17). In the current study, the authors defined “normal” renal function as eGFR by MDRD equation $\geq 60$ ml/min/1.73 m$^2$. However, the subjects in the 90th and greater percentile of Cys-C levels, evident by higher percentage of subjects with microalbuminuria, higher blood urea nitrogen, and lower eGFR. Furthermore, in the multivariate analysis, eGFR is associated with significant risk of all-cause and cardiovascular mortality. Hence, the data from the current study do not answer the question of whether indeed, Cys-C is an indicator of increased risk of long-term mortality independent of true renal function, or whether it is a better marker for mild renal dysfunction as compared to creatinine-based estimation of GFR. Pucci et al. (18) completed an elegant study comparing Cys-C with the creatinine-based C-G formula and the MDRD study equation for the assessment of early decreased renal function in 288 diabetic patients to the goal standard of determination of GFR by iohexol clearance. The authors found that Cys-C was better correlated with GFR than were creatinine-based C-G and MDRD, only in patients with normal renal function (GFR $\geq 60$ ml/min/1.73 m$^2$) but not in those with decreased GFR. The authors concluded that serum Cys-C is more useful as compared with conventional estimates based on serum creatinine measurement for detecting very early reduction of renal function. Shlipak et al. (16) also had the similar conclusion that Cys-C seems to identify a “preclinical” state of kidney dysfunction that is not detected with serum creatinine or eGFR. Although it is academically and scientifically interesting to determine whether Cys-C has prognostic value independent of true renal function, the findings of the study by Wu et al. (15) and previous studies have established that Cys-C has added prognostic value in subjects with normal creatinine-based eGFR.

**Future Research Directions**

It would be very clinically relevant to determine whether serial measurements of Cys-C has added prognostic value and whether therapeutic interventions will result in the decrease of Cys-C with improved clinical outcome. If indeed that is true, we should then test whether Cys-C may be used as a biomarker to guide therapy for patients.

**REFERENCES**


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