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Original Article

Biomarkers of kidney function and prediction of death from cardiovascular and other causes in the elderly: A 9-year follow-up study

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ABSTRACT

Background: Cystatin C is claimed to be superior to creatinine-based estimates of glomerular filtration rate (eGFRcr). The purpose of the study is to analyze whether cystatin C, creatinine, and/or estimated glomerular filtration rates (eGFR) predicted cardiovascular and/or non-cardiovascular deaths among Finnish elderly.
Methods: Hazard ratios (HR) of cystatin C, creatinine and eGFRs for cardiovascular and non-cardiovascular deaths.
Results: During a 9-year follow-up, 275 died, 192 deaths were a result of cardiovascular disease. In age-adjusted analyses, cystatin C predicted the risk of non-cardiovascular and cardiovascular death in men (HR for 0.1-unit increase 1.12 [95% CI, 1.04–1.19] for non-CVD deaths and 1.18 [1.09–1.28] for CVD deaths) and women (1.14 [1.07–1.21] and 1.14 [1.06–1.22], respectively). CKD-EPIcr-cyc predicted the risk of CVD deaths in men (HR for 5-unit decrease 1.17 [1.09–1.25]) and women (1.09 [1.02–1.17]) and non-CVD deaths in women (1.07 [1.01–1.14]). Also, MDRD (HR for 5-unit decrease 1.16 [1.05–1.27]) and CKD-EPI (HR for 5-unit decrease 1.15 [1.05–1.25]) predicted CVD deaths among men. After additional adjustments, predictive value of cystatin C remained significant. Also, the predictive value of CKD-EPIcr-cys remained significant in non-CVD deaths among women.
Conclusion: Cystatin C was clearly the best predictor for cardiovascular and non-cardiovascular deaths among Finnish elderly. Serum cystatin C is more accurate for clinical decision making than creatinine-based eGFR equations or the combined CKD-EPIcr-cys equation in persons older than 64 years.

1. Introduction

The reliability of the creatinine-based glomerular filtration rate estimating (eGFRcr) equations is questionable when the patient's muscle mass is more or less than average for age. This problem is particularly evident in elderly people, who are a very heterogeneous group of individuals, ranging from apparently healthy and active persons to diseased and physically handicapped individuals. In healthy aging, the age-related decline in GFR and decline in muscle mass cancel each other out and thus, serum or plasma creatinine remains stable [1,2]. However, poor diet or a disease process may enhance the loss of muscle mass and decline in creatinine concentration leading to falsely high eGFRcr values. On the other hand, elderly persons in good health and with higher-than-average muscle mass may be diagnosed with chronic kidney disease (CKD) although they actually have a GFR ≥60 ml/min/1.73 m^2.

Cystatin C is a non-glycosylated protein synthesized by all nucleated cells, freely filtered by the glomerulus and then reabsorbed and catabolised by the proximal tubules [3]. In contrast to creatinine, cystatin C concentration is less influenced by age, sex, muscle mass or diet [4,5].

The Kidney Disease Improving Global Outcome (KDIGO) 2012 Clinical Practice Guideline recommends the measurement of serum cystatin

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C and estimation of GFR by the combined CKD-EPIcr-cys equation in adults in whom eGFRcr is within the range of 45–59 ml/min/1.73 m^2 but who do not have markers of kidney damage [6].

We had the opportunity to compare eGFRcr equations and cystatin C concentration as a predictor of mortality in a well-defined cohort of elderly individuals.

2. Materials and methods

2.1. Study design and population

This study is a part of the longitudinal epidemiological study carried out in the municipality of Lieto in south-western Finland [7]. All persons born in or prior to the year 1933 ($N = 1596$) were invited to participate in the baseline examination which was carried out between March 1998 and September 1999. Of those eligible, 63 died before they were examined, and 273 refused or did not respond, leaving 1260 (82%) participants, 533 men and 727 women. Institutionalized individuals consisted 5% of the study population.

2.2. Measurements and definitions

At the Lieto health centre, venous blood samples were obtained with minimal stasis between 8 am and 10 am after an overnight fast. Samples were analyzed in the Central Laboratory of Turku University Hospital. Before laboratory visit, all participants were given verbal and written instructions. Cystatin C concentrations were determined from serum samples using a particle-enhanced nephelometric immunoassay (N Latex Cystatin C, BN II System; Dade Behring, Marburg, Germany) [8]. Creatinine was measured using the Jaffé reaction (Roche Diagnostics, Mannheim, Germany, and Hitachi 917; Hitachi Ltd., Tokyo, Japan). eGFR was estimated from plasma creatinine values using the Modification of Diet in Renal Disease (MDRD) [9], the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [10] and the combined CKD-EPIcr-cys [11] equations. Levels of cystatin C, creatinine, MDRD, CKD-EPI and CKD-EPIcr-cys outside ±3 SD (standard deviation) were excluded according to the ±3 SD criterion.

2.3. Potential confounding factors

Diabetes mellitus was defined based on a previous diagnosis in the medical records or fasting glucose concentration of 7 mmol/L or higher, acknowledging that type 2 diabetes may be present years before clinical recognition. Hypertension was categorised as present if a diagnosis was documented in the medical records. Coronary heart disease was diagnosed based on medical records or electrocardiogram findings. Body mass index (BMI), measured as kilograms per square meter, was classified as less than 20.0, 20.0 to 24.9, 25.0 to 29.9, 30.0 to 34.9 and 35.0 or higher according to the World Health Organization recommendations, except for the lowest cutoff value, which was placed at 20.0 instead of 18.5, to ensure sufficient numbers in the lowest class [12]. Physical functioning was assessed using a questionnaire adapted from the protocol of the Eleven Countries Study and included 4 items on mobility (capability to walk outdoors, between rooms, in stairs or at least 400 m) and 5 items on activities of daily living; i.e., dressing, eating, bathing, going to bed and using the toilet. Each had scores of 0 to 3 (0, unable to do; 1, some help needed; 2, with difficulty, but no help needed; 3, no limitations) [13]. According to the sum score, the functional index was categorized as less than 23, 23 to 26 or 27 (no limitations).

2.4. Outcome measures

Data from all participants who had died before January 2008 were obtained from the official Finnish Cause of Death Registry using unique personal identification numbers. Deaths resulting from ICD-10 codes I10–I15, I20–I25, I50, I60–I66, I69, I71 and I74 were classified as cardiovascular disease (CVD) deaths.

2.5. Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki. The Ethics Committee of the Hospital District of Varsinais-Suomi approved the study protocol. Participants provided written informed consent for the study.

2.6. Statistical analyses

Baseline differences were tested by Cox regression analyses. Because of the positively skewed distributions of cystatin C and creatinine values, natural logarithm-transformed values were used in analyses. Associations of cystatin C, creatinine and eGFR levels according to the MDRD, CKD-EPI and CKD-EPIcr-cys equations with CVD deaths and non-CVD deaths were examined with Cox regression analyses. The follow-up periods were calculated from the date of the baseline measurements to the end of the follow-up period of nine years or to the CVD death or non-CVD deaths. Age, diabetes, hypertension, CVD, BMI and functional index were considered as possible confounding factors. Firstly, Cox regression analyses were adjusted for age, and secondly with other possible confounding factors which were associated with CVD deaths and non-CVD deaths in men and women. The results are presented with hazard ratios (HRs) and their 95% confidence intervals. The proportional hazards assumptions were evaluated with martingale residuals and the assumptions were met. P-values <0.05 were considered statistically significant. All statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Mean age of 1260 participants was 74 years (range 64–100 years. During a 9-year follow-up, 275 (129 men, and 146 women) died; 192 deaths (85 in men, and 107 in women) were a result of cardiovascular disease.

3.1. Potential confounding factors as predictors for CVD and non-CVD deaths

Table 1 shows baseline characteristics of the participants. Age, diabetes, hypertension, coronary heart disease and low functional index predicted CVD deaths both among men and women. Low BMI (<20) predicted CVD deaths only in women. Significant predictors of non-CVD deaths were age and both low BMI and functional index in both genders.

3.2. Biomarkers of kidney function as predictors for CVD and non-CVD deaths

In Cox proportional hazards models adjusted for age, cystatin C significantly predicted the risk of CVD and non-CVD deaths both in men and women (Table 2). After additional adjustments (Table 3), the predictive value of cystatin C still remained significant. Creatinine did not predict non-CVD or CVD deaths either in men or in women. Creatinine-based MDRD and CDK-EPI significantly predicted CVD deaths in men in the age-adjusted model, but not in the model with additional adjustments. Creatinine–cystatin C-based CDK-EPIcr-cys predicted CVD deaths both among men and women and non-CVD deaths among women in the age-adjusted model; in the model with additional adjustments, the predictive value of CKD-EPIcr-cys remained significant only in non-CVD deaths in women.