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Original Article

Newer glomerular filtration rate estimating equations for the full age spectrum based on serum creatinine and cystatin C in predicting mortality in patients with ischemic stroke

Tanja Hojs Fabjan[a,d], Meta Penko[b], Radovan Hojs[c,d,*]

[a] Dept of Neurology, University Medical Centre, Maribor, Slovenia
[b] Clinic for Internal Medicine, Dept. of Cardiology, University Medical Centre, Maribor, Slovenia
[c] Clinic for Internal Medicine, Dept. of Nephrology, University Medical Centre, Maribor, Slovenia
[d] Faculty of Medicine, University of Maribor, Maribor, Slovenia

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ABSTRACT

Background: Renal dysfunction is associated with increased risk of mortality. The novel Full Age Spectrum (FAS) equations estimating the glomerular filtration rate (GFR) based on serum creatinine (FAScrea) and cystatin C (FAScysC) are validated across the entire age spectrum and are superior markers of renal function compared to other equations. Possible association of these equations with mortality in patients with ischemic stroke is not known.

Patients and methods: We included 390 patients (207 men, 183 women) in our observational cohort study who had suffered from an ischemic stroke and followed-up on for 3 years. Serum creatinine and cystatin C were measured at admission; GFR was estimated according to the FAScrea, CKD-EPIcrea, FAScysC and CKD-EPIcysC equations. The values of estimated GFRs were divided into quintiles.

Results: During the follow-up period, 173 (44.4%) patients died. The association of hazard ratios for FAScrea and CKD-EPIcrea with all-cause mortality was J-shaped and only significantly higher when comparing the fifth quintile hazard ratio for mortality with the first quintile ($P < 0.001$). For FAScysC and CKD-EPIcysC, hazard ratios increased from the first to the fifth quintile linearly. In an adjusted analysis, FAScrea and CKD-EPIcrea were not associated with all-cause mortality and the hazard ratios of the fifth quintile of FAScysC ($P = 0.008$) and CKD-EPIcysC ($P = 0.042$) were significantly associated with mortality compared to the first quintile.

Conclusions: In patients with an ischemic stroke, estimated GFR based on serum cystatin (FAScysC and CKD-EPIcysC) was a better predictor of all-cause and cardiovascular mortality than estimated GFR based on serum creatinine.

1. Introduction

Cardiovascular disease, including coronary heart disease and stroke, is the leading cause of death worldwide [1]. Renal dysfunction carries a substantial risk for cardiovascular morbidity and mortality, and the risk increases with a decline in kidney function [2]. It was shown that renal dysfunction is an independent predictor of mortality in patients who had suffered a stroke [3,4].

The glomerular filtration rate (GFR) is essential for the evaluation of patients with kidney disease. In clinical practice, and in most studies, GFR is commonly estimated based on serum creatinine concentration. In 2009, the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPIcrea equation) was developed and replaced the previously accepted Modification of Diet in Renal Disease (MDRD) equation [5]. Both equations are widely recognized to estimate GFR in adults, but lack precision in older adults [6]. In 2016, the Full Age Spectrum equation based on serum creatinine (FAScrea) was developed [6]. The important advantage of this new equation is validation across the full age spectrum [6]. The large external validation showed that the FAS equation is the most unbiased equation based on serum creatinine concentration and this equation demonstrated better performance in estimating GFR than the currently recommended CKD-EPIcrea equation [6].

In the last years, serum cystatin C was proposed as a new endogenous marker of GFR. Serum cystatin C does not depend on muscle mass, sex or age, and is not affected by inflammation, fever and/or outside agents [7,8]. Most authors share the opinion that malignant processes do not influence the serum cystatin C concentration [7,9].

* Corresponding author at: Klinika za interno medicino, Oddelek za nefrologijo, UKC Maribor, Ljubljanska 5, 2000 Maribor, Slovenia.
E-mail address: radovan.hojs@guest.arnes.si (R. Hojs).

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Serum cystatin C as a marker of renal function has limitations in patients with thyroid disorders and in patients with glucocorticoid therapy [10,11]. Serum cystatin C is a more sensitive marker of renal function than serum creatinine or estimated GFR based on creatinine [12]. It was shown that serum cystatin C is superior in predicting mortality and cardiovascular events among elderly and among elderly diabetic patients compared to serum creatinine or estimated GFR based on creatinine [13,14]. There is also some data showing that cystatin C was superior in predicting mortality in patients with ischemic stroke [15]. In 2017, the Full Age Spectrum equation based on serum cystatin C (FAScysC) was developed [16]. This new equation is also validated across the full age spectrum and demonstrates better performance in estimating GFR than the other currently recommended equations based on serum cystatin C [16]. The most widely used equation based on serum cystatin C is CKD-EPIcysC equation [17].

The role of the FAS equations in predicting mortality is not known. The aim of our study was to compare the association of the novel FAS equations based on serum creatinine and cystatin C in predicting all-cause and cardiovascular mortality risk in patients suffering from ischemic stroke. Additionally we analysed also well-known CKD-EPI equations in predicting mortality in these patients.

2. Patients and methods

In our observational cohort study we included 390 Caucasian patients who had suffered from an acute ischemic stroke and who were hospitalized at our department in a one-year period from 2005 to 2006. Patients were followed-up on for three years from the day of their admission to the hospital or until their death. Acute ischemic stroke was defined according to World Health Organization criteria [18]. Ischemic stroke was diagnosed if the patient had an appropriate clinical event and had a brain CT that showed a compatible low-density lesion or was normal. Patients with events resolving completely within < 24 h were excluded from the study. At admission, a quantitative measurement of neurologic deficit was performed according to the National Institutes of Health Stroke Scale (NIHSS1) [19]. No included patient had comorbid malignancy, clinically thyroid disease and no patient was on glucocorticoid therapy. Additionally, no patient had any clinically significant muscle disease.

Serum creatinine and cystatin C were measured upon admission to the hospital. Serum creatinine was measured by using the kinetic method according to Jaffé without deproteinisation (Roche Diagnostics). This is a compensated method based on manufacturer instructions and was described previously [20]. Serum cystatin C was measured by the particle-enhanced immunonephelometric method (Dade Behring). The values were recalculated to the certified reference standard, using the multiplication factor, according to the manufacturer's specifications.

GFR was estimated according to FAS equations based on serum creatinine (FAScrea) and cystatin C (FAScysC) [6,16]. GFR was estimated also with both CKD-EPI equations [5,17]. The values of the estimated GFR (FAScrea, FAScysC, CKD-EPIcrea and CKD-EPIcysC) were divided into quintiles. In the first 24 h serum total cholesterol, triglycerides and high-sensitive C-reactive protein (hsCRP) were measured.

Arterial hypertension and diabetes mellitus were defined according to the accepted guidelines [21,22]. Patients were divided into smokers (presently) and non-smokers. All necessary data was obtained via a questionnaire from patients and/or their relatives. Atrial fibrillation was confirmed with a standard 12-lead electrocardiogram.

The National Ethics Committee approved the study. Informed consent was obtained from each patient. The study was in adherence with the Declaration of Helsinki.

2.1. Statistical methods

SPSS for Windows software (version 24.0.0.0) was used to analyse the data. The arithmetic mean values and standard deviation were calculated. In comparing variables among patients who died or survived, a *t*-test or chi-square test was used where appropriate. Survival rates were analysed using Kaplan-Meier survival curves. Cox regression analyses were used to evaluate the association of each measure of renal function (FAScrea, CKD-EPIcrea, FAScysC and CKD-EPIcysC) with a hazard ratio for all-cause and cardiovascular mortality. In the adjusted model, we included variables that are known risk factors for stroke mortality: age, gender, initial stroke severity (NIHSS), hypertension, smoking, diabetes, atrial fibrillation, total cholesterol, triglycerides and hsCRP. A value of $P < 0.05$ was considered to be statistically significant.

3. Results

Of the 390 included patients, 183 were women (46.9%) and 207 (53.1%) were men. The mean age of patients upon admission to the hospital was 70.9 ± 11.6 years, ranging from 36 to 96 years of age. The mean estimated GFR according to the FAS equation based on serum creatinine was 58.2 ± 19.8 ml/min/1.73 m^2 and based on serum cystatin C was 49.3 ± 17.5 ml/min/1.73 m^2. The mean estimated GFR according to CKD-EPIcrea equation was 63.4 ± 20.2 ml/min/1.73 m^2 and according to CKD-EPIcysC 49.2 ± 20.3 ml/min/1.73 m^2. The majority of patients were classified in stage 2 or 3 CKD regardless which equation was used (Table 1).

All patients were followed-up for three years from the day of their admission to the hospital or until their death. During the follow-up period, 173 (44.4%) patients died. Patients who died were older at the onset of their stroke, had a higher NIHSS score on admission, had a lower estimated GFR according to both FAS and both CKD-EPI equations, lower serum total cholesterol, had higher serum hsCRP, more commonly had atrial fibrillation and were more often non-smokers (Table 2). No difference was found in gender, serum triglycerides, presence of diabetes and hypertension between patients who died or survived (Table 2).

Kaplan-Meier survival analysis showed progressively higher risk for death from the first quintile onward if GFR was estimated based on serum cystatin C (FAScysC and CKD-EPIcysC) and not, if GFR was estimated based on serum creatinine (Fig. 1).

The association of hazard ratio for estimated GFR equation based on serum creatinine (FAScrea and CKD-EPIcrea) with all-cause mortality appeared to be J-shaped. For FAScrea and CKD-EPIcrea equations only for the fifth quintile hazard ratio for mortality was significantly higher compared to the first quintile ($P < 0.001$). For estimated GFR equation

Table 1
Classification of patients in CKD stages according to the estimated GFR.

CKD stage	Equation			
	FAScrea*	FAScystC**	CKD-EPIcrea***	CKD-EPIcysC****
Stage 1 - number (%)	23 (5.9)	7 (1.8)	39 (10.0)	14 (3.6)
Stage 2 - number (%)	146 (37.4)	87 (22.3)	182 (46.7)	96 (24.6)
Stage 3 - number (%)	196 (50.3)	257 (65.9)	147 (37.7)	218 (55.9)
Stage 4 - number (%)	20 (5.1)	30 (7.7)	16 (4.1)	45 (11.5)
Stage 5 - number (%)	5 (1.3)	9 (2.3)	6 (1.5)	17 (4.4)

FAScrea* = Full Age Spectrum equation based on serum creatinine.
FAScystC** = Full Age Spectrum equation based on serum cystatin C.
CKD-EPIcrea*** = Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine.
CKD-EPIcysC**** = Chronic Kidney Disease Epidemiology Collaboration equation based on serum cystatin C.