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Cystatin C and derived measures of renal function as risk factors for mortality and acute kidney injury in sepsis – A post-hoc analysis of the FINNAKI cohort

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ABSTRACT

Purpose: To assess the association between cystatin C-derived estimates of kidney function and mortality and acute kidney injury (AKI) in sepsis.
Materials and methods: Post-hoc analysis of sepsis patients in the FINNAKI-cohort ($n = 802$). Primary outcome was 90-day mortality. We measured plasma cystatin C and creatinine at intensive care unit (ICU) admission and estimated glomerular filtration rates ($eGFR_{cys}$, $eGFR_{crea}$) and shrunken pore syndrome (SPS; defined as $eGFR_{cys}/eGFR_{crea}$ ratio < 0.7). Associations were assessed using Cox- or logistic regression.
Results: Increased cystatin C and decreased $eGFR_{cys}$ were associated with mortality in unadjusted analyses and in analyses adjusted for illness severity and creatinine. Hazard ratios (HRs) in unadjusted analyses were 3.30 (95% CI; 2.12–5.13, $p < 0.001$) and 3.26 (95% CI; 2.12–5.02, $p < 0.001$) respectively. SPS was associated with mortality in an unadjusted- (HR 1.78, 95% CI; 1.33–2.37, $p < 0.001$) and in an adjusted analysis (HR 1.54, 95% CI; 1.07–2.22, $p = 0.021$). All cystatin C-derived measures were associated with mortality also after adjustment for AKI development. Cystatin C was associated with AKI in unadjusted analyses but not in analyses adjusted for creatinine.
Conclusion: Cystatin C and derived measures of kidney function at ICU admission are associated with an increased 90-day mortality. Increased AKI incidence does not fully explain this association.

1. Introduction

Sepsis is a life-threatening disease caused by a dysregulated host response to infection [1]. Recent estimates suggest that 48 million cases of sepsis occur globally every year and mortality is estimated to be 20–25% [1,2]. Pre-existing chronic kidney disease and development of acute kidney injury (AKI) are associated with an even higher mortality [3-10] suggesting that early assessment of kidney function in sepsis patients may identify patients with increased risk of death.

Cystatin C, a 13.4 kDa serine protease inhibitor, is produced by nucleated cells in the body and is eliminated by filtration in the glomeruli. Compared with creatinine, cystatin C is less influenced by changes in body composition, nutritional status, and inflammation and estimates of glomerular filtration rate (GFR) based on plasma concentration of cystatin C are suggested to be more accurate than creatinine-based estimates [11-16]. Moreover, cystatin C is a much larger molecule than

Abbreviations: ACE, Angiotensin Converting Enzyme; AKI, Acute Kidney Injury; ARB, Angiotensin Receptor Blocker; CAPA, Caucasian Asian and Pediatric Adult; CI, Confidence Interval; CNS, Central Nervous System; COPD, Chronic Obstructive Pulmonary Disease; Crea, Creatinine; CRP, C Reactive Protein; Cys, Cystatin C; Da, Dalton; eGFR, Estimated Glomerular Filtration Rate; $eGFR_{crea}$, Estimated Glomerular Filtration Rate based on creatinine; $eGFR_{cys}$, Estimated Glomerular Filtration Rate based on cystatin C; ICU, Intensive Care Unit; IQR, Interquartile Range; GFR, Glomerular Filtration Rate; HR, Hazard ratio; LM-rev, Lund Malmö-revised; MDRD, Modification in Diet in Renal Disease; NSAID, Non-Steroidal Anti-Inflammatory Drug; OR, Odds Ratio; RRT, Renal Replacement Therapy; SAPS, Simplified Acute Physiology Score; SPS, Shrunken Pore Syndrome; Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4.

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creatinine (113 Da) and may therefore reflect other aspects of glomerular filtration than creatinine does. Taken together this indicates that cystatin C may be particularly valuable as a measure of renal function and for risk stratification in the critically ill [17-27].

Cystatin C has been shown to be more strongly linked to mortality than creatinine in large general-population cohorts [28-30]. Recently, a decreased ratio of cystatin C- to creatinine-derived GFR estimates was shown to be associated with increased mortality in general-population cohorts as well as in post-operative thoracic surgical patients [23,31-33]. Because a larger decrease in cystatin C filtration compared with creatinine filtration could theoretically be explained by a decrease in glomerular pore size, the name shrunken pore syndrome (SPS) was coined to describe this condition [23,34]. In mixed cohorts of critically ill patients, plasma concentration of cystatin C at intensive care unit (ICU) admission did not predict mortality in a small single center study [35] whereas some studies have suggested that cystatin C and estimates of GFR based on cystatin C are more strongly associated with mortality than estimates of GFR based on creatinine later in the course of ICU stay [36-38]. Whether cystatin C-based estimates of GFR and SPS are associated with an increased risk of death already at ICU admission in patients with sepsis is unclear.

2. Objectives

Based on the above, the primary objective of this study was to assess the association between mortality and plasma concentration of cystatin C, cystatin C-based estimates of GFR, and SPS at ICU admission in a cohort of sepsis patients. The secondary objective was to assess the association between cystatin C and development of AKI.

3. Methods and materials

3.1. Study population

This was a post-hoc analysis of the prospective observational FINNAKI study which studied risk factors, incidence, and outcome of AKI in a cohort of consecutively included patients enrolled at 17 Finnish ICUs between 1 September 2011 and 1 February 2012 [6]. The study protocol was approved by the Ethics Committee of the Department of Surgery, Helsinki, and Uusimaa Hospital District, including a delayed consent by either the patient or a proxy. The FINNAKI study included elective admissions with an ICU stay >24 h along with all emergency ICU admissions and has been described in detail previously [6]. Exclusion criteria were age < 18 years, chronic dialysis treatment, impending organ donation, non-Finnish nationals, patients who received intermediate care and patients who had received dialysis during a previous ICU stay.

3.2. Inclusion criteria

Patients from the FINNAKI cohort with severe sepsis (either at ICU admission or developed during study period) according to the sepsis-2 criteria were included if a plasma sample at admission was available [39].

3.3. Data and sample collection

Length of stay in the ICU, demographics, physiologic data, medical history and severity scores were gathered from the Finnish Intensive Care Consortium prospective database (Tieto Ltd., Helsinki, Finland). AKI was defined and staged using the KDIGO criteria using daily creatinine and hourly urine output measurements. AKI status was followed during the first five days [40] in the ICU. Pre-admission creatinine was defined as the most recent value within a year prior to admission, excluding the week prior to admission to the ICU. If baseline serum creatinine was unavailable the modification in diet in renal disease (MDRD) Eq. [41] was used to estimate pre-admission creatinine for assessment of AKI status assuming a glomerular filtration rate of 75 ml/min/1.73 m^2.

3.4. Plasma analysis

The plasma samples used for measurement of cystatin C and creatinine in this study were collected within two hours of arrival in the ICU. Cystatin C and creatinine plasma concentrations were measured using Olink CARDIOVASCULAR II and Olink INFLAMMATION panels (Olink Proteomics AB, Uppsala, Sweden). All samples were normalized, and quality controlled according to the manufacturer's recommendations. The Caucasian, Asian, Pediatric, and Adult (CAPA)-Eq. [42] was used when estimating GFR from plasma concentration of cystatin C ($eGFR_{cys}$) and the Lund-Malmö (LM)-rev-equation when estimating GFR from plasma concentration of creatinine ($eGFR_{crea}$) [43-45].

3.5. Outcomes

Primary outcome was 90-day mortality. Secondary outcomes were: a) development of AKI between 12 h and 5 days after admission at the ICU, and b) renal replacement therapy (RRT). Patients with AKI at ICU admission, patients who developed AKI within 12 h of ICU admission and patients with chronic kidney disease were excluded from analyses with AKI as an outcome.

3.6. Statistical analyses

No power analysis was performed and the number of patients fulfilling inclusion criteria in the FINNAKI cohort determined the sample size. The association between cystatin C, $eGFR_{cys}$ or SPS on one hand, and 90-day mortality, development of AKI or need for RRT on the other hand, was assessed using unadjusted and adjusted logistic regression analysis or Cox regression analysis. The proportional hazard assumption was assessed with graphical inspection and a test for independence between residuals and time. In the analysis of SPS we assessed two previously established thresholds to identify patients with SPS ($eGFR_{cys}/eGFR_{crea} < 0.6$ or < 0.7) [23,31,46]. In the first set of adjusted analyses, we adjusted for age, sex, comorbidities and covariates reflecting illness severity (chronic kidney disease, SAPS II score, mechanical ventilation during ICU stay, septic shock, and urinary tract infection). Comorbidities and covariates reflecting illness severity were introduced in the multivariable models if they had a $p < 0.20$ at univariate analyses for respective outome and were discarded by backward elimination. Covariates left after backward elimination are detailed in legends and table footnotes for respective outcomes. In a second set of adjusted analyses, we adjusted also for creatinine or $eGFR_{crea}$ to assess if the cystatin C derived measures of renal function added information to creatinine-derived measures of renal function. In a third adjusted analysis, we adjusted SPS for $eGFR_{cys}$ to assess if SPS added information to $eGFR_{cys}$. Statistical analyses were conducted using IBM SPSS 25.0 (SPSS, Chicago, IL, USA) and Stata SE 16.1 (Stata Corp 2019). Data are presented as median values with interquartile range [IQR] or as numbers with percentage.

4. Results

4.1. Patient characteristics

Patient characteristics and associations between the different outcomes assessed are presented in Table 1. Pre-admission creatinine was missing in 249 patients. A total of 233 (29%) of the patients were dead at 90 days after admission to the ICU. Chronic kidney disease was present in 49 patients at inclusion (6.1%). Within 12 h, 388 patients developed AKI (48%). A total of 176 (22%) patients developed AKI between 12 h and 5 days after admission at the ICU and 120 (15%) patients needed RRT during the ICU stay. The number of patients with SPS was

Table 1
Patient characteristics, hazard- and odds ratios in univariate analyses.

		Mortality HR (95% CI) $n = 802$	p	AKI* OR (95% CI) $n = 534$	p	RRT OR (95% CI) n = 802	p
Age (years)	65 (54–75)	1.04 (1.03–1.05)	<0.001	1.01 (1.00–1.03)	0.027	1.01 (0.99–1.02)	0.416
Gender (female)	288 (35.9%)	1.07 (0.82–1.40)	0.634	1.23 (0.84–1.81)	0.290	1.33 (0.90–1.98)	0.155
Weight (kg)	80 (69–90)	0.97 (0.98–0.99)	<0.001	1.01 (1.00–1.02)	0.008	1.00 (0.99–1.01)	0.739
Baseline creatinine (μmol/L)	76 (61–92)	1.00 (0.99–1.01)	0.114	1.01 (1.00–1.02)	0.036	1.01 (1.01–1.02)	<0.001
Severity of disease							
SAPS II score	42 (33–54)	1.05 (1.04–1.05)	<0.001	1.03 (1.02–1.05)	<0.001	1.06 (1.04–1.07)	<0.001
Vasopressor on day one	409 (51%)	1.45 (1.02–2.08)	0.041	2.22 (1.32–3.74)	0.003	2.80 (1.51–5.19)	0.001
Mechanical ventilation during ICU stay	559 69.7%)	1.78 (1.29–2.45)	<0.001	1.63 (1.07–2.48)	0.022	2.14 (1.31–3.48)	0.002
Septic shock	623 (77.7%)	1.61 (1.13–2.30)	0.008	3.36 (2.00–5.63)	<0.001	4.10 (2.03–8.26)	<0.001
Comorbidities							
Chronic kidney disease	49 (6.1%)	1.83 (1.18–2.84)	0.007	–	–	3.03 (1.61–5.69)	0.001
Renal transplant	8 (1%)	1.36 (0.44–4.26)	0.594	1.20 (0.11–13.37)	0.880	3.46 (0.82–14.66)	0.092
Diabetes	199 (24.8%)	0.80 (0.58–1.09)	0.159	1.40 (0.90–2.18)	0.137	1.80 (1.19–2.73)	0.006
Hypertension	419 (52.2%)	1.11 (0.85–1.44)	0.456	1.08 (0.74–1.57)	0.701	1.14 (0.77–1.69)	0.504
Systolic heart failure	82 (10.2%)	1.80 (1.25–2.59)	0.002	1.01 (0.54–1.87)	0.981	0.51 (0.23–1.15)	0.103
COPD	92 (11.5%)	1.04 (0.69–1.55)	0.867	0.58 (0.31–1.10)	0.093	0.44 (0.20–0.97)	0.041
Any malignancy	103 (12.8%)	2.06 (1.50–2.84)	<0.001	1.17 (0.67–2.04)	0.583	1.24 (0.72–2.15)	0.444
Chronic liver failure	36 (4.49%)	2.01 (1.24–3.25)	0.005	0.65 (0.24–1.79)	0.405	1.39 (0.59–3.25)	0.447
Laboratory results max 24 h pre-ICU admission							
Leukocytes (10^9/L)	12.3 (8.10–17.20)	0.99 (0.98–1.02)	0.850	1.01 (0.98–1.03)	0.652	0.99 (0.97–1.03)	0.797
CRP (mg/L)	162.0 (65.35–272.5)	0.99 (0.99–1.00)	0.027	1.00 (1.00–1.00)	0.083	1.00 (0.99–1.00)	0.363
Treatment 48 h pre-ICU							
Immunosuppressive	61 (7.6%)	1.29 (0.82–2.05)	0.273	0.92 (0.45–1.89)	0.816	1.13 (0.56–2.30)	0.733
ACE inhibitor/ARB	197 (24.6%)	1.14 (0.85–1.54)	0.388	1.06 (0.68–1.65)	0.807	0.85 (0.52–1.36)	0.490
NSAID	110 (13.7%)	0.78 (0.51–1.18)	0.243	0.79 (0.45–1.41)	0.430	1.33 (0.78–2.26)	0.298
Diuretic	316 (39.4%)	1.58 (1.21–2.07)	0.001	1.22 (0.83–1.80)	0.317	1.23 (0.82–1.85)	0.316
Albumin	8 (0.1%)	1.32 (0.42–4.13)	0.630	1.18 (0.16–6.12)	0.848	1.92 (0.28–8.45)	0.428
Hydroxyethyl starch	103 (12.8%)	0.87 (0.58–1.30)	0.496	2.11 (1.23–3.58)	0.006	1.58 (0.91–2.63)	0.090
Radiocontrast	178 (22.2%)	0.72 (0.51–1.01)	0.056	1.57 (1.04–2.38)	0.033	0.58 (0.34–0.99)	0.044
Source of infection							
Pulmonary	417 (52.0%)	1.08 (0.83–1.40)	0.566	0.79 (0.54–1.15)	0.222	0.37 (0.25–0.56)	<0.001
Abdominal	183 (22.8%)	1.06 (0.78–1.45)	0.697	1.22 (0.77–1.92)	0.401	1.56 (1.01–2.40)	0.043
Urinary tract	48 (6.0%)	0.74 (0.39–1.39)	0.343	2.38 (1.15–4.95)	0.020	1.99 (1.01–3.95)	0.048
Skin and soft tissue	67 (8.4%)	0.52 (0.28–0.95)	0.034	1.18 (0.60–2.29)	0.636	1.27 (0.66–2.44)	0.481
CNS	25 (3.1%)	0.51 (0.19–1.36)	0.178	0.55 (0.18–1.67)	0.295	0.23 (0.03–1.72)	0.152
Other**	38 (4.7%)	1.42 (0.70–2.87)	0.335	2.96 (0.89–9.83)	0.077	5.55 (2.30–13.37)	<0.001

Continuous variables are presented as median values (interquartile range) and qualitative variables are presented as number values (percentage). Odds ratios, 95% Confidence Interval (CI) and *p*-values are calculated using logistic regression. Hazard ratios (HRs) are calculated using cox regression. * Patients with AKI within 12 h after ICU admission were excluded in AKI analysis ** Endocarditis, catheter, foreign body, unknown.

79 (9.9%) when using a ratio of 0.6 as a cut off and 159 (20%) when using 0.7 as the cut-off. The flow of patients in the study is presented in Fig. 1.

4.2. 90-day mortality

A high plasma concentration of cystatin C, a decreased $eGFR_{cys}$ and the presence of SPS were associated with increased mortality in both the unadjusted analyses and the analyses adjusted for age, sex, comorbidities and covariates reflecting illness severity (Fig. 2, Fig. 3, Supplement table 1). The increased risk of 90-day mortality in the cystatin C and $eGFR_{cys}$ models remained after adjusting also for creatinine and $eGFR_{crea}$, respectively. Similarly, the increased risk of 90-day mortality in the SPS models remained after adjusting for $eGFR_{crea}$. In contrast to cystatin C-derived measures of renal function, creatinine and $eGFR_{crea}$ were not associated with an increased risk of death in the adjusted analyses (Supplement table 1). The association between SPS and 90-day mortality remained after adjusting for $eGFR_{cys}$. Because corticosteroids are suggested to influence plasma concentrations of cystatin C [47] and because corticosteroids are used in the treatment of septic shock, we performed a sensitivity analysis in which we also adjusted our models for treatment with corticosteroids. Adjustment for treatment with corticosteroids did not influence our results except for SPS with cut-off 0.6 (Supplement table 2).

To assess if the association between 90-day mortality and cystatin C, $eGFR_{cys}$ and SPS was coupled to the development of AKI, we performed a post hoc analysis in which we adjusted also for AKI within 5 days of admission. Cystatin C, $eGFR_{cys}$ and SPS were associated with 90-day mortality also in this analysis (Supplement table 3).

4.3. AKI

A total of 534 patients were included in the analysis of AKI development within 12 h to 5 days after admission to the ICU. A high plasma concentration of cystatin C and a low $eGFR_{cys}$ (fourth and first quartiles, respectively) were associated with AKI in the unadjusted analysis and in analyses adjusted for age, sex, comorbidities and covariates reflecting illness severity, but not in analyses adjusted also for creatinine or $eGFR_{crea}$ (Supplement table 4). SPS was not associated with AKI in any of the analyses.

4.4. RRT

A high plasma concentration of cystatin C and a low $eGFR_{cys}$ were both associated with RRT in the unadjusted analysis and in analyses adjusted for age, sex, comorbidities and covariates reflecting illness severity. No associations between cystatin C, $eGFR_{cys}$, and RRT were found in analyses adjusted also for creatinine or $eGFR_{crea}$ (Supplement table 5). SPS was not associated with an increased risk of RRT.

5. Discussion

We found that an increased plasma concentration of cystatin C, a decrease in a cystatin C-based estimate of GFR, and the presence of SPS in sepsis patients at ICU admission are associated with increased 90-day mortality in unadjusted and adjusted analyses. Cystatin C and a cystatin C-based estimate of GFR at ICU admission were associated with development of AKI and RRT in unadjusted analyses, but not in analyses adjusted for creatinine.

Plasma concentration of cystatin C is less influenced than creatinine by muscle mass, nutrition and other non-renal factors that are common in sepsis and is suggested to provide a better estimate of GFR [11,32,48]. Given that pre-existing renal disease is a risk factor for AKI, we hypothesized that cystatin C would be more strongly associated with increased risk of AKI. However, no association between AKI and cystatin C was detected in our analysis when adjusted for creatinine. Our findings align

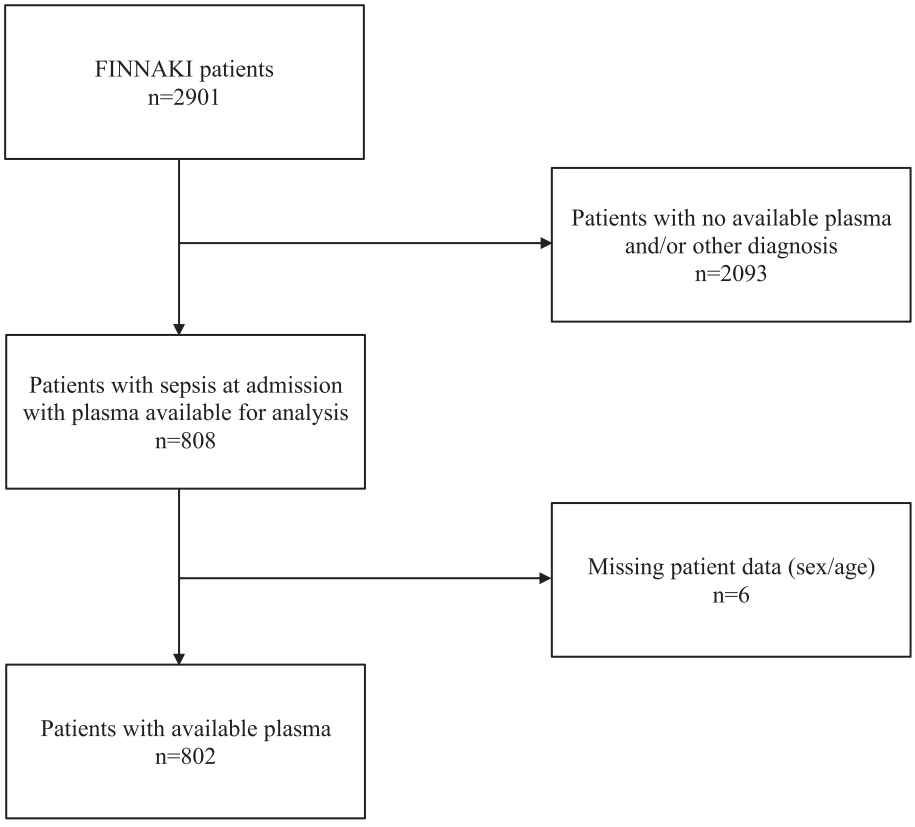

Fig. 1. Flow chart of participants. Out of 2901 patients 802 were included and their plasma analysed. Of these patients, 176 developed Acute Kidney Injury (AKI) between 12 h and 5 days after admission at the Intensive Care Unit (ICU), while 388 patients did not develop AKI.

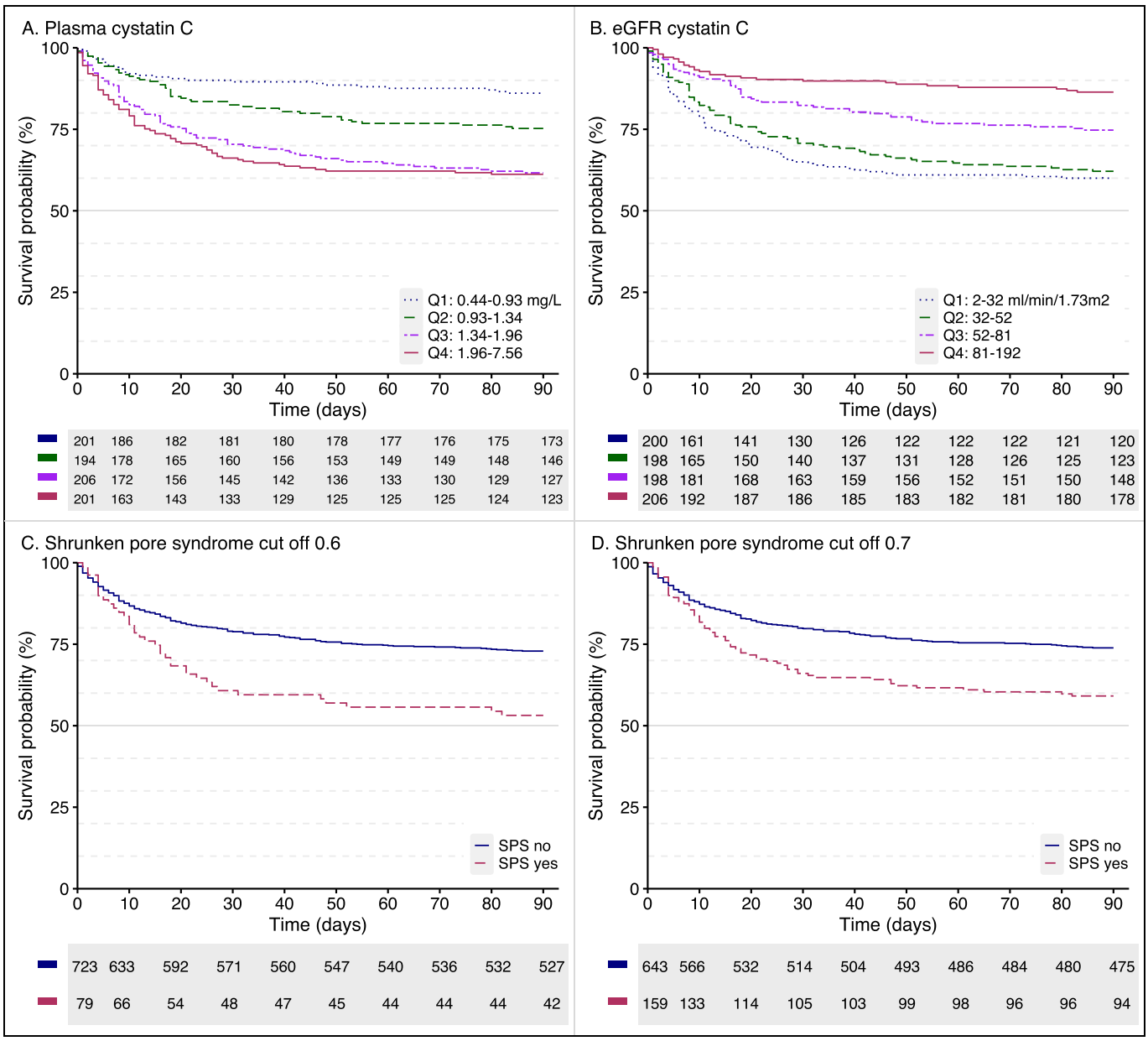

Fig. 2. Kaplan-Meyer curves for quartiles of plasma concentration of cystatin C (A), quartiles of $eGFR_{cys}$ (B), and SPS defined as a ratio of $eGFR_{cys}/eGFR_{crea} < 0.6$ (C) or < 0.7 (D).

with most studies in smaller mixed cohorts of critically ill patients and add to an increasing body of data suggesting that measurement of cystatin C does not offer a robust improvement in risk stratification over creatinine with regard to risk of AKI [49,50].

As mentioned in the introduction, compared with creatinine, plasma concentrations of cystatin C and cystatin C-based estimates of GFR in large general-population cohorts are more strongly associated with long-term mortality [28-30]. Our results suggest that cystatin C and estimates of glomerular filtration rate based on cystatin C at admission are associated with mortality also in sepsis patients. The result differs from a previous study in which an association between cystatin C at admission and mortality was not detected in a cohort of mixed critically ill patients [35]. The most likely reason for the difference in results is the comparatively lower power in the previous study but we cannot exclude other factors, such as the differences in case mix or analytical methodology, may have contributed. The results do, however, align with other larger studies showing an association between cystatin C later in course of the ICU stay and mortality [36-38]. The finding that the association remains in analyses adjusted for age, sex, comorbidities, covariates reflecting illness severity and creatinine or creatinine-based estimates of GFR is in agreement with previous studies and suggests that plasma concentration of cystatin C provides additional information to that obtained through measurement of creatinine concerning risk of death [28,36,51].

Depending on the definition of SPS and the studied population, the incidence seems to be 0.2–8.2% in studies comprising both healthy and sick populations [23,32,34]. Our results suggest it might be even more common in sepsis with an incidence ranging from 10 to 20% depending on the cut-off used to identify the syndrome. SPS is associated with increased risk of long-term mortality (1–5 years) in cohorts of healthy seniors, in mixed medical cohorts and cardiac surgery cohorts [31,32,46,52]. Our results suggest that SPS is associated also with shorter-term mortality in sepsis patients admitted to the ICU. Interestingly, the finding that the increase in risk of death is similar in analyses adjusted for age, sex, comorbidities and illness severity indicate that presence of SPS represents a baseline risk that is unaffected by acute

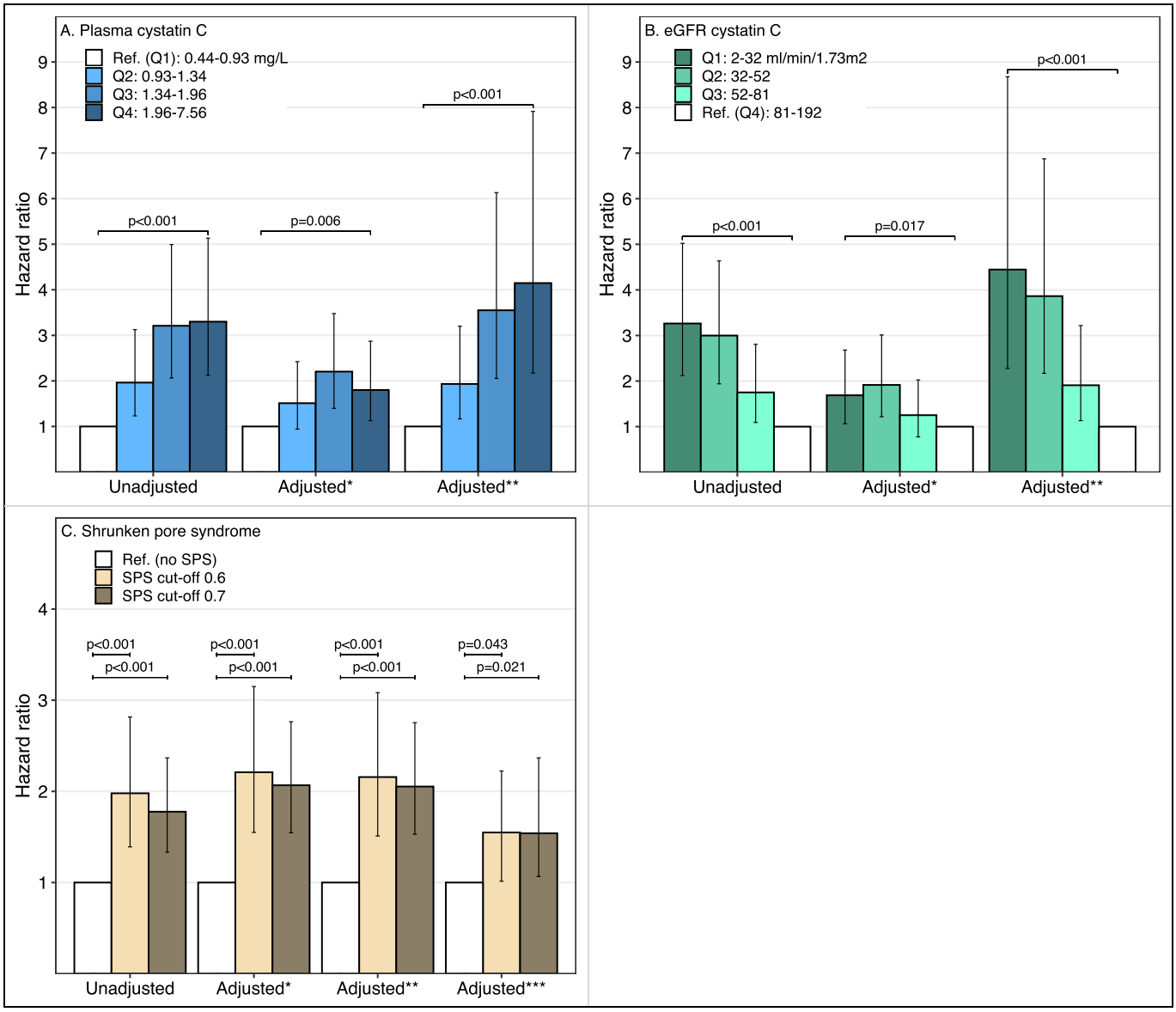

Fig. 3. Grouped bar plots showing unadjusted and adjusted hazard ratios (HRs) with confidence intervals of plasma cystatin C quartiles Q2 to Q4 (where Q1 is reference) (A), $eGFR_{cys}$ quartiles Q1 to Q3 (where Q4 is reference) (B) and small pore syndrome (SPS) with cut-off 0.6 and 0.7 (C). *P*-values are for the respective model. * Adjusted for age, sex, comorbidities and covariates reflecting illness severity (chronic kidney disease, SAPS II score, mechanical ventilation during ICU stay, septic shock, and urinary tract infection). **: same as *, but the cystatin C/$eGFR_{cys}$ models are also adjusted for creatinine/$eGFR_{crea}$ respectively. SPS model adjusted for $eGFR_{crea}$. *** same as ** but SPS model is also adjusted for $eGFR_{cys}$.

illness. This contrasts with the risk increase associated with increased plasma concentration of cystatin C and decreased cystatin C-based estimates of GFR, which decreased in the adjusted analyses. These observations align with the hypothesis that SPS identifies a subset of patients with a decrease in cystatin C-estimated GFR with a particularly high risk of death.

How can we explain our finding that cystatin C, a cystatin C-based estimate of GFR, and SPS are more strongly associated with an increased risk of death than is creatinine? Although creatinine and cystatin C based estimates of GFR commonly agree, the stronger association between cystatin C-based estimates of GFR and mortality could be related to the observation that cystatin C based estimates of GFR are less influenced by non-renal confounders and hence offer a better estimate of true GFR [11,20,21]. However, the recent finding that a decrease in cystatin C-based estimates of GFR is associated with increased mortality also in patients with normal GFR, as measured using iohexol, suggests that additional mechanisms are at play [46]. Cystatin C is about 2 orders of magnitude larger than both creatinine and tracers used to measure GFR, such as iohexol and Cr-EDTA. This means that cystatin C may detect a decreased filtration of larger molecules earlier than creatinine can. Because glomerular filtration is suggested to be of importance for clearance of proteins up to about 30 kDa, and because a large fraction of signalling and regulatory proteins have molecular masses from 5 to 30 kDa, such a change in kidney function may be of pathophysiological importance. This hypothesis is supported by a study demonstrating an increased plasma concentration of molecules below 40 kDa in the presence of SPS [23,53]. A pathophysiological explanation for the observation that cystatin C-based and creatinine-based estimates of GFR diverge in some patients and move together in some patients can thus be offered. A disease process that primarily affects the pore size in the filtration barrier and/or the thickness of the glomerular basement membrane would lead to a decrease in cystatin C-based estimates of GFR whereas creatinine-based estimates of GFR would be largely conserved. Recent data showing a correlation between increased thickness of the

glomerular basement membrane measured using electron microscopy and a decreased $eGFR_{cys}/eGFR_{crea}$-ratio provides support for the latter mechanism [54]. In contrast, a disease process that primarily causes loss of function of whole nephrons would be expected to result in similar decreases in cystatin C-based and creatinine-based estimates of GFR.

Given that AKI in critical illness has been associated with increased mortality, we tested the hypothesis that the association between mortality and cystatin C, cystatin C-based estimates of GFR, and SPS was mediated through development of AKI. Our findings that the cystatin C-based estimates of renal function were associated with similar risk of mortality also in analyses adjusted for development of AKI, and that cystatin C and creatinine offer similar discrimination with regard to development of AKI, does not support such a hypothesis.

5.1. Clinical implications

The clinical implications of the association between cystatin C and derived measures of renal function as risk factors for mortality in sepsis is uncertain at this point. Studies in other cohorts suggest that the increased mortality can be attributed to cardiovascular disease [53] but until the pathophysiological mechanisms are better understood potential interventions for high-risk patients are elusive.

5.2. Strengths and limitations

Strengths of this study include a relatively large sample size and the prospective multicentre design. Important limitations of the study include the exploratory post-hoc analyses which inherently may have introduced bias. Moreover, our findings in critically ill septic patients may not be generalizable in other critically ill patients. Finally, the relatively short follow-up period of 90 days may compromise the interpretations of the study findings.

6. Conclusion

We conclude that increased plasma concentration of cystatin C, a decrease in a cystatin C-based estimate of GFR, and the presence of SPS in sepsis patients at ICU admission are associated with increased 90-day mortality. Our results suggest that the increased risk is independent of age, sex, comorbidities, covariates reflecting illness severity, baseline creatinine, and development of AKI.

Authors' contributions

PB was the originator and supervisor of the study. STV and VP collected clinical data and laboratory samples. AG and JF analysed the samples. EL and AE processed the dataset. EL and PB drafted the manuscript. AÅ performed the statistical analyses. All authors read, critically revised, and approved the final manuscript.

Ethics approval and consent to participate

This was a post-hoc analysis of the FINNAKI study which was approved by the Ethics Committee of the Department of Surgery at the Helsinki University Hospital (reference number: 18/13/03/02/2010).

Consent for publication

Not applicable.

Availability of data and materials

The dataset is available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Erik Linné: Data curation, Writing – original draft, Visualization. **Alma Elfström:** Data curation, Writing – review & editing. **Anna Åkesson:** Formal analysis, Writing – review & editing. **Jane Fisher:** Investigation, Resources, Writing – review & editing. **Anders Grubb:** Investigation, Resources, Writing – review & editing. **Ville Pettilä:** Investigation, Resources, Writing – review & editing. **Suvi T. Vaara:** Investigation, Resources, Writing – review & editing. **Adam Linder:** Writing – review & editing. **Peter Bentzer:** Conceptualization, Methodology, Writing – original draft, Supervision, Project administration.

Declaration of Competing Interest

The authors have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154148.

References

[1] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for Sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
[2] Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. Lancet. 2020;395(10219):200–11.
[3] Bellomo R, Kellum JA, Ronco C, Wald R, Martensson J, Maiden M, et al. Acute kidney injury in sepsis. Intensive Care Med. 2017;43(6):816–28.
[4] Martensson J, Bellomo R. Sepsis-induced acute kidney injury. Crit Care Clin. 2015;31(4):649–60.
[5] Singh P, Rifkin DE, Blantz RC. Chronic kidney disease: an inherent risk factor for acute kidney injury? Clin J Am Soc Nephrol. 2010;5(9):1690–5.
[6] Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med. 2013;39(3):420–8.
[7] Perinel S, Vincent F, Lautrette A, Dellamonica J, Mariat C, Zeni F, et al. Transient and persistent acute kidney injury and the risk of hospital mortality in critically ill patients: results of a multicenter cohort study. Crit Care Med. 2015;43(8):e269–75.
[8] Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int. 2012;81(9):819–25.
[9] Wald R, Quinn RR, Adhikari NK, Burns KE, Friedrich JO, Garg AX, et al. Risk of chronic dialysis and death following acute kidney injury. Am J Med. 2012;125(6):585–93.
[10] Linder A, Fjell C, Levin A, Walley KR, Russell JA, Boyd JH. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. Am J Respir Crit Care Med. 2014;189(9):1075–81.
[11] Vinge E, Lindergard B, Nilsson-Ehle P, Grubb A. Relationships among serum cystatin C, serum creatinine, lean tissue mass and glomerular filtration rate in healthy adults. Scand J Clin Lab Invest. 1999;59(8):587–92.
[12] Salgado JV, Salgado BJ, Neves FA. Cystatin C may better reflect the effect of obesity on renal function. Obesity (Silver Spring). 2012;20(6):1136.
[13] Friedman AN, Strother M, Quinney SK, Hall S, Perkins SM, Brizendine EJ, et al. Measuring the glomerular filtration rate in obese individuals without overt kidney disease. Nephron Clin Pract. 2010;116(3):c224–34.
[14] Schück O, Teplan V, Stollova M, Skibova J. Estimation of glomerular filtration rate in obese patients with chronic renal impairment based on serum cystatin C levels. Clin Nephrol. 2004;62(2):92–6.
[15] Odden MC, Tager IB, Gansevoort RT, Bakker SJ, Katz R, Fried LF, et al. Age and cystatin C in healthy adults: a collaborative study. Nephrol Dial Transplant. 2010;25(2):463–9.
[16] Jonsson AS, Flodin M, Hansson LO, Larsson A. Estimated glomerular filtration rate (eGFRCystC) from serum cystatin C shows strong agreement with iohexol clearance in patients with low GFR. Scand J Clin Lab Invest. 2007;67(8):801–9.
[17] Herget-Rosenthal S, Marggraf G, Husing J, Goring F, Pietruck F, Janssen O, et al. Early detection of acute renal failure by serum cystatin C. Kidney Int. 2004;66(3):1115–22.
[18] Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. Curr Opin Nephrol Hypertens. 2015;24(3):295–300.
[19] Stevens LA, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int. 2009;75(6):652–60.

[20] Grubb A, Bjork J, Nyman U, Pollak J, Bengzon J, Ostner G, et al. Cystatin C, a marker for successful aging and glomerular filtration rate, is not influenced by inflammation. Scand J Clin Lab Invest. 2011;71(2):145–9.
[21] Martensson J, Martling CR, Oldner A, Bell M. Impact of sepsis on levels of plasma cystatin C in AKI and non-AKI patients. Nephrol Dial Transplant. 2012;27(2):576–81.
[22] Delanaye P, Cavalier E, Morel J, Mehdi M, Maillard N, Claisse G, et al. Detection of decreased glomerular filtration rate in intensive care units: serum cystatin C versus serum creatinine. BMC Nephrol. 2014;15:9.
[23] Grubb A. Shrunken pore syndrome - a common kidney disorder with high mortality. Diagnosis, prevalence, pathophysiology and treatment options. Clin Biochem. 2020;83:12–20.
[24] Risch L, Herklotz R, Blumberg A, Huber AR. Effects of glucocorticoid immunosuppression on serum cystatin C concentrations in renal transplant patients. Clin Chem. 2001;47(11):2055–9.
[25] Williams WW, Hogan JW, Ingelfinger JR. Time to eliminate health care disparities in the estimation of kidney function. N Engl J Med. 2021;385(19):1804–6.
[26] Hsu CY, Yang W, Parikh RV, Anderson AH, Chen TK, Cohen DL, et al. Race, genetic ancestry, and estimating kidney function in CKD. N Engl J Med. 2021;385(19):1750–60.
[27] Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New Creatinine- and Cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737–49.
[28] Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013;369(10):932–43.
[29] Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA, et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. JAMA. 2011;305(15):1545–52.
[30] Willey JZ, Moon YP, Husain SA, Elkind MSV, Sacco RL, Wolf M, et al. Creatinine versus cystatin C for renal function-based mortality prediction in an elderly cohort: the northern Manhattan study. PLoS One. 2020;15(1):e0226509.
[31] Dardashti A, Nozohoor S, Grubb A, Bjursten H. Shrunken pore syndrome is associated with a sharp rise in mortality in patients undergoing elective coronary artery bypass grafting. Scand J Clin Lab Invest. 2016;76(1):74–81.
[32] Purde MT, Nock S, Risch L, Medina Escobar P, Grebhardt C, Nydegger UE, et al. The cystatin C/creatinine ratio, a marker of glomerular filtration quality: associated factors, reference intervals, and prediction of morbidity and mortality in healthy seniors. Transl Res. 2016;169(80–90):e1–2.
[33] Grubb A. Glomerular filtration and shrunken pore syndrome in children and adults. Acta Paediatr. 2021;110(9):2503–8.
[34] Grubb A, Lindstrom V, Jonsson M, Back SE, Ahlund T, Rippe B, et al. Reduction in glomerular pore size is not restricted to pregnant women. Evidence for a new syndrome: 'Shrunken pore syndrome'. Scand J Clin Lab Invest. 2015;75(4):333–40.
[35] Ahlström A, Tallgren M, Peltonen S, Pettilä V. Evolution and predictive power of serum cystatin C in acute renal failure. Clin Nephrol. 2004;62(5):344–50.
[36] Bell M, Granath F, Martensson J, Lofberg E, Ekbom A, Martling CR, et al. Cystatin C is correlated with mortality in patients with and without acute kidney injury. Nephrol Dial Transplant. 2009;24(10):3096–102.
[37] Ravn B, Prowle JR, Martensson J, Martling CR, Bell M. Superiority of serum Cystatin C over Creatinine in prediction of long-term prognosis at discharge from ICU. Crit Care Med. 2017;45(9) e932-e40.
[38] Jung CY, Joo YS, Kim HW, Han SH, Yoo TH, Kang SW, et al. Creatinine-Cystatin C ratio and mortality in patients receiving intensive care and continuous kidney replacement therapy: a retrospective cohort study. Am J Kidney Dis. 2021;77(4):509–516.e1.
[39] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international Sepsis definitions conference. Crit Care Med. 2003;31(4):1250–6.
[40] Nephrology ISo. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1).
[41] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann Intern Med. 1999;130(6):461–70.
[42] Grubb A, Horio M, Hansson LO, Björk J, Nyman U, Flodin M, et al. Generation of a new cystatin C-based estimating equation for glomerular filtration rate by use of 7 assays standardized to the international calibrator. Clin Chem. 2014;60(7):974–86.
[43] Bjork J, Grubb A, Sterner G, Nyman U. Revised equations for estimating glomerular filtration rate based on the Lund-Malmo study cohort. Scand J Clin Lab Invest. 2011;71(3):232–9.
[44] Bjork J, Grubb A, Larsson A, Hansson LO, Flodin M, Sterner G, et al. Accuracy of GFR estimating equations combining standardized cystatin C and creatinine assays: a cross-sectional study in Sweden. Clin Chem Lab Med. 2015;53(3):403–14.
[45] Nyman U, Grubb A, Larsson A, Hansson LO, Flodin M, Nordin G, et al. The revised Lund-Malmo GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. Clin Chem Lab Med. 2014;52(6):815–24.
[46] Åkesson A, Lindstrom V, Nyman U, Jonsson M, Abrahamson M, Christensson A, et al. Shrunken pore syndrome and mortality: a cohort study of patients with measured GFR and known comorbidities. Scand J Clin Lab Invest. 2020;80(5):412–22.
[47] Tsushita H, Tanaka R, Suzuki Y, Sato Y, Itoh H. Effects of dose and type of corticosteroids on the divergence between estimated glomerular filtration rates derived from cystatin C and creatinine. J Clin Pharm Ther. 2020;45:1390–7.
[48] Grubb A. Cystatin C is indispensable for evaluation of kidney disease. Ejifcc. 2017;28(4):268–76.
[49] Bagshaw SM, Bellomo R. Cystatin C in acute kidney injury. Curr Opin Crit Care. 2010;16(6):533–9.
[50] Klein SJ, Brandtner AK, Lehner GF, Ulmer H, Bagshaw SM, Wiedermann CJ, et al. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2018;44(3):323–36.
[51] Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med. 2005;352(20):2049–60.
[52] Herou E, Dardashti A, Nozohoor S, Zindovic I, Ederoth P, Grubb A, et al. The mortality increase in cardiac surgery patients associated with shrunken pore syndrome correlates with the eGFRcystatin C/eGFRcreatinine-ratio. Scand J Clin Lab Invest. 2019;79(3):167–73.
[53] Almen MS, Bjork J, Nyman U, Lindstrom V, Jonsson M, Abrahamson M, et al. Shrunken pore syndrome is associated with increased levels of atherosclerosis-promoting proteins. Kidney Int Rep. 2019;4(1):67–79.
[54] Öberg CM, Lindström M, Grubb A, Christensson A. Potential relationship between eGFRcystatin C/eGFRcreatinine-ratio and glomerular basement membrane thickness in diabetic kidney disease. Phys Rep. 2021 Jul;9(13) e14939.