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Predictive value of cystatin C for the identification of illness severity in adult patients in a mixed intensive care unit

Dyanne M. Dalcomune [a,b], Jorge Terrão [b], Marcella L. Porto [c,f], Elisardo C. Vasquez [a,c], Marcelo P. Baldo [d,e], Thiago M.C. Pereira [a,f,*]

[a] Pharmaceutical Sciences Graduate Program, Vila Velha University (UVV), Vila Velha, ES, Brazil
[b] Meridional Hospital, Cariacica, ES, Brazil
[c] Laboratory of Translational Physiology, Health Sciences Center, Federal University of Espirito Santo, Vitoria, Brazil
[d] Laboratory of Cardiovascular Pathophysiology, Department of Physiological Sciences, Federal University of Espirito Santo, Vitoria, Brazil
[e] Department of Pathophysiology, Montes Claros State University - UNIMONTES, Montes Claros, MG, Brazil
[f] Federal Institute of Education, Science and Technology (IFES), Vila Velha, ES, Brazil

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ABSTRACT

Objectives: This study compared serum cystatin C (CysC) with conventional biomarkers of renal function in terms of their ability to predict illness severity in patients in a mixed intensive care unit (ICU). The present study also tested the hypothesis that increased CysC could predict illness severity in different clinical conditions in adult patients admitted to the ICU.

Design and methods: The performance of serum creatinine, urea and CysC, as well as the Glomerular Filtration Rate (GFR) estimates (Cockcroft–Gault/MDRD/Larsson and CKD-EPI Equations) in predicting illness severity was compared in 60 critically ill patients. Adult patients admitted to the hospital were screened for eligibility in this prospective and observational study. The mean patient age was 52 ± 19 years. The average APACHE II score was 9.5 ± 6 for the entire sample. The patients were assigned to two different degrees of severity, and the internally derived cut off value was an APACHE II score < 10 or ≥ 10.

Results: Both serum CysC and urea showed significant correlations with APACHE II, even after controlling for age. Urea and CysC levels, as well as the GFR estimated by the method of Larsson and Cockcroft–Gault, remained significantly increased in patients in the APACHEII ≥ 10 group. The ROC curve analyses indicated that both urea and CysC levels have high sensitivity and specificity in the prediction of illness severity using the APACHE II as a gold standard prognostic stratification system. Furthermore, CysC was more accurate than the Larsson, CKD-EPI CysC, CKD-EPI Cr-CysC, Cockcroft–Gault and CKD-EPI Cr CFR estimation methods compared with the MDRD method. Additionally, CysC was a good predictor in both young and old patients, whereas urea was not predictive of illness severity.

Conclusions: Our findings suggest that CysC and GFR estimates (Larsson or CKD-EPI CysC methods) are good predictors of illness severity in adult patients hospitalized in a mixed ICU.

1. Introduction

Illness severity scoring systems have become central tools for both risk stratification and follow-up patient outcomes in intensive care units (ICUs) [1]. In this regard, the APACHE II (Acute Physiology and Chronic Health Evaluation II) score has been used as a satisfactory marker of prognosis in adult patients in ICUs [2]. In clinical practice, serum creatinine remains the main kidney biomarker that is used in several ICU risk-scoring systems worldwide; however, this measure is influenced by various factors related to nitrogen metabolism [3,4]. In this context, new renal biomarkers, such as cystatin C (CysC), are increasingly used and may be novel substitutes for the improvement of management and the avoidance of poor outcomes in the ICU.

CysC is a cysteine proteinase that exhibits several physiological advantages compared with creatinine [5]. A non-glycosylated protein, CysC is likely expressed at a stable rate by all nucleated human cells [6] and is relatively unaffected by non-renal morbidities [7–9]. As a result of its non-significant protein binding, positive charge at physiological pH and low molecular weight (~13 kDa), CysC can be freely filtered by the glomerulus and fully reabsorbed by the proximal tubules,

* Corresponding author at: Pharmaceutical Sciences Graduate Program, Vila Velha University (UVV), Av. Comissario Jose Dantas de Melo 21, 29102-920, Boa Vista, Vila Velha, ES, Brazil.
E-mail addresses: dydalcomune@gmail.com (D.M. Dalcomune), jterrao@tommasi.com.br (J. Terrão), cella.porto@gmail.com (M.L. Porto), evasquez@terra.com.br (E.C. Vasquez), marcelobaldo@ymail.com (M.P. Baldo), pereiratmc@gmail.com (T.M.C. Pereira).

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thereby representing a suitable biomarker for kidney function evaluation [10–12]. Recently, many researchers have demonstrated a strong relationship between CysC levels and several specific diseases. These levels have been tightly associated with adverse events and mortality, regardless of kidney function [12–14], and CysC has also been studied as a marker of poor prognosis in elderly patients [15,16]. However, there are insufficient studies to validate the routine incorporation of CysC measurements into risk-stratification protocols for patients admitted to a mixed ICU. Thus, one objective of this study was to compare serum CysC levels with conventional biomarkers of renal function. A second objective was to determine whether CysC levels are predictive of illness severity in different clinical conditions in adult patients hospitalized in a mixed ICU, thereby optimizing the management of their clinical treatment.

2. Materials and methods

2.1. Patients

This prospective and observational study included 60 consecutive adult patients (>18 years of age) who were admitted to the ICU in Meridional Hospital, Cariacica-ES, Brazil, from November 2013 to May 2014. The study followed the rules recommended by the Meridional Hospital Clinical Trials Committee. For the first 24 h of the ICU stay, all of the patients were classified according to the APACHE II criteria. This study was previously approved by the Brazilian Ethical Committee for human research 'Plataforma Brasil' (#648.184), and informed written consent was attained at admission. The exclusion criteria were as follows: a length of stay for less than 48 h, a life expectancy less than 72 h, morbid obesity (BMI > 40 kg/m^2), chemotherapy treatment, acute or chronic kidney injury or non-informed consent.

2.2. Data collection

Clinical follow-up and daily laboratory tests were performed (i.e., serum urea, creatinine, and C-reactive protein), which also included CysC measurements for 4 days for all patients during their ICU stay. The primary measurements were related to the patient's (i) gender; (ii) age; (iii) body mass index (BMI); (iv) diagnosis; (v) mechanical ventilation; (vi) use of vasopressor drugs, (vii) urine output; and (viii) noninvasive estimated GFR (glomerular filtration rate) based on the Cockcroft–Gault, Modification of Diet in Renal Disease (MDRD-Original Study Equation) [17], Larsson [18], and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [19] formulas. It is important to emphasize that these equations estimate creatinine/CysC clearance and do not directly measure the GFR; however, these formulas have been consistently used as GFR estimates in clinical practice [8,17]. All of the formulas used in the study to estimate the GFR (including CKD-EPI) are shown in Table 1.

2.3. Blood samples

Serum biomarkers were obtained from blood withdrawn during the scheduled daily examinations in admitted patients for 3 days following admission. The blood samples were collected in EDTA-containing Vacutainer glass tubes (Becton, Dickinson and Co, Franklin Lakes, NJ) and centrifuged at 2000 *g* for 10 min; the serum was then stored at −20 °C. The serum concentrations of creatinine and urea nitrogen were determined using the Jaffe [20] and urease-indophenol methods [21], respectively. The serum concentration of CysC was measured using the turbidimetric method [12]. All of the measurements were obtained via an automatic biochemical analyzer (AU 400 or 680, Olympus/Beckman Coulter, Munich, Germany).

2.4. Statistical analysis

All of the data are expressed as the means ± SD or percentages. Comparisons between the groups were performed using the Chi-square test (X^2), Student's t-test and two-way analysis of variance (ANOVA), as appropriate. When the ANOVA indicated significant differences, Tukey's test was applied as a post-hoc analysis. Total and partial Pearson correlation analyses were carried out to estimate the associations between the biomarkers and the APACHE II score severity. The model was adjusted for age. Logistic regression was used to estimate the associations between the APACHE II and race and gender. The prediction ability of CysC, urea and creatinine measurements and the sensitivities and specificities of the indexes were determined via ROC curve analysis. Differences in the areas under the ROC curve (AURC) were compared, and the optimal cutoff points were defined as the measures that represented the largest concomitant sensitivity and specificity. The statistical analyses were performed using Prism software (Prism 6.0, GraphPad Software, Inc., San Diego, CA, USA) and MedCalc 12.1.4.0 statistical software (MedCalc Software, Mariakerke, Belgium). The differences were considered significant when $p < 0.05$.

3. Results

3.1. General characteristics

Following exclusions (19% or 14/74), 60 patients met the inclusion criteria. The clinical and demographic characteristics of the entire sample are shown in Table 2. The mean age was 52 ± 19 years, and men represented 57% of the entire sample. The average APACHE II score was 9.5 ± 6. To assign patients into different illness severity categories, the patients were allocated to two groups based on their APACHE II classification. The internal derived cut-off value was defined as an APACHE II score of 10, i.e., patients with scores <10 or ≥10 were assigned to different groups. Patients with an APACHE II score ≥ 10 were significantly older than the patients with a better prognosis. Moreover, the serum concentrations of urea and serum CysC were significantly increased in these patients (Table 2). Four patients with an APACHE II score ≥ 10

Table 1
GFR-estimating equations used in the study.

	GFR estimate equations
Cockcroft-Gault	140 − age (years) × weight (kg) / (Scr × 72) × 0.85 if female
MDRD	186 × Scr$^{-1.154}$ × age (years)$^{-0.203}$ × 0.742 if female × 1.212 if black
Larsson	(77.24 × Scys)$^{-1.2623}$
CKD-EPI creatinine	141 × min(Scr/κ, 1)α × max(Scr/κ, 1) − 1.209 × 0.993Age [×1.018 if female] [×1.159 if black], where α is −0.329 for females and −0.411 for males
CKD-EPI CysC	133 × min(Scys/0.8, 1) − 0.499 × max(Scys/0.8, 1) − 1.328 × 0.996Age [×0.932 if female]
CKD-EPI Cr-CysC	135 × min(Scr/κ, 1)α × max(Scr/κ, 1) − 0.601 × min(Scys/0.8, 1) − 0.375 × max(Scys/0.8, 1) − 0.711 × 0.995Age [×0.969 if female] [×1.08 if black], where α is −0.248 for females and −0.207 for males

κ is 0.7 for females and 0.9 for males, max is the maximum of Scr/κ or 1, min is the minimum of Scr/κ or 1, Scr is serum creatinine in (mg/dL), and Scys is serum cystatin C in (mg/L).