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Diagnostic accuracy of procalcitonin and presepsin for infectious disease in patients with acute kidney injury

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ABSTRACT

Procalcitonin (PCT) and presepsin (PSEP) are sepsis markers, but their diagnostic accuracy may be compromised in acute kidney injury (AKI). We evaluated their diagnostic accuracy in patients with/without AKI. This retrospective study comprised 91 patients with at least one criterion of systematic inflammatory response syndrome. AKI markers plasma neutrophil gelatinase-associated lipocalin (NGAL), plasma cystatin C (CysC), and estimated glomerular filtration rate (eGFR) were measured upon hospital admission and on days 1, 3, 5, and 7. Patients were divided into non-AKI and AKI groups. APACHE II severity scores were determined. PCT and PSEP levels were increased significantly in non-AKI and AKI patients with infection. NGAL, CysC, and eGFR in patients with infection were associated with PCT, PSEP, and APACHE II score, and levels of PCT and PSEP were correlated significantly with disease severity. PCT and PSEP are useful markers of bacterial infections in AKI but different thresholds should be applied.

1. Introduction

Procalcitonin (PCT) is a precursor of the peptide hormone calcitonin, and has a molecular weight of ≈13 kD (Zajac et al., 1985). PCT, interleukin (IL)-6, and tumor necrosis factor-α have been used as diagnostic markers for sepsis. PCT, in particular, has been reported to be superior to endotoxin, β-D-glucan, IL-6, and C-reactive protein (CRP) for differentiation between bacterial infections such as sepsis and non-bacterial infections (Aikawa et al., 2005). However, PCT levels are known to be increased in non-infectious systemic inflammatory response syndrome (SIRS) (Meisner et al., 2006). Cluster of differentiation (CD)14 is a glycoprotein expressed on the surface of macrophages and/or monocytes. CD14 serves as a receptor complex for lipopolysaccharides and signal transduction via Toll-like receptor 4 (Pugin et al., 1993). CD14 is divided into two types of soluble isoforms (49 kD and 55 kD) (Bazil and Strominger, 1991). Previously, we reported that levels of soluble CD14 (55 kD) are increased in patients with multiple-organ failure (Endo et al., 1994). Presepsin (also known as "soluble CD14-ST" and "PSEP") has been identified as a 13-kD truncated N-terminal fragment of CD14 produced by stimuli such as phagocytosis in response to bacterial infection (Nakamura et al., 2008). Several studies have confirmed the usefulness of PSEP as a marker for the diagnosis of sepsis (Endo et al., 2012; Liu et al., 2013; Ulla et al., 2013) However, it has been reported recently that the diagnostic accuracies of PCT and PSEP in patients with acute kidney injury (AKI) are lower than those in patients without AKI because PCT and PSEP are thought to be eliminated through the kidneys and/or liver, and it has been suggested that PCT and PSEP may not be reliable indicators of sepsis in patients with more advanced AKI (Nakamura et al., 2014, 2015). Amour et al. (2008) reported that after major aortic surgery, the accuracy of PCT was not significantly different between groups with or without renal dysfunction, but that the optimal cutoff value was significantly different (non-renal dysfunction, 0.81 vs. renal dysfunction 2.57 ng/mL, $P < 0.05$). Thus, if the diagnostic accuracies of PCT and PSEP in patients with AKI are not lower than those in patients without AKI, determination of the optimal cutoff values for PCT and PSEP in sepsis patients with AKI would be useful for daily clinical practice. Studies (Nakamura et al., 2014, 2015) have been retrospective and from a single center using only RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria, and markers of AKI, such as plasma levels of neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C (CysC), as well as the estimated glomerular filtration rate (eGFR), were not investigated. Therefore, in the present study, patients attending the emergency room in two medical institutions, and who fulfilled at least one of the criteria for SIRS, were divided into non-AKI and AKI groups using these three markers of AKI. Plasma levels of PCT and PSEP were measured to evaluate their diagnostic accuracy for infection in patients with AKI.

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2. Materials and methods

2.1. Ethical approval of the study protocol

Ethical approval for the study protocol (approval number H24–42) was provided by the Ethics Committee of Iwate Medical University (Morioka, Japan).

2.2. Patients

Blood samples were collected from patients admitted to the emergency rooms of Iwate Medical University Hospital and Kochi Health Sciences Center between June 2010 and June 2011 who had at least one of the SIRS criteria (body temperature >38 °C or <36 °C; heart rate >90 beats per min; respiratory rate >20 breaths per min; partial pressure of carbon dioxide <32 mmHg, abnormal white blood cell count) (ACCP/SCCM Consensus Conference Committee, 1992). Written informed consent was obtained from all 91 patients enrolled in accordance with the guidelines of each institution. Levels of PCT, PSEP, NGAL, CysC, and plasma creatinine (Cr) were measured in blood specimens collected upon hospital admission (upon arrival (day 0)) as well as on days 1, 3, 5, and 7 (at 7 a.m.). Blood specimens were categorized retrospectively into six groups according to the confirmed diagnosis of each patient (SIRS; non-SIRS; infection without SIRS; sepsis; severe sepsis; septic shock) (Ishikura et al., 2014; Takahashi et al., 2015). Diagnoses of SIRS, sepsis, severe sepsis, and septic shock were made according to the seven criteria set by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM Consensus Conference Committee, 1992). "Non-SIRS" was defined as patients without infection and a SIRS score < 2. "Infection without SIRS" was defined as patients with infection but a SIRS score < 2. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was used as an index of disease severity (Knaus et al., 1985), and the Sepsis-related Organ Failure Assessment score was calculated as an index of the severity of organ dysfunction (Vincent et al., 1996). Definitive diagnoses were deliberated upon and decided by two physicians with expertise in infection control (certified by the Japanese College of Infection Control Doctors) and a clinical research coordinator. Exclusion criteria were: age <13 years, undergoing chronic hemodialysis, or experiencing cardiopulmonary arrest upon hospital arrival. Blood collection was suspended if patients recovered with a SIRS score <1 or died.

2.3. Measurements

PSEP concentrations were measured using a compact automated immunoanalyzer (PATHFAST®; Mitsubishi Chemical Medience, Tokyo, Japan) based on a chemiluminescent enzyme immunoassay (Mitsubishi Chemical Medience). Briefly, whole blood was collected into a conventional blood-collection tube (Terumo, Tokyo, Japan) containing EDTA-2 K as an anticoagulant. The sample was assayed within 4 h after collection using the PATHFAST PSEP assay. PCT concentrations were measured using an Elecsys BRAHMS PCT assay (Roche Diagnostics, Tokyo, Japan). NGAL concentrations were measured using an NGAL Rapid ELISA kit (Bioport, Copenhagen, Denmark). Cr concentrations were measured using a Iatoro LQ CRE(A) II assay kit (LSI Medience, Tokyo, Japan). CysC concentrations were measured using a Iatoro Cys-C assay kit (LSI Medience). IL-6 concentrations were measured using an Immulyze 2000 assay system (Siemens Healthcare Diagnostics, Tokyo, Japan). CRP concentrations were measured using a CRP-LATEX(II)X2 assay kit (Denka Seiken, Tokyo, Japan). EDTA-treated plasma was used for control samples.

2.4. Classification of AKI

NGAL is expressed in various human tissues, and has a molecular weight of 25 kDa. The 25-kDa monomeric form of NGAL is secreted by injured kidney tubule epithelial cells, so NGAL has been reported to be a useful marker for AKI (Haase-Fielitz et al., 2014). We applied a cutoff value of 150 ng/mL (Cruz et al., 2010; Haase-Fielitz et al., 2009; Shapiro et al., 2010) to discriminate between non-AKI and AKI. It has been reported that the diagnostic accuracy of AKI (area under the concentration curve (AUC)) for NGAL is 0.78–0.82 (Cruz et al., 2010; Haase-Fielitz et al., 2009; Shapiro et al., 2010). CysC is a 13-kD inhibitor of cysteine protease. It is filtered freely through the glomerular membrane and reabsorbed and metabolized completely by proximal tubular cells without being secreted. CysC has been reported to be an early predictor of AKI (Ghonemy and Amro, 2014; Ralib et al., 2014). A cutoff value of 0.98 mg/L (Ghonemy and Amro, 2014) was used to discriminate between non-AKI and AKI, and it has been reported that the diagnostic accuracy of AKI (AUC) is 0.87 (Soto et al., 2010). A low eGFR is also a predictor of AKI (Goo et al., 2014; Ulucay et al., 2012), and eGFR <60 mL/min per 1.73 m^2 has been reported to be a risk factor for AKI (Kopolovic et al., 2013; Liu et al., 2014), so this value was used as a cutoff to discriminate between non-AKI and AKI. eGFR was calculated using equations for Japanese patients as follows (Matsuo et al., 2009):

$$\text{Males}: \text{eGFR}\left(\text{mL}/\text{min}/1.73\ \text{m}^2\right) = 194 \times (\text{serum Cr})^{-1.094} \times (\text{age})^{-0.287}$$

$$\text{Females}: \text{eGFR}\left(\text{mL}/\text{min}/1.73\ \text{m}^2\right) = 194 \times (\text{serum Cr})^{-1.094} \times (\text{age})^{-0.287} \times 0.739$$

2.5. Statistical analyses

Comparisons between two groups were made using the Mann–Whitney *U*-test. The Spearman rank order correlation coefficient was employed for the analysis of correlations. We used the cutoff value obtained by receiver operating characteristic (ROC) analysis with the Youden index. $P < 0.05$ was considered significant. Two-group comparisons, correlations, and multiple linear regression analyses were carried out using JMP software (SAS Institute, Cary, NC, USA). ROC analysis was done using Dr. SPSS II software (IBM, Armonk, NY, USA). Two AUC comparisons were made using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3. Results

3.1. Patient characteristics

Ninety-one patients (58 men (mean age, 68.28 years) and 33 women (mean age, 73.93 years)) were enrolled. Confirmed diagnoses were: gastroenterological disease ($n = 20$); respiratory disease ($n = 11$); trauma ($n = 12$); circulatory disease ($n = 3$); renal disease ($n = 8$); burns ($n = 8$); cerebral hemorrhage ($n = 2$); pancreatitis ($n = 1$); hepatobiliary disease ($n = 9$); cellulitis/phlegmon ($n = 6$); drug poisoning ($n = 1$); and "other" ($n = 10$). A total of 403 blood specimens were collected at different time points and categorized into six groups according to condition (non-SIRS; SIRS; infection without SIRS; sepsis, severe sepsis; septic shock). Characteristics and diseases of patients are shown in Table 1. Of 403 blood specimens, 174 indicated a diagnosis of non-infection (non-SIRS and SIRS) and 229 samples indicated a diagnosis of infection (infection without SIRS, sepsis, severe sepsis, septic shock).

3.2. Comparison of median levels of PCT and PSEP between patients without and with infection in AKI patients

Patients were divided into non-AKI and AKI groups according to the three AKI makers. Using NGAL, 171 samples were classified as non-AKI (<150 ng/mL) and 232 as AKI (≥150 ng/mL). Using CysC, 196 samples were classified as non-AKI (<0.98 mg/L) and 207 as AKI (≥ 0.98 mg/L).