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Original article

The predictive value of proteinuria in acute pancreatitis

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ABSTRACT

Background/objectives: Acute pancreatitis has a highly variable clinical course. Early and reliable predictors for the severity of acute pancreatitis are lacking. Proteinuria appears to be a useful predictor of disease severity and outcome in a variety of clinical conditions. This study aims to investigate the predictive value of proteinuria on admission for the severity of acute pancreatitis compared with other commonly used predictors; the APACHE II score, Modified Glasgow score and C-reactive protein (CRP).
Methods: This is a post-hoc analysis of 64 patients admitted with acute pancreatitis treated in one teaching hospital, who participated in a previous randomized trial. Proteinuria was defined as a Protein/Creatinine (*P*/*C*) ratio >23 mg/mmol. The primary endpoint was severe acute pancreatitis. Secondary endpoints included infectious complications, need for invasive intervention, ICU stay and in-hospital mortality.
Results: Proteinuria was present in 30/64 patients (47%). Eleven patients (17%) had severe acute pancreatitis. There was no difference in incidence of severe acute pancreatitis between patients with and without proteinuria: 6/30 patients (20%) versus 5/34 patients (15%) respectively ($p = 0.58$). Likewise, the occurrence of infectious complications, need for intervention and ICU stay and mortality did not differ significantly ($p = 0.58$, $p = 0.99$, $p = 0.33$ and $p = 0.60$ respectively). The diagnostic performance of the *P*/*C* ratio for the prediction of severe pancreatitis was inferior to the Modified Glasgow score ($p = 0.04$) and CRP ($p = 0.03$).
Conclusion: Proteinuria on admission does not seem to be a reliable predictor for disease severity in acute pancreatitis. The diagnostic performance of the *P*/*C* ratio is inferior to the Modified Glasgow score and CRP.

Introduction

Acute pancreatitis has a highly variable clinical course ranging from mild to very severe disease associated with (peri)pancreatic necrosis, organ failure and death. Severe acute pancreatitis occurs in approximately 20% of patients presenting with acute pancreatitis [1,2]. Much effort has been put into the search for early and reliable predictors of severity in acute pancreatitis. At present, the Modified Glasgow score (also known as the Imrie score), APACHE II score and C-reactive protein (CRP) are most commonly used to predict severity in daily practice and clinical studies. The Modified Glasgow score was designed and validated to be calculated 48 h after admission, which may be considered a disadvantage [3]. The APACHE II score can be assessed on admission but is much less accurate compared with APACHE II scores obtained 48 h after admission [4–6]. Measuring CRP as a marker for the severity of acute pancreatitis is attractive and simple. However, CRP levels at onset of the disease cannot reliably distinguish between severe and mild acute pancreatitis, since it may take as long as two days for the CRP to reach its highest levels [7,8].

Proteinuria has shown to be a useful predictor of disease severity and outcome in a variety of clinical conditions [9–12]. The

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aim of this study was to compare the diagnostic performance of proteinuria with that of the currently used APACHE II score, Modified Glasgow score and CRP for the prediction of the severity and outcome of acute pancreatitis.

Methods

Study design

For this study, data from a subgroup of patients registered in the prospective database of the randomized controlled trial – the PRObiotics in PAncreatitis TRIAl (PROPATRIA) – from the Dutch Pancreatitis Study Group were retrospectively analyzed [13]. In the PROPATRIA, all patients older than 17 years admitted with a first episode of acute pancreatitis were registered in 8 university medical centers and 7 non-university training hospitals between 2004 and 2007. Acute pancreatitis was defined as the combination of abdominal pain and serum amylase or lipase levels to at least three times the upper limit of normal [13]. For the present study, only patients who were admitted at one of the participating centers of the PROPATRIA - the St. Antonius Hospital Nieuwegein – were included. This comprised of all patients from the entire clinical spectrum of acute pancreatitis, of whom urine samples of the day of admission were available. In addition to the exclusion criteria of the PROPRATRIA study [13], patients were excluded in case of pre-existent kidney disease.

Outcomes

The primary endpoint was severe acute pancreatitis, defined as (peri)pancreatic necrosis as demonstrated on contrast enhanced CT and/or new onset organ failure [1]. This is in accordance with the definition used in the PROPATRIA. Secondary endpoints included infectious complications, need for invasive intervention (i.e. percutaneous- or endoscopic catheter drainage or necrosectomy), ICU stay and in-hospital mortality. Organ failure was defined in accordance with the PROPATRIA [13]: systolic bloodpressure below 90 mmHg despite fluid resuscitation or need for vasopressive therapy (cardiocirculatory insufficiency), PaO_2 below 60 mmHg despite FiO_2 of 30% or the need for mechanical ventilation (pulmonary insufficiency), serum creatinine levels higher than 177 μmol/L or need for hemofiltration or hemodialysis (renal insufficiency) [1,13]. Infectious complications included bacteremia (i.e. positive bloodculture), urosepsis (i.e. dysuria with bacteremia on the same day, without urinary catheter in situ), pneumonia (i.e. coughing, dyspnea, infiltrative abnormalities on chest film, lowered arterial blood gas with positive sputum culture, positive endotracheal tube culture for patients in the ICU) and infected pancreatic necrosis (i.e. positive culture of peripancreatic fluid or pancreatic necrosis) [13].

Data collection

According to the PROPATRIA protocol APACHE II scores and Modified Glasgow scores were prospectively obtained on admission and within 48 h after admission respectively. CRP levels were monitored during 48 h after admission. The highest value was registered. Angiotensinconverting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) reduce proteinuria [14]. Therefore, medical records were checked for use of these drugs.

Urine analysis on the day of admission was not part of the study protocol of the PROPATRIA. However, urine samples are frequently performed in patients with acute abdominal pain on admission in the emergency ward in the St. Antonius Hospital in line with local protocols. In patients in whom urine samples were performed, urine was first tested by a standard urine dipstick with a threshold of 150 mg proteins per liter. For positive urinary dipstick measures, total urine protein in the untimed ("spot") urine samples was quantified by turbidimetry (Cobas 6000, Roche Diagnostics) with a measuring range of 0.040–2.000 g/L. Urine creatinine was measured to calculate total Protein/Creatinine (*P*/*C*) ratio. We defined proteinuria as a *P*/*C* ratio of >23 mg/mmol, in accordance with the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NFK-KDOQI) guidelines [14].

Statistics

Data were analyzed using SPSS version 19.0. Normally distributed data were reported as means (±standard deviation) and non-normally distributed data as medians (interquartile range [IQR]). Differences have been tested using the student's *T*-test and Mann-Whitney-U test respectively. For categorical data, X^2 test or Fisher's exact test were used as appropriate.

Baseline characteristics and the occurrence of clinical endpoints were compared for patients with and patients without proteinuria. Using Receiver Operating Characteristic (ROC) analysis, the Area Under the Curve (AUC) of the *P*/*C* ratio, APACHE II score, Modified Glasgow score and CRP have been calculated for the primary endpoint, severe acute pancreatitis, in order to determine and compare their diagnostic performances. The AUC's of the *P*/*C* ratio, APACHE II score, Modified Glasgow score and CRP were then compared using De Long's test. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated and presented for various cut-off values of the *P*/*C* ratio and for the currently used cut-off values of the APACHE II score, Modified Glasgow score and CRP. A *p*-value of <0.05 was considered statistically significant for all analyses.

Results

Patients

In the prospective database of the PROPATRIA, 731 patients with acute pancreatitis were enrolled in 15 Dutch hospitals. The subgroup of patients admitted to the St. Antonius Hospital comprised of 107 patients. A total of 64/107 patients (60%) could be included in the present study. The selection process is shown in Fig. 1.

Baseline characteristics of the included and the excluded patients were compared and are shown in Table 1. The median time between the onset of symptoms and hospital admission was 1.0 day (IQR 0.0–2.0) for the included population compared with 0.0 days (IQR 0.0–1.0) for the excluded population ($p = 0.03$). In the excluded population, 18/43 patients (42%) had a history of cardiovascular disease compared with 9/64 patients (14%) in the included population ($p = 0.001$). Furthermore, patients in the included population were slightly younger than patients in the excluded population, mean 55 (±18) years and 62 years (±17) years respectively ($p = 0.04$). Concerning outcome, new onset organ failure was less often present, 3/64 (5%) in the included population versus 9/43 (21%) in the excluded population ($p = 0.01$). Though, there was no significant difference in the incidence of severe acute pancreatitis between the included and the excluded population.

Study parameters

In the study population 23/64 patients (40%) had an APACHE II score $\geq$ 8 on admission, 22/64 patients (34%) had an Modified

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