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The association between portal system vein diameters and outcomes in acute pancreatitis

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ABSTRACT

Background/objectives: Acute pancreatitis (AP) progresses to necrotizing pancreatitis in 15% of cases. An important pathophysiological mechanism in AP is third spacing of fluids, which leads to intravascular volume depletion. This results in a reduced splanchnic circulation and reduced venous return. Non-visualisation of the portal and splenic vein on early computed tomography (CT) scan, which might be the result of smaller vein diameter due to decreased venous flow, is associated with infected necrosis and mortality in AP. This observation led us to hypothesize that smaller diameters of portal system veins (portal, splenic and superior mesenteric) are associated with increased severity of AP.
Methods: We conducted a post-hoc analysis of data from two randomized controlled trials that included patients with predicted severe and mild AP. The primary endpoint was AP-related mortality. The secondary endpoints were (infected) necrotizing pancreatitis and (persistent) organ failure. We performed additional CT measurements of portal system vein diameters and calculated their prognostic value through univariate and multivariate Poisson regression.
Results: Multivariate regression showed a significant inverse association between splenic vein diameter and mortality (RR 0.75 (0.59–0.97)). Furthermore, there was a significant inverse association between splenic and superior mesenteric vein diameter and (infected) necrosis. Diameters of all veins were inversely associated with organ failure and persistent organ failure.
Conclusions: We observed an inverse relationship between portal system vein diameter and morbidity and an inverse relationship between splenic vein diameter and mortality in AP. Further research is needed to test whether these results can be implemented in predictive scoring systems.

1. Introduction

Acute pancreatitis (AP) has an annual incidence of 13–45/100,000 [1]. In 85% of cases the disease course is limited to interstitial pancreatitis without organ failure. However, in about 15% of cases the disease progresses to necrotizing pancreatitis with a mortality rate up to 20% [2]. One of the pathophysiological hallmarks of AP disease progression is third spacing of fluids, which leads to reduced intravascular volume that may progress to

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Abbreviations

AP	Acute pancreatitis
APACHE II	Acute Physiology and Chronic Health Evaluation II score
ASA	American Society of Anesthesiologists
BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
CTSI	CT severity index
DM	Diabetes mellitus
ICU	Intensive care unit
RR	Relative risk
SD	Standard deviation
SMV	Superior mesenteric vein

hypovolemic shock [3,4]. The physiologic response is to preserve circulation to vital organs at the expense of the gastrointestinal tract with vasoconstriction of the splanchnic circulation (blood flow of the gut, spleen, pancreas and liver) resulting in hypoperfusion of the mesenteric organs [5–8]. Reduced perfusion leads to reduced venous return and lower cardiac preload in severe AP [9].

Contrast-enhanced computed tomography (CE-CT) permits evaluation of patency of veins that drain into the portal venous circulation such as the portal, splenic and superior mesenteric (SMV) veins. In a multicenter prospective cohort of 228 patients with severe AP, non-visualisation of the portal and splenic vein on early CT scan was associated with infected necrosis and mortality [10]. The authors postulated that non-visualisation might be the result of smaller vessel diameter and partial volume effects due to decreased venous flow. This observation led us to hypothesize that smaller diameters of portal system veins (portal, splenic and SMV) are associated with increased severity of AP.

We conducted a post-hoc analysis of prospective trial data with the primary aim to investigate the association between diameters of portal system veins and mortality in AP. Our secondary aim was to investigate the association between diameters of portal system veins and AP-related morbidity.

2. Methods

In this study we adhered to the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) guidelines [11]. Both original trials were approved by a Medical Ethics Committee. All participants of the original trials provided written informed consent. This study follows the declaration of Helsinki.

2.1. Study design and participants

We conducted a post-hoc analysis of data from two multicenter randomized controlled trials carried out in the Netherlands between 2004 and 2013 (see Supplementary table 1 for trial details) [12,13]. One trial included AP patients with a predicted severe disease course at admission [12]. According to the study protocol, all patients had a CE-CT scan at 7–10 days after admission regardless of disease course. The other trial included patients with mild biliary pancreatitis [13]. A mild disease course was defined as absence of local complications (e.g. necrosis, fluid collections), absence of persistent organ failure, CRP<100 mg/L, no need for opioids and tolerance of normal diet. In this trial, patients received a CE-CT scan at the discretion of the treating physician. From the second trial we included patients who received a CE-CT scan within 7 days of admission. In all patients we performed additional CE-CT measurements. We excluded scans that did not include the pelvic region, were not digitally available or demonstrated evidence of alternative diagnoses (chronic pancreatitis or pancreatic malignancy).

2.2. CE-CT measurements

Diameters of the portal, splenic and superior mesenteric veins proximal to the confluence were measured retrospectively in the axial plane by two radiologists (TB and DdC), blinded for the study endpoints. Furthermore, the presence of arteriosclerosis in the aorta, celiac trunk, inferior or superior mesenteric artery was evaluated as a measure of cardiovascular disease.

2.3. Endpoints and variables

The primary endpoint was AP-related mortality. The secondary endpoints were the occurrence of necrotizing pancreatitis, infected necrosis, organ failure or persistent organ failure. We defined necrotizing pancreatitis according to the revised Atlanta criteria [14]. Infected necrosis was defined as a positive culture of peripancreatic fluid or pancreatic necrosis obtained by either fine needle aspiration, during the first percutaneous drainage or during the first surgical intervention. Organ failure was defined as [15]:

- Pulmonary: PaO_2 <60 mmHg despite FiO_2 of 30%, or the need for mechanical ventilation
- Renal: serum creatinine >177μmol/L after rehydration, or need for hemofiltration/hemodialysis
- Circulatory: systolic blood pressure <90 mmHg (despite adequate fluid resuscitation), or need for vasopressor support

Persistent organ failure was defined as organ failure lasting >48 h.

We collected data on the following potentially confounding variables: age, gender, body mass index (BMI), diabetes mellitus (DM), aetiology (biliary, alcoholic, idiopathic or other), comorbidity (according to American Society of Anesthesiologists (ASA) score) and presence of arteriosclerosis on CT scan [16–21]. Finally, the predicted severity of AP was confirmed and recorded as defined by Acute Physiology and Chronic Health Evaluation (APACHE II) score above 7, Imrie score above 2 or C-reactive protein (CRP) above 150 mg/L.

2.4. Statistical analyses

Continuous variables are presented as mean with standard deviation or as median with range, categorical variables as frequencies with percentages. First, we performed univariate Poisson regression analyses to assess the uncorrected prognostic value of vein diameters. If a univariate analysis showed a significant association, we performed a multivariate Poisson regression analysis with confounder correction. We included all confounders with P-values below 0.1 on univariate analysis (by Student's t-test or χ^2 test, as appropriate). Finally, in an exploratory subgroup analysis we compared mean vein diameters in patients with predicted mild and predicted severe acute pancreatitis by Student's t-test. The primary and secondary analyses were performed in the patients from one trial [12]. The subgroup analysis was performed by comparing patients from both trials.

All results are expressed as a relative risk (RR) with 95% confidence interval (CI). A two-tailed P-value below 0.05 is regarded as significant. All analyses were performed by using IBM SPSS version

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