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Intestinal fatty acid-binding protein level as a predictor of 28-day mortality and bowel ischemia in patients with septic shock: A preliminary study☆

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ABSTRACT

Purpose: We sought to evaluate the levels of intestinal fatty acid-binding protein (I-FABP), a biomarker of enterocyte injury, as a predictor of 28-day mortality and bowel ischemia in septic shock patients.
Material and methods: In this preliminary prospective observational study, 57 adult septic shock patients under mechanical ventilation were enrolled. Serum I-FABP levels and prognostic biomarkers were recorded upon intensive care unit (ICU) admission.
Results: The overall 28-day mortality rate of participants was 23% (13/57). Non-survivors displayed significantly higher lactate ($p = 0.009$), I-FABP ($p = 0.012$), and N-terminal pro-B-type natriuretic peptide ($p = 0.039$) levels compared to survivors. Only I-FABP was associated with 28-day mortality (odds ratio, 1.036; 95% confidence interval, 1.003–1.069; $p = 0.031$) in a multiple logistic regression analysis adjusted for the Acute Physiology and Chronic Health Evaluation II score. When divided into low and high I-FABP groups based on the optimum cut-off value of 19.0 ng/mL for predicting 28-day mortality, high-I-FABP patients had a significantly higher incidence of non-occlusive mesenteric ischemia (NOMI) (2% [1/43] vs 29% [4/14]; $p = 0.011$).
Conclusions: I-FABP level at ICU admission can serve as a predictor of 28-day mortality in septic shock patients and is associated with the incidence of NOMI.

1. Introduction

Gastrointestinal dysfunction, which is considered to be derived from gastrointestinal perfusion abnormalities in septic patients, plays a pivotal role in the progression of sepsis and multiple organ failure (MOF) [1]. Subsequently, gastrointestinal dysfunction is associated with poor outcome [2,3], probably because of dysregulated crosstalk among the intestinal epithelium, mucosal immune system, and endogenous microflora [3,4]. Enterocytes comprise >80% of the cells in the intestinal epithelium and act as a barrier to prevent translocation of luminal antigens, microbiota and their toxic products into the blood flow [5]. Although enterocyte injury is expected to be the primary cause of bacterial dissemination, systemic inflammatory response, and finally poor outcome in these patients, the presence of enterocyte injury is generally not assessed.

Intestinal fatty acid-binding protein (I-FABP) is a low-molecular-weight (14–15 kDa) cytosolic, water-soluble protein specifically expressed by enterocytes from the duodenum to the ileum [6]. I-FABP is rapidly released into the systemic circulation upon enterocyte injury and is thus believed to be a useful marker of enterocyte injury, especially in acute small bowel ischemia [7-9]. Additionally, I-FABP levels have been reported to increase in small intestinal allograft rejection [10], ileitis associated with ulcerative colitis [11], and necrotizing enterocolitis [12]. A recent study reported that elevated I-FABP level was associated with shock state and 28-day mortality in general ICU patients [13]. Moreover, previous studies on adult abdominal and pneumonia-

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induced sepsis [14] and child meningococcal sepsis [15] also identified an association between elevated I-FABP levels and poor outcome.

Despite the existence of correlative studies, it remains unclear whether I-FABP is useful as a prognostic factor in patients with septic shock. The goal of the current preliminary study was to evaluate the predictive ability of ICU baseline I-FABP levels for 28-day mortality in adult septic shock patients, and also to elucidate the relationship between I-FABP and the incidence of small bowel ischemia, especially non-occlusive mesenteric ischemia (NOMI), after ICU admission.

2. Material and methods

2.1. Study design and oversight

We conducted a single-center, preliminary prospective observational study in an eight-bed general ICU at the Nagasaki University Hospital (Nagasaki, Japan) from May 2012 to March 2015. The present study was approved by the Institutional Review Board of Nagasaki University Hospital (No. 12042382), and written informed consent was obtained from the patients' relatives after thorough explanation of the study.

2.2. Study population

Adult (≥18 years of age) septic shock patients under mechanical ventilation, who were expected to stay in the ICU for >48 h, were enrolled. All patients were diagnosed with septic shock before ICU admission. Septic shock was defined as sepsis-induced persistent hypotension not responsive to fluid resuscitation and that required vasopressor support, along with tissue hypoperfusion or organ dysfunction [16]. Patients with confirmed or strongly suspected intestinal ischemia and/or necrosis, medical history of small intestine resection, chronic small bowel disease, pregnancy, uncontrolled bleeding, or terminal stage of comorbidity, i.e., high possibility of death within several months as assessed by an outside medical specialist, were excluded.

2.3. Data collection

Baseline values were recorded at ICU admission and within the first 24 h of admission, and included the following: age; sex; body mass index; admission route; comorbidities; Acute Physiology and Chronic Health Evaluation (APACHE) II score [17]; Sequential Organ Failure Assessment (SOFA) score [18]; mean arterial pressure (MAP); heart rate; central venous pressure (CVP); inotropic score [19]; post-admission interventions for septic shock management including vasopressin, steroids, continuous renal replacement therapy (CRRT), and polymyxin B-direct hemoperfusion (PMX-DHP) [20]; fluid balance; site of infection; causative organism; and bacteremia status. Patient outcome, including all-cause 28-day mortality and in-hospital mortality, was also recorded. All-cause 28-day mortality was used to evaluate the predictive ability of ICU baseline I-FABP levels for mortality in accordance with the prearranged study protocol.

Standard blood chemistry tests were performed at admission to gauge sepsis severity, including evaluation of arterial lactate [21,22], serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) [23], procalcitonin [24], and endotoxin activity (EA) [25] as prognostic biomarkers of sepsis. Lactate levels were measured using an ABL800 FLEX system (Radiometer Medical, Copenhagen, Denmark); the normal range is 0.5–1.6 mmol/L. NT-proBNP and procalcitonin levels were determined by electrochemiluminescence immunoassays (Roche Diagnostics, Indianapolis, IN, USA). The manufacturer-recommended cut-off point for NT-proBNP to rule out heart failure was 125 pg/mL and the cut-off point for procalcitonin to diagnose sepsis was 0.5 ng/mL. EA was determined by chemiluminescent EA assays (Spectral Diagnostics, Toronto, ON, Canada), as described previously [25]. EA levels were classified as follows: low (0.0–0.39), intermediate (0.40–0.59), and high (≥0.60). All of these data were measured at Nagasaki University Hospital.

Clinical suspicion of bowel ischemia was evaluated by two independent attending intensivists. Reasons for suspicion included newly developed abdominal distention, persistent or newly developed lactic acidosis and/or shock, and gastrointestinal bleeding. The frequency of abdominal contrast CT and surgery to diagnose and remediate bowel ischemia and definitive diagnosis by a radiologist and/or surgeon, respectively, was also collected.

2.4. Serum I-FABP measurement

Blood was collected at ICU admission (day 0) and on days 1–7, 10, and 14 to examine serum I-FABP levels. Samples were separated and the serum was frozen at −20 °C until assayed. All measurements were performed in a blinded fashion at a laboratory (DS Pharma Biomedical Co., Ltd. Osaka, Japan), using an enzyme-linked immunosorbent assay highly specific for human I-FABP (DS Pharma Biomedical Co., Ltd. Osaka, Japan) [26]. Previous studies applying this method determined that the mean I-FABP level in healthy adults was 1.1 ± 0.9 ng/mL (range: 0.1–5.5 ng/mL) [26], and the cut-off point for diagnosing vascular intestinal ischemia was 9.1 ng/mL [9]. Attending intensivists were blind to patient I-FABP results, and the results therefore had no influence on the treatment of patients.

2.5. Clinical management

All patients were principally treated in accordance with the Surviving Sepsis Campaign Guidelines (SSCG) [27,28]. Fluid was administered with a minimum CVP of at least 8 cm H_2O. Echocardiography was also used for fluid management. Norepinephrine was used as a first-choice vasopressor to maintain MAP ≥ 65 mm Hg. The initial target MAP in patients with atherosclerosis and/or hypertension was arranged to be slightly higher by the attending intensivists. If norepinephrine was ineffective after >0.4–0.5 μg/kg/min, vasopressin (up to 0.03 units/min) was used. Olprinone, a phosphodiesterase 3 inhibitor, was used as an inotropic agent alone or with low-dose dopamine or dobutamine. Hydrocortisone was administered in cases with suspected adrenal deficiency according to the SSCG recommendation. PMX-DHP and recombinant soluble thrombomodulin were used as needed to stabilize hemodynamic parameters and treat disseminated intravascular coagulation (DIC), respectively [20,29]. Immunoglobulin and antithrombin supplementation for DIC, although not recommended in SSCG, was also used as decided by the intensivists.

One or more antibiotics as the initial empiric therapy were administered and de-escalated on the basis of clinical response and culture results. Lung-protective ventilator support and CRRT were also performed as a part of the management strategy when indicated. Enteral feeding was started slowly after hemodynamic stabilization unless a specific contraindication was present.

2.6. Statistical analysis

Baseline data including demographic characteristics, interventions, prognostic variables, and I-FABP levels were compared between survivors and non-survivors after 28 days in the ICU. Categorical variables are presented as frequencies and percentages, and quantitative variables as the median and interquartile range (IQR). Associations between variables were analyzed using Fisher's exact and Wilcoxon's rank-sum testing.

First, we estimated unadjusted and adjusted odds ratios (OR), 95% confidence intervals (95% CI), and p values for the APACHE II score, I-FABP levels, and prognostic biomarkers of 28-day mortality using simple and multiple logistic regression models. The small population of non-survivors in this study prevented us from adjusting more than two factors in a multiple logistic regression to estimate the mortality.