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Original article

Serum alkaline phosphatase as a predictor of worsening renal function in patients with acute decompensated heart failure

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ABSTRACT

Background: Venous congestion has come into focus as an important hemodynamic factor for worsening renal function (WRF) in patients with acute decompensated heart failure (ADHF). Serum alkaline phosphatase (ALP) was reported as a biological marker of liver congestion in ADHF. The purpose of this study was to determine whether ALP is a predictor of WRF in patients with ADHF.
Methods: We enrolled consecutive patients admitted to a single cardiovascular center with ADHF, and defined WRF as an increase in creatinine of >0.3 mg/dl during hospitalization and chronic kidney disease (CKD) as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. The patients were classified into tertiles by ALP level (<203, 203–278, and >278 IU/L).
Results: A total of 972 patients (mean age, 76 ± 13 years; 54% male) were retrospectively analyzed. WRF was identified in 132 patients (13.6%). In multivariate logistic regression analysis, baseline CKD [odds ratio (OR) 2.46, 95% confidence interval (CI) 1.48–4.08, $p < 0.001$], serum albumin (OR 0.52, 95% CI 0.35–0.77, $p = 0.001$), and diabetes (OR 2.07, 95% CI 1.37–3.12, $p < 0.001$) were associated with WRF. Compared with the lowest tertile (ALP <203 IU/L), an adjusted OR of WRF was 1.69 (95% CI 1.02–2.79, $p = 0.04$) in the middle tertile (ALP, 203–278 IU/L) and 1.95 (95% CI 1.20–3.21, $p = 0.008$) in the highest tertile (ALP >278 IU/L).
Conclusion: Serum ALP is an independent predictor of WRF in the clinical course of ADHF.

Introduction

Acute decompensated heart failure (ADHF) is a common systemic syndrome associated with poor outcomes [1]. A cardio-renal interaction had been observed in ADHF, and worsening renal function (WRF) during the clinical course of ADHF has been recognized as an independent risk factor for adverse outcomes [2–4]. Previous studies have consequently proposed that progressive pump failure or cardiogenic shock may progress to renal injury because of impaired organ perfusion [5,6]. Venous congestion has come into focus as a more important hemodynamic factor for the development of WRF than the above-mentioned impaired renal perfusion theory [7,8]. Hepatic dysfunction due to passive venous congestion is particularly common in patients with ADHF [9]. Among the several markers for hepatic dysfunction, serum alkaline phosphatase (ALP) has been reported to correlate with the severity of tricuspid regurgitation (TR) and right-sided filling pressure [10]. However, the direct association between ALP and WRF in patients with ADHF has remained unclear. Therefore, this study aimed to determine whether ALP predicts WRF in this cohort.

Methods

Study population

We enrolled consecutive patients admitted with ADHF to the Cardiovascular Center, St. Luke's International Hospital, Tokyo, Japan between 1 September 2003 and 31 December 2013. A total of 1536 patients were hospitalized with the diagnosis of ADHF based on standard international criteria [1,11]. Serum ALP data at the time of admission were available in 1115 patients (73%) and the following exclusion criteria were applied: age <18 years, history of primary liver disease, an estimated glomerular filtration ratio (eGFR) of <15 ml/min/1.73 m^2 on admission, and those on hemodialysis or peritoneal dialysis. The eGFR was calculated with the following formula: $eGFR = 194 \times \text{serum creatinine}^{-1.094}$ (mg/dl) $\times$ $\text{age}^{-0.287}$ (years) [$\times$ 0.739 (for women only)] [12]. We

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defined the development of WRF as an increase in serum creatinine of >0.3 mg/dl during hospitalization [2,8,13], and chronic kidney disease (CKD) as an eGFR <60 ml/min/1.73 m^2. All laboratory samples were obtained on the first day of hospitalization and analyzed in the same laboratory. The study design was approved by the appropriate ethics review boards in St. Luke's International Hospital.

Statistical analysis

Continuous data are expressed as mean ± standard deviation, non-parametric data as median [interquartile range (IQR)] and categorical data as a ratio. An unpaired *t*-test and Mann–Whitney *U* test were performed for continuous data, and the chi-square and Fisher exact tests were performed for categorical data. We pre-specified that the patients would be divided into three groups based on tertiles of their baseline ALP level (lowest, <203 IU/L; middle, 203–278 IU/L; highest, >278 IU/L), and we used these tertile categories in the following analyses. For comparison of three groups, analysis of variance or Kruskal–Wallis test were used. If they were significant, differences in baseline ALP level were further evaluated with Tukey post hoc tests. We performed univariate analysis for factors that showed differences between groups with WRF and without WRF. To determine the independent relationships between the variables and WRF, multivariate logistic regression analysis was performed for variables with a statistically significant difference in univariate logistic regression ($p < 0.1$). We also included putative factors from previous reports, including age, gender, systolic blood pressure, and brain natriuretic peptide (BNP) [2,5,14]. Odds ratios (ORs) and confidence intervals (CIs) are reported for the multivariate analyses. Because our goal was to determine whether the initial variables and parameters on admission including hepatic function tests may be predictors of WRF, we did not investigate the impact of in-hospital treatment choices on WRF. Statistical significance was set at a 2-tailed probability of $p < 0.05$, and statistical analyses were performed with R (The R Foundation, Vienna, Austria, version 3.0.0).

Results

Baseline characteristics

We included 972 patients with a mean age of 76 ± 13 years (54% male) and a mean baseline eGFR of 50.3 ± 24.2 ml/min/1.73 m^2. The patient characteristics on admission are summarized in Table 1, with a comparison between patients who did and did not develop WRF. We found a difference in baseline eGFR (38.8 ± 17.4 ml/min/1.73 m^2 vs 52.2 ± 24.7 ml/min/1.73 m^2, $p < 0.001$), hemoglobin (10.6 ± 2.0 g/dl vs 11.4 ± 2.4 g/dl, $p < 0.001$), and albumin (3.1 ± 0.5 g/dl vs 3.3 ± 0.5 g/dl, $p < 0.001$) between the patients with and without WRF. The hemodynamic parameters such as blood pressure and heart rate were similar between the two groups on admission. Diabetes mellitus was more common in patients with WRF than in those without WRF. Parameters tested by echocardiography such as ejection fraction (EF), the ratio of early diastolic transmitral flow velocity to tissue Doppler mitral annular early diastolic velocity (E/E'), and the left ventricular diastolic dimension were similar between the groups.

ALP and other liver function tests

ALP was higher in patients with WRF than in those without WRF, at 249 (IQR, 209–342) IU/L and 236 (IQR, 189–306) IU/L, respectively ($p = 0.004$). Conversely, total bilirubin (T-bil), alanine transaminase (ALT), aspartate transaminase (AST), and γ-glutamyltransferase (GGT) were lower in patients with WRF than in those without WRF.

Predictors of WRF

WRF developed in 132 patients (13.6%). Table 2 illustrates the results of the univariate logistic regression analysis for the development of WRF during hospitalization in patients with ADHF. Among the liver function tests, only ALP was associated with development of WRF. According to the post hoc analysis, a significantly higher incidence of WRF existed for the middle ($p = 0.05$) and highest ($p = 0.01$) ALP tertiles compared with that of the lowest tertile (8.9%, 15.1%, and 16.6%, from low to high; Fig. 1). In the multivariate logistic regression analysis, the independent predictors of WRF were baseline CKD (OR 2.46, 95% CI 1.48–4.08, $p < 0.001$), baseline albumin (OR 0.52, 95% CI 0.35–0.77, $p = 0.001$), and diabetes (OR 2.07, 95% CI 1.37–3.12, $p < 0.001$) (Table 3). The adjusted ORs of ALP for the development of WRF in the middle tertile and highest tertile compared with the lowest tertile were 1.69 (1.02–2.79, $p = 0.04$) and 1.95 (1.20–3.21, $p = 0.008$), respectively (Table 3).

Demographic parameters according to tertiles of ALP level

Table 4 reveals the demographic and echocardiographic parameters by ALP tertiles. The mean age, sex, and eGFR were similar among all ALP tertiles, and there were no differences in common renal risk factors such as hypertension and diabetes. BNP had a weak but significant correlation with the ALP level ($r = 0.17$, $p = 0.001$), and mean proteinuria on spot urine analysis was different between the highest and lowest tertiles [highest tertile, 0.42 g/g creatinine (0.16, 1.16) vs lowest tertile, 0.28 g/g creatinine (0.12, 0.79), $p = 0.043$]. Furthermore, although the EF and E/E' were similar for all groups, we found a statistical difference in the severity of TR between the highest tertile and the lowest tertile ($p = 0.005$). Moreover, the mean TRPG in the highest tertile was higher than that in the lowest tertile in post hoc test (35.9 ± 19.1 mmHg vs 32.2 ± 15.1 mmHg, $p = 0.034$).

Discussion

The development of WRF in patients with ADHF is an independent predictor of adverse outcomes. Although previous reports have often studied the cause and prognosis of WRF, the direct association between liver dysfunction and WRF in patients with ADHF has remained unclear. Our results showed that serum ALP, as a variable that reflects liver dysfunction, is an independent predictor of patients with ADHF developing WRF.

WRF in ADHF

The kidney is easily affected by the systemic congestion and low perfusion levels associated with ADHF. The incidence of WRF has been reported to be approximately 10–30% among hospitalized patients with ADHF [14–16]. We observed WRF in 132 patients (13.6%) in this study, which was comparable with previous studies. Several reports have evaluated the predictors of WRF in patients with ADHF. The most recent meta-analysis reported that baseline renal function, age, hypertension, and diabetes were associated with WRF [5]. Baseline renal function and diabetes were also independent predictors of WRF in our study, consistent with the results of previous studies [2,5,14,17]. We did not find age to be an independent predictor of WRF. However, the role of age as a predictor of WRF is still controversial. Forman et al. suggested that age-related systemic effects were not specifically related to the onset of WRF, which was comparable with our study [2]. In addition, we revealed that the baseline serum albumin level was an independent predictor of WRF. Because serum albumin is a key factor for colloid osmotic pressure, low osmotic pressure in