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Original Article

High-sensitivity C-reactive Protein and Other Factors as Outcome Predictors in Acute Decompensated Heart Failure

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Abstract

Objective: Patients with acute decompensated heart failure (ADHF) have high mortality and rehospitalization rates. Although circulating levels of high-sensitivity C-reactive protein (hs-CRP) are an accurate prognostic factor in chronic heart failure, no data are available to indicate whether hs-CRP can predict outcomes in patients with ADHF.

Materials and Methods: We prospectively evaluated serum hs-CRP levels, patient characteristics, laboratory data, medications and management during hospitalization and two end points (inhospital mortality and 6-month readmission rate for heart failure) in 80 patients who presented with ADHF.

Results: No correlation was found between initial hs-CRP at admission and the two end points. The result was the same for all patients after excluding those in whom infection was a predisposing factor for ADHF. Cardiogenic shock significantly predicted inhospital mortality (odds ratio [OR]=15.76; 95% confidence interval [CI]=1.8–180.06; p=0.026). A high serum peak creatinine level (OR=1.39; 95% CI=0.98–1.98; p=0.064) and ischemic heart disease as the etiology of heart failure ((OR=2.48; 95% CI=0.93–6.58; p=0.068) could predict 6-month readmission with borderline significance.

Conclusion: Hs-CRP may have no value as a predictor of the outcomes of inhospital mortality and 6-month readmission for heart failure in ADHF. Many clinical factors such as cardiogenic shock were found to be associated with inhospital mortality, and high serum peak creatinine levels and ischemic heart disease as the etiology of heart failure were found to be associated with 6-month readmission. Therefore, early detection of these high-risk groups to predict inhospital outcomes is possible. [*Tzu Chi Med J* 2009;21(4):296–301]

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1. Introduction

Heart failure is a highly prevalent disease [1] with a high rate of mortality and repeated admissions [2–5]. Extremely high inhospital and post-discharge mortality rates have been found in patients with acute decompensation [6,7]. A high readmission rate was also found after each discharge [3,4,8]. Heart failure is a complex clinical condition. Some data have shown activation of the immune system, such as elevation of serum interleukin-6, tumor necrosis factor-alpha (TNF-α) and adhesion molecules such as soluble cell adhesion molecules, which are involved in the pathogenesis of congestive failure and related to the severity and mortality of chronic heart failure [9–11]. C-reactive protein (CRP) is a powerful marker of inflammation. It can predict future cardiovascular events and mortality in men and women [12,13] and predicts future mortality after acute myocardial infarction [14]. Pye et al found that heart failure is a cause of raised serum levels of CRP [15]. One study has reported that serum high sensitivity C reactive protein (hs-CRP) is elevated in chronic congestive heart failure [16]. Some studies have demonstrated that elevated serum hs-CRP levels are an independent predictor of performance and clinical outcomes in chronic heart failure [17–19]. Recently, N-terminal pro B-type natriuretic peptide was shown to be a good prognostic indicator for acute decompensated heart failure (ADHF) [20,21]. It predicted inhospital or post-discharge death and rehospitalization in patients with ADHF [22–24]. Since there are no reports of a relationship between CRP and the outcomes of patients with ADHF, we designed a prospective observation trial to evaluate this relationship. We also evaluated the ability of other clinical factors and laboratory data at admission to establish outcome predictions for patients presenting with ADHF.

2. Materials and methods

Patients admitted to the intensive care unit of Buddhist Dalin Tzu Chi General Hospital with a primary diagnosis of congestive heart failure with pulmonary congestion or edema were enrolled in this study. After being admitted to the intensive care unit, we collected and analyzed baseline characteristics and serum data including hs-CRP, troponin-I, blood urea nitrogen (BUN), creatinine, sodium, potassium, white blood cell count and hemoglobin. A series of BUN and creatinine levels were measured and the peak levels of BUN and creatinine were recorded. The etiology of congestive heart failure was classified as ischemic heart disease (IHD), dilated cardiomyopathy, valvular heart disease (VHD) or "others", as judged by history, clinical information, laboratory data, and echocardiography or cardiac catheterization. We also recorded any predisposing factors for ADHF including acute coronary syndrome, infection, arrhythmia and "others" (including sodium and fluid overload, poor drug compliance, extreme hypertension and unknown causes) as judged by the staff physician. The left ventricular ejection fraction was obtained within 24 hours after admission with M-mode measurement or with a modified Simpson's method if asynergic segments of the left ventricle were found. Other recorded data included clinical condition during hospitalization (renal failure requiring hemodialysis, gastrointestinal bleeding, nosocomial infection, respiratory failure requiring endotracheal intubation and ventilator support, and arrhythmia, including atrial fibrillation and ventricular tachycardia), medications and specific management including percutaneous coronary intervention and cardiac surgery (coronary artery bypass graft surgery or valvular surgery), intra-aortic balloon counterpulsation and extracorporeal membrane oxygenation. End points included inhospital mortality and rehospitalization for heart failure within 6 months after discharge. Informed consents were obtained from the patients or their families, and the study protocol was approved by the Research Committee and the Institutional Review Board of Buddhist Dalin Tzu Chi General Hospital (B09501003).

2.1. Statistical analysis

Patient and clinical data and specific clinical outcomes of patients with ADHF were tabulated as the mean, range and standard deviation for continuous variables and number and percentage for categorical factors. To identify factors that predicted outcome and/or determinants for inhospital death, 6-month rehospitalization and hospital stays, logistic regression was performed to detect factors influencing inhospital death and 6-month rehospitalization because of the binary outcomes of these two outcomes. Linear regression was used to detect factors influencing the length of hospital stay (continuous variable). Univariate analysis was first utilized to identify each variable's effect singly on the inhospital death rate, 6-month rehospitalization and duration of hospital stay. Age was then considered a potential confounder for further multivariate analysis and hs-CRP was our main hypothesized outcome factor, both of which with all significant variables found in univariate analysis were used for multivariate analysis (unless severe collinearity was detected). Odds ratios, and B and p values with 95% confidence intervals (CI) for each variable were utilized to estimate the relative risk of inhospital death and 6-month rehospitalization by logistic regression. SPSS 12.0 (SPSS Inc., Chicago, IL, USA) was utilized for all statistical analyses and the significance level (p value) was set at 0.05.

3. Results

A total of 80 patients were enrolled in our study. Table 1 shows baseline patient characteristics, hospital management and outcomes. The mean age of patients was 71 years. Most of the patients presented with renal insufficiency with an average initial serum BUN level (BUNi) of 30 mg/dL and a creatinine level of 1.8 mg/dL. Renal function in most of the patients deteriorated during hospitalization where the average peak serum BUN level (BUNp) increased to 47 mg/dL and creatinine level increased to 2.2 mg/dL. The average left ventricular ejection fraction was 44%. The mean serum hs-CRP levels at admission were 53 mg/L. The inhospital mortality rate was 8.8% and the average hospital stay was 17 days. More than one half of the patients (51.3%) with ADHF were readmitted within 6 months.

Univariate analysis for inhospital mortality and 6-month rehospitalization for heart failure by logistic regression demonstrated that BUNp, the difference between the peak and initial serum levels of BUN (BUNd), respiratory failure requiring intubation and ventilator support, and presentation with cardiogenic shock and dopamine use predicted inhospital mortality. In addition, initial serum level of creatinine, peak serum level of creatinine, and ischemic heart disease as the etiology of heart failure predicted 6-month rehospitalization for heart failure. Neither hs-CRP nor troponin-I predicted inhospital mortality or rehospitalization within 6 months using univariate analysis. After excluding those patients where infection was a predisposing factor for ADHF, there was no relationship between hs-CRP and the above two outcomes.

Univariate analysis for duration of hospital stay by linear regression showed that BUNi, BUNd, VHD as the etiology of heart failure, respiratory failure requiring intubation and ventilator support, gastrointestinal bleeding, hemodialysis, infection, and management with dopamine, Levophed, percutaneous coronary intervention, and cardiac surgery during hospitalization predicted a longer hospital stay.

Table 2 shows the results of multivariate analysis for inhospital mortality by logistic regression. Only cardiogenic shock showed significance in predicting high inhospital mortality ($p=0.026$).

Table 3 shows the results of multivariate analysis for 6-month rehospitalization for heart failure by logistic regression. Only IHD as the etiology of heart failure and a high peak creatinine level predicted 6-month rehospitalization with borderline significance. Many factors predicted a long hospitalization, including BUNp (B value=0.17; 95% CI=0.02–0.31; $p=0.030$), gastrointestinal bleeding during hospitalization (B value=12.16; 95% CI=0.32–23.99; $p=0.044$), endotracheal intubation during hospitalization (B value=12.60;

Table 1 — Baseline characteristics, inhospital management and outcomes ($n=80$)*

Age (yr)	71±15 (21–97)
Gender	
Male	46 (57.5)
Female	34 (42.5)
Body weight (kg)	57.5±13.5 (29.6–102.5)
Body height (cm)	158±9 (140–178)
Diabetes	
Yes	32 (40)
No	48 (60)
Hypertension	
Yes	44 (55)
No	36 (45)
Smoking	
Yes	36 (45)
No	44 (55)
BUNi (mg/dL)	30±17 (8–106)
BUNp (mg/dL)	47±33 (12–210)
Crei (mg/dL)	1.8±1.2 (0.5–7.7)
Crep (mg/dL)	2.2±1.6 (0.5–7.7)
Troponin-I (mg/dL)	1.0±6.0 (0–51)
WBC ($\times 10^3/\mu L$)	10.42±6.04 (3.22–46.49)
Hemoglobin (g/dL)	12.0±2.8 (5.2–20.1)
Sodium (mmol/L)	135±4 (125–144)
Potassium (mmol/L)	4.12±0.80 (2.60–6.64)
LVEF (%)	44±19 (8–88)
hs-CRP (mg/L)	53±57.7 (1.2–260.2)
Gastrointestinal bleeding	
Yes	14 (17.5)
No	66 (82.5)
Hemodialysis	
Yes	5 (6.3)
No	75 (93.8)
Endotracheal intubation	
Yes	23 (28.8)
No	57 (71.3)
Infection	
Yes	45 (56.3)
No	35 (43.8)
Atrial fibrillation	
Yes	37 (46.3)
No	43 (53.8)
Ventricular tachycardia	
Yes	3 (3.8)
No	77 (96.3)
Pulmonary congestion/edema	
Yes	80 (100)
No	0 (0)
Cardiogenic shock	
Yes	9 (11.3)
No	71 (88.8)

(Continued)

Table 1 — (Continued)

Etiology of heart failure	
IHD	42 (52.5)
DCM	15 (18.8)
VHD	14 (17.5)
Others	9 (11.3)
Factors predisposing to ADHF	
ACS	35 (43.8)
Infection	15 (18.8)
Arrhythmia	9 (11.3)
Others	21 (26.3)
Medications used	
Dopamine	12 (15)
Dobutamine	22 (27.5)
Norepinephrine	2 (2.5)
Nitroglycerine	75 (93.8)
Statin	10 (12.5)
ACEI/ARB	63 (78.8)
Beta blocker	15 (18.8)
Spirolactone	19 (23.8)
Aspirin/clopidogrel	48 (60)
PCI/cardiac surgery	
Yes	16 (20)
No	64 (80)
IABP	
Yes	2 (2.5)
No	78 (97.5)
ECMO	
Yes	1 (1.3)
No	79 (98.8)
Inhospital mortality	7 (8.8)
6-mo rehospitalization	41 (51.3)
Hospital stay (d)	17±23 (1–180)

*Data presented as mean±standard deviation (range) or *n* (%). BUNi=initial blood urea nitrogen; BUNp=peak blood urea nitrogen; Crei=initial creatinine; Crep=peak creatinine; WBC=white blood cell; LVEF=left ventricular ejection fraction; hs-CRP=high-sensitivity C-reactive protein; IHD=ischemic heart disease; DCM=dilated cardiomyopathy; VHD=valvular heart disease; ADHF=acute decompensated heart failure; ACS=acute coronary syndrome; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; PCI=percutaneous coronary intervention; IABP=intra-aortic balloon counterpulsation; ECMO=extracorporeal membrane oxygenation.

95% CI=1.84–23.35; $p=0.022$), and use of dopamine (B value=14.71; 95% CI=0.82–28.60; $p=0.038$).

4. Discussion

Evidence suggests that neurohormonal and immune mechanisms play a central role in the pathogenesis of congestive heart failure (CHF). The main components thought to be relevant to the pathogenesis of CHF are adhesion molecules, autoantibodies, nitric oxide, endothelin-1 and proinflammatory cytokines such as interleukin-1, interleukin-6 and TNF-α [25]. Proinflammatory cytokines have also been implicated in the progression of heart failure [26]. Elevation of interleukin-6 and TNF-α in chronic heart failure predict a 24-month mortality in one study [9]. Increases in the level of circulating soluble cell adhesion molecules are related to the severity of chronic heart failure and composite clinical outcomes (death, heart transplantation or hospitalization with worsening heart failure) in another study [11]. CRP is an acute phase reactant produced in the liver. Data have suggested that hs-CRP is an independent predictor of mortality, functional limitation, 5 year-survival rate and the composite end points of death, heart transplantation and hospitalization with worsening heart failure in patients with chronic heart failure [18,19]. Elevation of serum CRP levels is also found in ADHF [27]. However, there is still a lack of evidence concerning the role of hs-CRP in ADHF. Our results show that there may be no relationship between serum hs-CRP at admission for ADHF and our two main outcomes, inhospital mortality and 6-month readmission. Since there was a high correlation between infection and CRP, we excluded those patients with infection as a predisposing factor for ADHF, and there was still no correlation between hs-CRP and our main outcomes. A previous study indicated that serum CRP levels predicted 24-month mortality in patients with acute myocardial infarction since acute coronary syndrome is also an inflammatory process [14]. However, we did not find any correlation between infection or acute coronary syndrome as predisposing factors for ADHF and our two main outcomes. This result may be because the mechanism of ADHF is very complex and

Table 2 — Multivariate analyses of logistic regressions on inhospital mortality for patients with acute decompensated heart failure (*n*=80)

Variable	OR	95% CI	*p*
Age (yr)	1.07	0.98–1.16	0.16
BUNp (mg/dL)	0.76	0.33–1.74	0.52
Use of dopamine	4.36	0.48–39.57	0.19
hs-CRP (mg/L)	1.01	0.99–1.03	0.15
Cardiogenic shock	15.76	1.38–180.06	0.026

OR=odds ratio; CI=confidence interval; BUNp=peak serum blood urea nitrogen level; hs-CRP=high sensitivity C-reactive protein.

Table 3 — Multivariate analyses of logistic regressions on 6-month rehospitalization for patients with acute decompensated heart failure (*n*=80)

Variable	OR	95% CI	*p*
Age (yr)	0.99	0.96–1.03	0.86
Crep (mg/dL)	1.39	0.98–1.98	0.064
Etiology-IHD	2.48	0.93–6.58	0.068
hs-CRP (mg/L)	0.38	0.99–1.01	0.86

OR=odds ratio; CI=confidence interval; Crep=peak creatinine; IHD=ischemic heart disease; hs-CRP=high sensitivity C-reactive protein.

inflammation may play only a small role. Some studies have recommended measuring hs-CRP levels for risk assessment for patients with chronic heart failure [17,18]. The present study implies that routine hs-CRP determination in ADHF may be unnecessary.

The average hospital stay was 17 days in our series and the longest was 180 days. The duration of hospital stay may influence medical costs and psychological stress in patients, their families, and even their physicians. This study shows that inhospital morbidity, such as gastrointestinal bleeding and respiratory failure requiring endotracheal intubation predicted longer hospital stays. It is reasonable that these conditions complicate the hospital course and require more time to treat with modalities such as blood transfusion, panendoscopy and artificial ventilation. In one study, renal dysfunction was common among patients hospitalized with ADFH and the severity at admission correlated with outcomes such as mortality, length of hospital stay, and total hospitalization [28]. Our data also showed that BUNp correlated with the duration of hospital stay. Use of dopamine usually implies a worse hemodynamic condition and a prolonged hospital stay is possible. We believe that a shorter hospitalization in our study may not have indicated a better outcome, as in cases of early mortality. The significance of these data needs further careful assessment.

Repeated hospitalization is common among chronic heart failure patients. A previous report showed that patients with heart failure were admitted to the hospital 2.05 times per year and spent 27.6 days in the hospital each year [29]. Readmission rates after hospitalization for ADHF were reported to be 21.3–68.2% [3,22,30]. Studies have also shown that repeated hospitalization increases long-term mortality in patients with CHF [31]. In our study, more than half of the patients admitted with ADHF were rehospitalized within 6 months after discharge. Philbin and DiSalvo developed a risk score for predicting readmission [22]. Positive score items included black race, Medicare or Medicaid insurance, home health care services after discharge, IHD, VHD, diabetes, renal disease, chronic lung disease, idiopathic cardiomyopathy, prior cardiac surgery and use of telemetry. Higher risk scores predicted higher readmission rates [22]. In our series, only IHD as the etiology of heart failure and high peak creatinine levels tended to predict 6-month readmission. A previous study showed that nurse-directed multidisciplinary intervention can reduce rehospitalization for elderly patients with congestive heart failure, resulting in improved quality of life and reduced total costs [32]. Although no factor was found to be a strong predictor in our study, improving post-discharge multidisciplinary care may be beneficial to reduce total costs and to improve the patients' quality of life. Inhospital mortality in our study was 8.8%, which was higher than that in other series in which the rates were approximately 4% [24,33,34]. These previous studies found many clinical features that predicted inhospital mortality, including low blood pressure, high admission levels of BUN and creatinine, low sodium levels (<132 mmol/L), dyspnea at rest and elevated heart rate at admission [24,33–35]. Our data only showed cardiogenic shock to be correlated with higher inhospital mortality. There is no doubt that cardiogenic shock is a life-threatening condition and further efforts to prevent it may be valuable in reducing inhospital mortality.

5. Conclusion

Although hs-CRP is an accurate prognostic factor in chronic heart failure, it did not predict inhospital mortality, 6-month readmission for heart failure, or duration of hospitalization in patients with ADHF in our study. Cardiogenic shock can predict inhospital mortality. Peak serum creatinine levels and ischemic heart disease tended to predict 6-month readmission for heart failure. We ultimately need to modify these predictive factors to reduce inhospital mortality and rehospitalization of ADHF patients. The small case number was the greatest limitation to this study. In particular, it may have limited our ability to observe statistical significance for many variables. A large-scale study is required in the future.

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