



## Depression is associated with increased C-reactive protein levels in patients with heart failure and hyperuricemia

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Psychological depression is considered a major determinant of health status in patients with heart failure (HF). The incidence of depression in HF is four to five times higher than that in the general population.<sup>[1]</sup> HF and depression share common pathophysiological features, which include stimulation of the hypothalamus-pituitary-adrenal (HPA) axis and sympathetic activity, and elevated levels of pro-inflammatory cytokines.<sup>[2,3]</sup> Over the past decades, growing evidence implicates inflammation activation, as an important pathway, is involved in disease progression in chronic HF.<sup>[4]</sup> High sensitivity C-reactive protein (hs-CRP), an inflammation cytokine, exerts a detrimental effect on the cardiovascular systems, such as cardiac fibroblasts, myocytes, and vascular cells, by amplifying the inflammatory responsible for adverse ventricular remodeling.<sup>[5,6]</sup> Similarly, the link between inflammation and depression also has been well documented over the past two decades. A large amount of evidence shows that subjects with depression have increased level of hs-CRP compared with those without depression.<sup>[7]</sup> In patients with HF and hyperuricemia, an elevation in uric acid (UA) is associated with impaired renal function and increased oxidative stress, resulting in bigger inflammatory burden.<sup>[8,9]</sup> However, whether the link between hs-CRP and depression still exists in such population remains unclear. Therefore, we conducted this cross-sectional study to assess the association between hs-CRP and depression patients with HF and hyperuricemia.

The protocol of this cross-sectional study was approved by the institutional ethics committee. This study complied with the Declaration of Helsinki. Inclusion criteria were adult HF patients with New York Heart Association (NYHA) function Class II-IV and systolic dysfunction (left ventricular ejection fraction  $\leq$  45%) and serum uric acid  $>$  7 mg/dL

(417  $\mu$ mol/L). We reviewed medical records of 114 patients with HF who were treated in our institute between April 2014 and October 2016. The diagnosis of CHF was based on clinical symptoms and a combination of clinical signs and echocardiogram. The exclusion criteria were signs of infection, terminal illness, chronic liver disease, cachexia, acute myocarditis, acute coronary syndrome, and renal function insufficiency (serum creatinine  $\geq$  200  $\mu$ mol/L). Patients were also excluded from the analysis when variables (i.e., depression rating score and hs-CRP levels) were not available from the same time point (defined as a maximum interval of two days). The detailed clinical characteristics and medications are listed in Table 1.

Study personnel with previous experience or training in clinical psychiatry provided physician-facilitated support, designing to build rapport and trust with the study participants. Participants were also screened for suicidal ideation. The seventeen-item Hamilton Depression Rating Scale was measured to reflect the severity of depression.

**Table 1. Baseline clinical characteristics.**

Variables	Value
Age	51.57 $\pm$ 13.9
Male	92
BMI, kg/m <sup>2</sup>	25.21 $\pm$ 4.16
NYHA class II/III/IV	7/44/63
LVEF, %	32.69 $\pm$ 7.38
Depression rating score	12.52 $\pm$ 8.90
Laboratory test	
SUA, $\mu$ mol/L	559.17 $\pm$ 137.94
C-reactive protein, mg/L	4.26 $\pm$ 4.15
Blood glucose, mmol/L	5.17 $\pm$ 1.31
Total Cholesterol, mmol/L	4.01 $\pm$ 0.91
Triglyceride, mmol/L	1.31 $\pm$ 0.62

Data were presented as mean  $\pm$  SD or *n*. BMI: body mass index; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SUA: serum uric acid.

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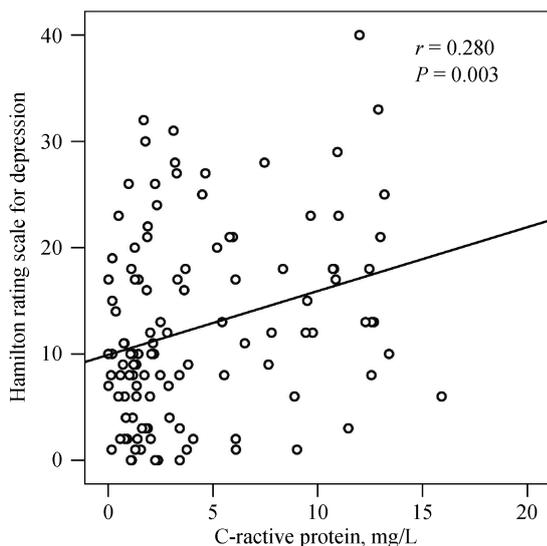
Fasting blood samples for creatinine and hs-CRP level analysis were taken in the morning. Hs-CRP concentration was measured using an image automatic immunoassay system (Beckman-Coulter, Fullerton, CA). For quality control, during operation of the Beckman Coulter analyzer, at least two levels of control material were analyzed daily. In addition, these controls were run with each new calibration, with each new reagent cartridge.

Statistical analyses were carried out using SPSS 16.0 statistical package. The Pearson correlation coefficients were derived. We also conducted partial correlation using the following as co-variables to rule out any potential bias: age, gender, body mass index (BMI), lipid profile, New York Heart Association functional class (NYHA), and left ventricle ejection fraction (LVEF). A multiple linear regression was used to model the dependence of depression severity on age, gender, BMI, and lipid profile, hs-CRP, NYHA functional class, and LVEF. Standardized coefficients were calculated to reflect the relationship between depression and the above variables.

The univariate correlation coefficient between depression rating scale and hs-CRP is shown in Figure 1. The analysis using Pearson's correlation coefficient indicated that there was a statistically significant linear relationship between concentrations of hs-CRP and Hamilton Depression Scale ( $r = 0.28$ ,  $P = 0.003$ , Figure 1).

The correlation between hs-CRP and Hamilton depression rating scale remained unchanged in partial correlation in which age, gender, BMI, lipid profile NYHA functional class, and LVEF were taken as co-variables.

In multiple linear regression models, standardized coefficients were calculated (Table 2). Finally, the relationship



**Figure 1.** The correlation between C-reactive protein and Hamilton rating scale for depression.

**Table 2.** Linear regression of depression and other variables.

Predictor	Standardized coefficient	P value
Age	0.01	0.91
Gender	-0.13	0.13
hs-CRP	0.27	< 0.01
Triglyceride	0.01	0.91
TCL	-0.11	0.24
BMI	-0.29	< 0.01
LVEF	-0.003	0.97
NYHA functional class	0.18	0.06

BMI: body mass index; hs-CRP: high sensitive C-reactive protein; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association; TCL: total cholesterol.

between hs-CRP and Hamilton Depression Scale was confirmed, which was consistent with the unadjusted results.

To our knowledge, this is the first cross-sectional study to assess the association between hs-CRP and depression in patients with HF and hyperuricemia. Our study showed that there was a weak but robust association between increased hs-CRP levels and severity of depression in such patients.

The progresses of HF and depression share some common pathways that include dysfunction of HPA axis, sympathetic and inflammatory activation. Recent studies suggest there is a cytokine-mediated communication between the immune system and the brain in the pathogenesis of depression.<sup>[10]</sup> Major depression is associated with increased levels of inflammation markers. Antidepressants can induce an anti-inflammatory response independent of antidepressant action,<sup>[11]</sup> while injection of *Salmonella abortus equi* endotoxin in healthy volunteers could cause an increased in tumor necrosis factor alpha (TNF-alpha), soluble TNF receptors, interleukin (IL)-6, IL-1 receptor antagonist, and cortisol, resulting in low mood, anxiety, and reduced cognitive performance.<sup>[12]</sup> Thus, depression may be viewed as a psychoneuroimmunological disorder that includes not only a traditional monoamine deficiency, but also a persistency of low-grade inflammation. The link between inflammation and HF has also been well established. In HF, increased translocation of bacterial lipopolysaccharide across the intestinal wall due to bowel wall edema could lead to low-grade inflammation.<sup>[13]</sup> Moreover, activation of sympathetic nervous system and renin-angiotensin-aldosterone system in HF can induce pro-inflammatory cytokines overproduction.<sup>[14]</sup> This may contribute to the development of depression in HF. More importantly, dysfunction of the HPA axis has been observed both in depression and HF.<sup>[15-17]</sup> An elevation of inflammatory cytokines in the circulation may activate HPA axis, decrease levels of serotonin and other neurotransmitters in the brain, and increase oxidative stress in the brain.<sup>[18]</sup> Cortisol over-production in HF can negatively affect the central nervous system, the

immune system, and glucose and lipid metabolism.<sup>[19]</sup> These detrimental effects could contribute to the impaired mood, cognition, and perception seen in depression.

Confounding factors, such as BMI, lipid profile, age, gender, associated with elevated hs-CRP may also be implicated and modulate the relationship between the CRP gene and depression, therefore affect the result.<sup>[20]</sup> This may be especially important in the elderly HF population who have a high prevalence of comorbid chronic disorders. However, our data only showed there was only an inverse relationship between BMI and depression, which is consistent with the findings that profound muscle wasting and severe weight loss is a predictor of worsened prognosis in HF.

There are several limitations to the study. First, this is a cross-sectional study, and our results were designed to assess the association between inflammatory marker, i.e., hs-CRP, and depression in HF with hyperuricemia. We did not collect the follow-up data and test whether hs-CRP levels reduced after HF clinical status improved after treatment. Second, the interactions between inflammation, depression and HF are complex. Circulating hs-CRP level may be acting as a surrogate for unrecognized confounders that affect the risk for depression and HF progression. Nevertheless, our data showed that hs-CRP level in the circulation was an independent marker for depression in patients with HF and hyperuricemia.

Consistent with findings in other population, serum hs-CRP appears to be an independent marker for severity of depression in HF with hyperuricemia. This supports etiological role for inflammation in the genesis of depression. A clear understanding of the role of inflammation in the pathogenesis of depression and HF may help to devise more targeted interventions.

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