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Monocyte to HDL cholesterol ratio is associated with discharge and 3-month outcome in patients with acute intracerebral hemorrhage

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ABSTRACT

Background: Monocyte and monocyte to high-density lipoprotein ratio (MHR) recently emerged as markers of inflammation and have been reported to be novel prognostic indicators of cardiovascular diseases. We investigated the association of monocyte and MHR with hospital discharge and 3-month outcome after acute intracerebral hemorrhage (ICH).

Methods: A total of 316 patients with acute ICH were enrolled from November 2011 to March 2014. Demographic characteristics, lifestyle risk factors, medical history, admission laboratory parameters, and monocyte level were recorded. Clinical outcome was disability or death (defined as having a modified Rankin Scale score ≥ 2) upon discharge or at 3 months.

Results: 202 patients (63.9%) experienced disability or death at hospital discharge, and 176 patients (55.7%) at 3 months post-ICH. Admission monocyte level was associated with clinical outcome at 3 months (adjusted OR, 4.17; 95% CI, 1.45–12.00; *P*-trend = 0.028) when highest and lowest quartiles were compared. However, no significant association was found between monocyte and discharge outcome (*P*-trend = 0.102). Compared to the lowest category of MHR, the highest category was associated with a 3.87-fold increase in the odds of disability or death at discharge (95% CI, 1.17–12.76; *P*-trend = 0.045) and 3.08-fold increased odds of disability or death at 3-month (95% CI, 1.05–9.08; *P*-trend = 0.024).

Conclusions: In patients with acute ICH, higher MHR was associated with increased risk of disability or death at discharge and at 3 months post-ICH, however higher monocyte was only associated with increased risk of 3-month disability or death.

1. Introduction

Intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes. Approximately 40% of ICH patients die within 30 days [1] and the majority of survivors are left with severe disability [2]. Previous studies reported that severe neurological deficit upon presentation, large hematoma volume, hematoma growth, hematoma location and the presence of intraventricular bleeding were associated with poor outcomes in ICH patients [3–5]. Recently, preclinical and clinical studies indicated that inflammatory processes in brain injury after ICH could also affect ICH prognosis [6,7].

White blood cell (WBC) count and its' subsets have been reported to be not only associated with larger ICH volume but also early neurological deterioration and bad outcomes [8–10]. Monocytes as a distinct type of WBC, play a pro-inflammatory role after ICH and has been shown to adversely affect patient prognosis. Clinical studies found that high level of admission monocyte count was significant associated with the 30-day mortality in ICH patients [11,12].

In addition, increasing number of studies have indicated that high density lipoprotein (HDL) has anti-inflammatory properties that may reduce the risk of cardiovascular events [13,14]. Recently, monocyte-to-HDL cholesterol (HDL-C) ratio (MHR) has emerged as a novel inflammation marker and reported to be strongly linked to cardiovascular events. Kanbay et al. first reported that high MHR was related to cardiovascular events in patients with chronic kidney disease [15]. Canpolat et al. also suggested that MHR is an independent predictor of atrial fibrillation recurrence after cryoballoon-based catheter ablation [16]. Moreover, other studies found that increased MHR was independently

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associated with in-hospital major adverse cardiovascular events (MACEs) in coronary artery disease (CAD) patients [17,18].

To date, there has been no study that investigated the association of MHR with ICH outcome. Thus, in the present study, we aimed to investigate the relationship between admission monocyte count and MHR with discharge and 3-month outcomes after ICH.

2. Methods

2.1. Study participants

From November 2011 to March 2014, we prospectively identified acute ICH patients from the Second Affiliated Hospital of Soochow University in China. The method for the recruitment of study participants have been described elsewhere [19,20]. Briefly, patients with computerized tomography (CT) confirmed ICH were potentially eligible for the study. After excluding patients with trauma, brain tumor, hemorrhagic transformation of ischemic stroke, and vascular cerebral malformations, a total of 413 potentially eligible participants were enrolled. Additional exclusion criteria were as follows: 1) requirement for neurosurgical procedures (n = 10); 2) time from onset to admission over 48 h (n = 42); 3) no modified Rankin Scale score at 3-month (n = 27); and 4) no serum monocyte count or HDL-C data (n = 18) measurements. 316 patients with available data were finally included in this study. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University, and informed consent was obtained from all participating patients in this study.

2.2. Data collection

Demographic characteristics, lifestyle risk factors, medical history, clinical laboratory tests, imaging data (CT and magnetic resonance imaging) were collected at the time of enrollment. Trained neurologists assessed the baseline stroke severity using the National Institutes of Health Stroke Scale (NIHSS). Current smoking status was defined as having smoked at least one cigarette per day for 1 year or more. Hematoma volume was assessed by two neuroradiologists who were blinded to the clinical data and follow-up CT scans using the formula ABC/2 [21]. Using a standard mercury sphygmomanometer, blood pressure (BP) measurements were performed in the supine position for admission. Blood samples were collected within 24 h of hospital admission. The WBC and differential counts were determined by the BC-6800 (Mindray, China). Serum HDL-C and other biochemical parameters were analyzed enzymatically on an Olympus Au5400 automatic biochemical analyzer (First Chemical Co., LTD, Japan) using the commercial reagents. The MHR was calculated as the ratio of monocyte count to HDL-C level.

2.3. Outcomes assessment

Patient outcome was assessed using the modified Rankin Scale (mRS) at hospital discharge and again at 3 months post-ICH, and clinical outcome was disability or death (defined as having a modified Rankin Scale score ≥ 2) [22,23]. Deaths were reported by family members or work associates and/or obtained from death certificates and medical records.

2.4. Statistical analysis

Patients were divided into quartiles based on admission monocyte count (Q1: <0.25, 10^9/L; Q2: 0.25–0.33, 10^9/L; Q3: 0.34–0.46, 10^9/L; Q4: ≥0.47, 10^9/L) and MHR (Q1: <0.18; Q2: 0.18–0.26; Q3: 0.27–0.37; Q4: ≥0.38). Continuous variables were summarized as mean (± standard deviation) or median (interquartile range), and categorical variables were expressed as frequency (percent). For group comparisons, Continuous variables were compared between groups using variance analysis or Wilcoxon rank-sum test, and chi-square test was applied for categorical variables. Furthermore, multivariable logistic regression was used to assess the associations between monocyte count and MHR with discharge and 3-month disability or death among acute ICH patients. Potential confounders such as age, sex, time from onset to admission, current smoking status, systolic BP, triglyceride, total cholesterol, low density lipoprotein cholesterol, history of hypertension, history of diabetes mellitus, history of stroke, location of hematoma, hematoma volume and baseline NIHSS score were adjusted for in the multivariable model. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed for each group, and the lowest quartile was set as the reference category. Tests for linear trend in the ORs across admission monocyte count and MHR quartiles were performed with both as ordinal variables. To assess the robustness of these associations, several sensitivity analyses were carried out by including all patients with time from onset to admission within 7 days or using mRS 3 to 6 as poor outcome. A 2-sided P-value < 0.05 was established as the level for statistical significance. All analyses were conducted using the SAS statistical software (version 9.2, Cary, North Carolina, USA).

3. Results

A total of 316 acute ICH patients (206 men and 110 women) were included in the main analysis. The mean age was 65 (±13.6). The baseline characteristics of patients according MHR quartile are shown in Table 1. In comparison to participants with a lower MHR, those with a higher MHR level were more likely to be male with a prior history of stroke, had increased levels of triglyceride and white blood cells, and lower level of HDL cholesterol and total cholesterol.

The current study showed there were 202 patients (63.9%) with disability or death (mRS score of 2–6) at hospital discharge, and 176 patients (55.7%) at 3 months. Admission monocyte level was associated with 3-month disability or death (adjusted OR, 4.17; 95% CI, 1.45–12.00; P-trend = 0.028) when highest and lowest quartiles were compared (Table 2). However, there was no significant association between monocyte and discharge outcome (P-trend = 0.102). In comparison to the lowest category of MHR, the highest category was associated with a 3.87-fold increase in the odds of disability or death at discharge (95% CI, 1.17–12.76; P-trend = 0.045) and 3.08-fold increased odds of disability or death at 3-month (95% CI, 1.05–9.08; P-trend = 0.024) in the multivariable models (Table 3). Sensitivity analysis including all patients with time from onset to admission within 7 days further confirmed these associations of monocyte to HDL ratio with discharge and 3-month disability or death; however, no significant associations between monocyte to HDL ratio with discharge and 3-month poor outcome (mRS ≥ 3) was observed (Supplemental Table 1).

4. Discussion

In the present study, we demonstrated that high admission MHR was associated with disability or death at discharge and 3 months among acute ICH patients. High level of monocyte count also increased the rate of 3-month disability or death. However, no significant relationship between high monocyte count levels and discharge outcome was observed.

Increasing evidence suggests that inflammatory mechanisms are involved in early and delayed brain injury after ICH [24,25] and the inflammatory markers include WBC, neutrophils, monocyte and C-reactive protein [8,9,11,26]. Previous studies reported that increased WBCs predicted subsequent early neurological deterioration, was associated with large hematoma volume and increased mortality in patients with ICH [8–10]. Monocytes as a distinct type of WBC, play a pro-inflammatory role after ICH and may affect its prognosis. Animal studies found that monocyte infiltrated in and around the hematoma within 12 h after ICH, which peaked in concentration at day 5[27,28] and was associated motor dysfunction [29]. In clinical studies, there were also significant