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Hypoalbuminemia, systemic inflammatory response syndrome, and functional outcome in intracerebral hemorrhage

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ABSTRACT

Purpose: Hypoalbuminemia and systemic inflammatory response syndrome (SIRS) are reported in critically-ill patients, but their relationship is unclear. We sought to determine the association of admission serum albumin and SIRS with outcomes in patients with intracerebral hemorrhage (ICH).
Methods: We used a multicenter, multinational registry of ICH patients to select patients in whom SIRS parameters and serum albumin levels had been determined on admission. Hypoalbuminemia was defined as the lowest standardized quartile of albumin; SIRS according to standard criteria. Primary outcomes were modified Rankin Scale (mRS) at discharge and in-hospital mortality. Regression models were used to assess for the association of hypoalbuminemia and SIRS with discharge mRS and in-hospital mortality.
Results: Of 761 ICH patients included in the registry 518 met inclusion criteria; 129 (25%) met SIRS criteria on admission. Hypoalbuminemia was more frequent in patients with SIRS (42% versus 19%; $p < 0.001$). SIRS was associated with worse outcomes (OR: 4.68, 95%CI, 2.52–8.76) and in-hospital all-cause mortality (OR: 2.18, 95% CI, 1.60–2.97), while hypoalbuminemia was not associated with all-cause mortality.

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Conclusions: In patients with ICH, hypoalbuminemia is strongly associated with SIRS. SIRS, but not hypoalbuminemia, predicts poor outcome at discharge. Recognizing and managing SIRS early may prevent death or disability in ICH patients.

1. Introduction

Hypoalbuminemia is common in critical illness but its role in outcomes has not been as well established [1]. It may have multiple causes, including malnutrition, acute and chronic inflammation, infection, renal disease, and is associated with poor overall health and frailty. It is also a recognized prognostic factor in multiple acute life threatening injuries [2-4]. In acute ischemic stroke, hypoalbuminemia is associated with poor outcome [5-8], and is a strong predictor of early death in subarachnoid hemorrhage [9,10]. Little is known about the significance of serum albumin levels as a prognostic factor in spontaneous intracerebral hemorrhage (ICH) [11].

ICH induces an acute-phase inflammatory response (APR) [12]. APR is a cytokine-driven process that can determine a host's systemic inflammatory response syndrome (SIRS). Approximately 20% of patients with ICH develop SIRS with an increased risk of poor functional outcome at discharge [13]. Patients with APR often have a decrease in serum albumin concentration, which is primarily caused by reduced albumin liver synthesis and albumin passage from the vascular into the extravascular space due to enhanced endothelial permeability [3,14]. Whether low albumin is a marker of a severe systemic inflammatory response or independently associated with outcome in ICH patients is unknown.

The aim of this study was to compare the frequency of hypoalbuminemia in ICH patients with or without SIRS and to test the hypothesis that initial serum albumin is independently associated with poor functional outcome in patients with ICH. The secondary objectives were to examine the relationship between SIRS and albumin levels in ICH patients, and test interaction between SIRS and serum albumin levels in predicting functional outcome at discharge and in-hospital mortality.

2. Materials & methods

2.1. Patient population

The study population consisted of patients registered in the *Multi-National survey on Epidemiology, Morbidity and Outcomes in Intracerebral Hemorrhage* (MNEMONICH) with data extracted from the registry on December 31, 2015. MNEMONICH (NCT2567162 ClinicalTrials.gov) is an ongoing, international, multicenter, observational, collaborative database of consecutive patients aged ≥18 years with spontaneous ICH from participating centers in Europe, South America, and the United States [15,16]. Details on participating centers, study period, demographic and laboratory data are given in Supplemental Table 1. In MNEMONICH, spontaneous ICH is defined as acute brain intraparenchymal bleeding confirmed by computed tomography (CT) scan, in the absence of an underlying cause other than small vessel disease. Patients with anticoagulant-associated ICH are also included. Bleeding due to brain tumors, vascular malformations, aneurysms, and trauma are excluded. Registered data included demographics, clinical, laboratory, and neuro-radiological findings collected at the participating centers. Data quality and consistency are regularly monitored by the coordinating center (Rieti, Italy). All ICH patients included in MNEMONICH are managed according to local guidelines, based on either the guidelines of the American Heart Association/American Stroke Association or the European Stroke Organization [17-19]. Approval by the local Ethics Committee was obtained by each center prior to participation in MNEMONICH.

2.2. Inclusion criteria

Consecutive patients with ICH enrolled in MNEMONICH were considered eligible for the current analysis based on the following criteria: (1) spontaneous ICH presenting within 24 h of symptom onset confirmed on CT of sufficient quality for calculation of ICH volume; (2) a blood sample with albumin determination within 24 h after ICH onset; and (3) complete follow-up on December 31, 2015. We excluded patients who had undergone hematoma evacuation during their acute admission due to the potential confounding effect of surgery.

2.3. Clinical and radiological variables

Clinical data including age, sex, past medical history, and previous medication use (including oral anticoagulants and antiplatelet medications) were all collected through interviews with patients or their relatives. Prospectively recorded admission variables included Glasgow Coma Scale (GCS), systolic and diastolic blood pressure, blood glucose, ICH score, and time from symptom onset to CT. All definitions and coding are based on the NINDS common data elements (https://www.commondataelements.ninds.nih.gov/Stroke.aspx#tab=Data_Standards).

At each center, experienced neurologists or neuro-radiologists blinded to clinical data, functional outcome, and albumin results assigned ICH locations for all patients as lobar, deep, brain stem, or cerebellar. Volumetric hematoma measurements were performed according to ABC/2 method by local investigators [20]. To determine inter-rater reliability of the measurements for all investigators, a random sample of 19 CT scans were also analyzed by a central reader (MDN, Rieti, Italy). Finally, intraventricular extension of hemorrhage (IVH) was determined as categorical variable (present or absent).

2.4. Serum albumin determination

At each center, serum albumin levels were analyzed by the local clinical laboratory using different analytical methods (bromocresol purple dye-binding in 3, bromocresol green dye-binding method in 1 center). Because assay methods have a marked effect on the concentration results mainly in hypoalbuminemic patients [21], albumin values were standardized calculating the Z-score value for each independent cohort, by subtracting the mean and dividing by the standard deviation, and adding 3 units to each value in order to avoid negative results.

2.5. Systemic inflammatory response syndrome (SIRS)

In the present analysis, we considered only occurrence of SIRS at admission. SIRS was defined according to standard criteria as 2 or more of the following: (1) temperature of >38 °C (100.4 °F) or <36 °C (96.8 °F), (2) heart rate (HR) of >90 beats per minute, (3) respiratory rate (RR) of >20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) of <32 mm Hg, and (4) WBC count of >12,000/μL or <4000/μL or >10% band forms [22]. All patients were strictly monitored during the first 7 days after admission to identify any clinical sign suggestive of potentially clinical infection to explain SIRS at admission. In the presence of clinical suspicion of infection, culture results were obtained from different sources. The physicians directly in charge of the patient evaluated each positive culture result to determine whether it represented true infection or merely contamination and as a possible cause of SIRS at