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# Serum macrophage migration inhibitory factor concentrations correlate with prognosis of traumatic brain injury

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ABSTRACT

*Background:* Macrophage migration inhibitory factor (MIF) is a well-known pro-inflammatory cytokine. Serum MIF concentrations are associated with the severity and prognosis of ischemic stroke.

*Methods:* In this prospective, observational study, white blood cell (WBC) count and serum concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and MIF among 108 severe traumatic brain injury (TBI) patients and 108 controls were measured. We determined whether serum MIF concentrations are associated with inflammation, severity, in-hospital major adverse events (IMAEs) (i.e., in-hospital mortality, acute lung injury, acute traumatic coagulopathy, progressive hemorrhagic injury and posttraumatic cerebral infarction) and long-term clinical outcome (i.e., 6-month functional outcome) after TBI.

*Results:* As compared to the controls, serum CRP, IL-6, TNF-α and MIF concentrations were significantly increased. MIF concentrations correlated with WBC count, CRP, IL-6 and TNF-α concentrations and Glasgow coma scale (GCS) scores. MIF in serum was independently associated with IMAEs and long-term clinical outcome. Area under receiver operating characteristic curve of MIF concentrations was similar to GCS scores'. Moreover, MIF concentrations markedly improved the predictive value of GCS scores for 6-month unfavorable outcome.

*Conclusion:* Increased serum MIF concentrations have close relation to inflammation, trauma severity and clinical outcomes, substantializing MIF as a good prognostic biomarker after TBI.

## 1. Introduction

Traumatic brain injury (TBI) is one of the common forms of trauma [1–3]. Severe TBI represents one of the most leading causes of disability and mortality [4–6]. Although the mechanisms underlying secondary brain injury are not clearly explored, a growing body of evidence has determined that inflammation plays a key role in this process [7–10]. In-hospital major adverse events (IMAEs) mainly consist of acute lung injury (ALI), acute traumatic coagulopathy (ATC), progressive hemorrhagic injury (PHI), posttraumatic cerebral infarction (PTCI) and in-hospital mortality. Occurrence and progression of IMAEs are associated with inflammation and IMAEs can lead to poor long-term prognosis after head trauma [11–18].

Macrophage migration inhibitory factor (MIF), a small secreted protein of 12.5 kD, is expressed by various cells including fibroblasts, monocytes/macrophages, insulin secreting β-cells of the pancreas, pituitary cells and endothelial cells [19–21]. Accumulating evidence shows that MIF functions as a proinflammatory cytokine, and is involved in inflammation-associated pathophysiology such as sepsis, autoimmune liver disease, cancer, and rheumatoid arthritis [22–25]. Notably, MIF expression concentration increases in microglia of rat traumatic spinal cord [26]; moreover, MIF can activate inflammatory responses of astrocytes in rat traumatic spinal cord [27]. Interestingly, MIF promotes cell death and aggravates neurologic deficits after experimental stroke [28]; also, deletion of MIF attenuates neuronal death and promotes functional recovery after compression-induced spinal cord injury in mice [29]. In addition, MIF gene expression in human stroke is possibly up-regulated by hypoxia [30]. Recently, it was found that serum MIF concentrations were associated with infarct volumes and long-term outcomes in patients with acute ischemic stroke [31]. These data indicates that MIF might be a prognostic biomarker for some neurological diseases including TBI. However, it remains unclear in regard to change of serum MIF concentrations after TBI.

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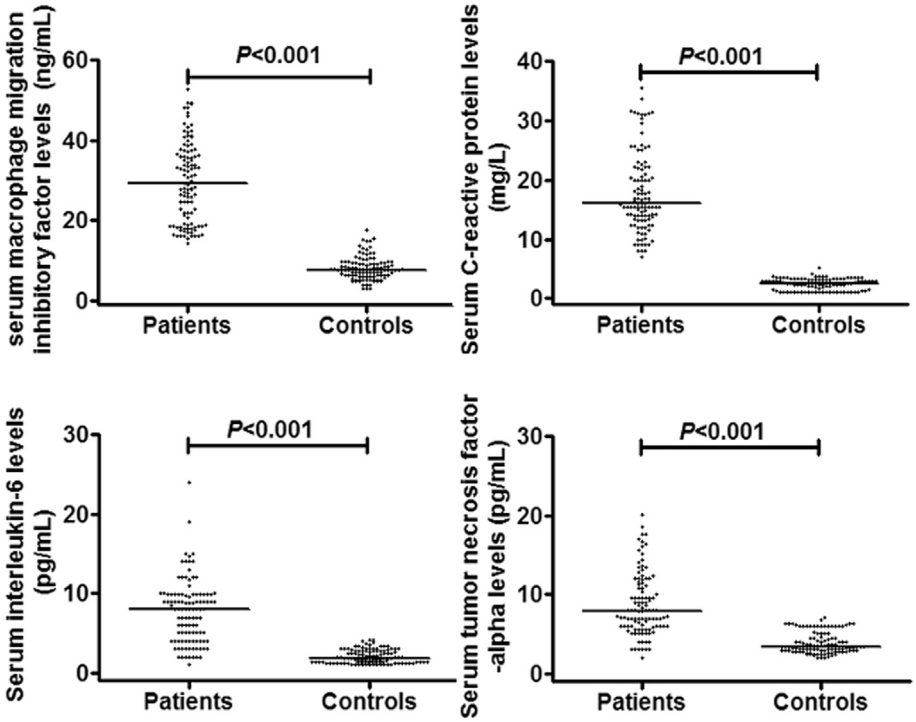


**Fig. 1.** Comparisons of serum macrophage migration inhibitory factor, C-reactive protein, interleukin-6 and tumor necrosis factor-alpha levels between healthy controls and patients with severe traumatic brain injury.

## 2. Methods

### 2.1. Study population

This prospective, observational study only included these patients with isolated head trauma, postresuscitation Glasgow coma scale (GCS) score of ≤ 8 or less, ≥ 2 head computed tomography (CT) scans in the first 72 h and at least 4 head CT scans in the first week after injury at The Hangzhou First People's Hospital during the period of May 2010 and November 2015. Isolated head trauma was defined as CT scan - confirmed brain injury without other major extracranial injuries, such as pelvis or femur fractures, or severe abdominal or thoracic invasive injuries, as indicated by an extracranial abbreviated injury scale score < 3. This study excluded those patients with age of < 18 y, admission time of > 6 h since trauma, recent infection (within a month), previous head trauma, neurological disease including ischemic or hemorrhagic stroke, use of antiplatelet or anticoagulant medication, or other prior systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart or lung disease, diabetes mellitus and hypertension. In addition, a total of 108 gender- and age-matched healthy individuals were recruited as controls. This study was carried out in accordance with the ethical standards of the responsible committee on human experimentation in The Hangzhou First People's Hospital. Written informed consent was obtained from someone responsible for them.

### 2.2. Clinical and radiological assessment

Head trauma severity was evaluated in terms of GCS scores. Abnormal cisterns, midline shift > 5 mm and traumatic subarachnoid hemorrhage were recorded on initial CT scan. CT classification was performed using Traumatic Coma Data Bank criteria on initial CT scan according to Marshall et al. [32]. Diagnosis of PHI and PTCI was made on the follow-up CT scan. PHI was defined as any increase in size or number of the hemorrhagic lesion, including newly developed ones [33]. Diagnosis of PTCI was made according to the following criteria: (1) distinctly hypodense lesions within a defined cerebral vascular territory; (2) hypodense lesions located in boundary zones between the defined cerebral vascular territories or situated in the terminal zones of perforating arteries within the deep white matter [34]. All CT scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information. ALI was diagnosed according to the international consensus criteria, which include acute onset, the ratio of partial pressure of arterial oxygen to fractional inspired oxygen ≤ 300, bilateral infiltrates on chest radiograph, and no clinical evidence of left arterial hypertension [35].

For follow-up, structure telephone interviews were performed by 1 doctor, blinded to clinical information and biomarker concentrations. Participants were followed up until death or completion of 6 months after head trauma. An unfavorable outcome was defined as a Glasgow outcome scale score of 1–3 at 6 month. The end point was unfavorable outcome within 6 months after head trauma.

### 2.3. Immunoassay methods

Venous blood was drawn from patients on admission and from controls at study entry. Coagulation test or blood routine test were completed using the routine laboratory assay. ATC was defined as an activated partial thromboplastic time > 40 s and/or international normalized ratio > 1.2 and/or a platelet count < $120 \times 10^9$/l [36,37]. Serum was obtained by centrifugation at 3000 × *g* and then stored at − 80 °C before measuring. Serum MIF, C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) concentrations were determined with commercially available enzyme-linked immunosorbent assay (ELISA) kits (MIF: R & D Systems; CRP, IL-6 and TNF-α: Cusabio Biotech) according to the manufacturer's protocol. All ELISA determinations were performed in triplicate and the results were averaged. The person carrying out the assays was blinded to the clinical information.