Response to Letter Regarding Article, “Monocyte Count and 30-Day Case Fatality in Intracerebral Hemorrhage”

We appreciate the letter from Hu et al1 on our recent publication.2 Our response addresses 2 points raised in their letter: (1) evidence that infiltrating neutrophils (not monocytes) play a role in intracerebral hemorrhage (ICH)–induced brain injury and (2) their multivariate logistic regression analysis of 321 patients with ICH, which found (contrary to our analysis) that higher total white blood cell and neutrophil counts, but not monocyte count, were independently associated with mortality.

We agree that there is a preponderance of evidence that neutrophils are present in and around the hematoma after ICH. However, we note that neutrophils facilitate monocyte recruitment to the injury site, and recent experiments have found that monocytes were more numerous than other leukocytes at the site of injury early after ICH.1,4 Fewer inflammatory monocytes at the ICH site were associated with improved motor function,4 and reducing monocyte recruitment has been associated with less behavioral disability. Finally, we note that until recently, phagocytic microglia (the first nonneuronal cells to react to brain injury) have been difficult to distinguish from infiltrating monocytes/macrophages.5 Thus, the early evidence for neutrophils may have reflected limitations of cell identification techniques.

The patients enrolled by Hu et al1 (n =321) and in our investigations (n=186 and 240) were similar with regard to age, sex, and time from symptom onset to blood draw. There were obvious racial/ethnic differences, including 100% Chinese in the analysis by Hu et al1 compared with 78% white and 22% black in our first cohort,6 and 37% white, 33% black, and 30% Hispanic in the second.2 In addition, the patients enrolled by Hu et al1 had larger median ICH volume (16.5 mL [interquartile range (IQR), 6.8–36.2] versus 12.8 mL [IQR 4.9–29.4],6 and 9.9 mL [IQR 4.4–26.7]) and lower median Glasgow Coma Scale (11 [IQR, 6–13] versus 14 in both of our publications [IQR, 10 to 15 and 11 to 15]).

To achieve better linearity, ICH volume was log transformed in our regression models. A model without log transformation of ICH volume, particularly with larger hematomas and higher associated white blood cell and neutrophil counts, could result in predominance of those cell types in the model. It was not evident to us whether Hu et al1 transformed variables and what effect that may have on their findings. Furthermore, we note that neutrophils are the primary component of total white blood cells. As such, we posit that the independent association of white blood cells identified by Hu et al1 is driven primarily by neutrophils. Ultimately, sufficient preclinical and now clinical data exist implicating both neutrophils and monocytes as putative mediators of secondary injury after ICH. Additional research is needed to further characterize the role of specific leukocytes in the secondary inflammatory response after ICH.

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Disclosures

None.

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