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The authors reply

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We thank Drs. Weiss and Thabut (1) for their interest in our article on osmotic shifts in hepatic encephalopathy (HE) and appreciate the opportunity to articulate the rationale for aspects of our study methods in greater detail (2).

We share the author's sentiment regarding the utility of CT. MRI is often not practical in acutely ill patients (3). Furthermore, qualitative techniques may be insensitive to disease processes. An analysis of our data that was not incorporated into the publication illustrates this point: qualitative review by neuroradiologists identified signs of cerebral edema in fewer than 10% of the 103 assessment intervals in our study in contrast to the significant findings on quantitative analysis. Optimizing and adapting quantitative CT research techniques for routine clinical use is a promising opportunity for future work.

We agree with the authors that the decision whether to include both acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) in a HE study is complicated given the substantial uncertainties about the exact molecular and cellular pathways involved in HE pathophysiology. For example, the glutamine-osmotic hypothesis referenced by the authors has been challenged by multiple studies, and alternative hypotheses proposed (4). The intention of our study was to explore acute osmotic shifts as a novel mechanism of neurologic deterioration in the severe HE phenotype. Based on that objective, we elected to combine ALF and ACLF cases for several reasons: 1) The International Society for Hepatic Encephalopathy and Nitrogen Metabolism published a consensus statement in which they stated that ACLF should not be excluded from proof-of-concept trials or studies exploring pathophysiologic mechanisms in HE (5); 2) we assessed ALF versus ACLF as a group variable and found it was not associated with our radiographic or clinical endpoints; 3) in

models stratified by type of liver failure (reported in Supplement 5), we confirmed that osmolality change was strongly associated with the radiographic and clinical endpoints for both ALF and ACLF. In fact, the estimated effects of osmolality change were greater in ACLF than ALF, which contradicts the supposition that osmotic compensatory mechanisms are compromised in ALF but not ACLF. Additionally, an alternative interpretation of ammonia in the stratified CSF models is that physicians may have treated hyperammonemia more aggressively in ALF than ACLF because of perceptions regarding the risk of cerebral edema.

While the risk of catastrophic injury or death from brain herniation is lower in ACLF than ALF, we cannot assume that cerebral edema is necessarily unimportant in ACLF or that baseline cerebral atrophy protects patients from mechanisms of brain tissue injury other than direct compression. Moreover, the mechanisms that contribute to chronic cognitive dysfunction in cirrhotic patients, even post-transplantation, are unknown. Analogous to lung tissue injury caused by edema and mechanical stretching in acute respiratory distress syndrome, cerebral edema is a recognized mechanism of brain injury even without herniation, yet little is known about those injurious pathways in HE (6). Serial neurologic assessments and quantitative CT analysis may enable future research to elucidate the pathophysiologic processes of HE with greater sensitivity and precision.

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