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## Reply

**Constantine J. Karvellas, M.D., S.M., F.R.C.P.C.<sup>1</sup>, R. Todd Stravitz, M.D.<sup>2</sup>, Holly Battenhouse, M.Sc.<sup>3</sup>, William M. Lee, M.D.<sup>4</sup>, and Michael L. Schilsky, M.D.<sup>5</sup> for the US Acute Liver Failure Study Group**

<sup>1</sup>Divisions of Hepatology and Critical Care Medicine, University of Alberta, Edmonton, Canada

<sup>2</sup>Division of Gastroenterology and Hepatology, Virginia Commonwealth University, Richmond, VA

<sup>3</sup>Faculty of Medicine, Medical University of South Carolina, Charleston, SC

<sup>4</sup>Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX

<sup>5</sup>Division of Digestive Diseases and Transplant and Immunology, Yale University School of Medicine, New Haven, CT

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## TO THE EDITOR

We applaud the discussion stimulated by our retrospective evaluation of therapeutic hypothermia (TH) in acute liver failure (ALF) published recently in *Liver Transplantation*.<sup>1</sup> In this study of ALF patients from the US Acute Liver Failure Study Group (97 patients received TH; 1135 did not), TH was found to be generally safe (not associated with increased rates of bleeding or infection). In the acetaminophen (APAP) subgroup (TH group, 61; control group, 537), we explored a significant interaction term found in the multivariate model when we were examining the interaction between age and hypothermia in APAP ALF patients (see Table 1). We found that APAP ALF patients under the age of 25 years may potentially benefit from TH [odds ratio (OR) for age of 25 years, 2.735; 95% confidence interval (CI), 1.001–7.467]. In this subgroup, there were 101 patients (TH patients and controls); hence, we concluded that TH may potentially be associated with benefits in patients younger than 26 years with APAP ALF. One potential explanation for this is the lack of cortical atrophy in younger patients with a potentially increased risk of intracranial hypertension in hyperacute liver failure.<sup>2</sup>

Although it is true that our data show a statistically significant deleterious effect on patients older than 63 years old with APAP ALF (OR for age of 64 years, 0.167; 95% CI, 0.028–0.999), there were only 13 patients (TH patients and controls) who were older than 63 years. Because these patients made up only 2.2% of the overall APAP cohort and 1% of the overall cohort, we believe that it is not prudent to draw any significant conclusions on the basis of this subcohort. Although we attempted to account for severity of illness in our logistic

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Address reprint requests to Constantine J. Karvellas, M.D., S.M., F.R.C.P.C., Critical Care and Hepatology, University of Alberta, 1-40 Zeidler Leducor Centre, 8540-112 Street, Edmonton AB, Canada T6G 2X8. Telephone: 780-492-4390; FAX: 780-492-5643; dean.karvellas@ualberta.ca.

regression, we cannot be certain that this small cohort of older APAP patients did not have other medical issues that were not taken into account in this model. This also highlights a flaw in simply plotting the ORs; not all data points are equally weighted.

In summary, in the majority of ALF patients, TH did not have a helpful or harmful effect. This result is consistent with a recently completed European study.<sup>3</sup> For younger APAP patients (n = 101), there was a beneficial effect, and this has physiological plausibility. For the small subset of older patients (n = 13), there may have been a harmful effect from hypothermia, but the pool of subjects was so small that it would be unwise to attribute causality to TH.

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ORs for Interaction Term of Therapeutic Hypothermia at Different Ages (Outcome 21-Day Spontaneous Survival) for 582 Patients With APAP-Induced ALF

TABLE 1

Age (Years)	OR	95% CI
20*	3.913	1.115–13.734
25*	2.735	1.001–7.467
30	1.911	0.862–4.238
38.68 (mean)	1.026	0.528–1.994
40	0.934	0.934
50	0.456	0.163–1.277
60	0.223	0.047–1.059
64 <sup>†</sup>	0.167	0.028–0.999

NOTE: When we adjusted for other confounding factors, younger APAP patients were more likely to spontaneously survive to 21 days when they were treated with TH, and older APAP patients were less likely to spontaneously survive when they were treated with TH.

\* The OR is >1 (protective, does not cross unity) for those 18 to 25 years old (OR for age of 25 years, 2.735; 95% CI, 1.001–7.467).

<sup>†</sup>The OR is <1 (deleterious, does not cross unity) for those more than 64 years old (OR for age of 64 years, 0.167; 95% CI, 0.028–0.999).