# Reply to: "Potential role of ketamine in burn-associated cholestasis"

*To the Editor:*

We thank Dr Meunier and colleagues[1] for their letter pointing out a potential relationship between cholestasis and ketamine infusion, which can be used to maintain sedation and analgesia in critically ill patients with severe burn injury, limiting the need for opioid administration.[2] Nasal, oral and intravenous use of ketamine, especially in drug-abuse patients from Asia, was associated with drug-induced liver injury (DILI), including cholangiopathy, bile duct dilatation and sclerosing cholangitis.[3,4]

On June 20, 2017, the French National Agency for the Safety of Medicines and Health Products (Agence nationale de sécurité du médicament) reported cases of DILI associated with repeated and/or prolonged use of ketamine at high doses in patients with burn injury.[5] These cases involved cholangitis-type diseases in patients repeatedly exposed to ketamine at high doses (more than 100 mg/day), or prolonged use (between 1 month and 5 months of treatment), or during repeated painful procedures (200 to 400 mg/h for 3 to 6 h).

After being alerted that intravenous ketamine could contribute to burn-associated cholestasis (BAC), we decided to restrict its use in our burn unit. We observed in some patients, as did Dr Meunier and colleagues, partial or total regression of cholestasis within months after hospital discharge and ketamine interruption. However, causality is hard to establish in these very sick patients with multiple causes of cholestasis, including infraclinical hepatic ischemia, systemic inflammation, sepsis, and hypercatabolic response.[6,7] We report here our preliminary results.

The sample comprised 344 patients, including 282 (82%) patients before and 62 (18%) patients after our ketamine restriction policy. Median (interquartile range [IQR]) total surface burn area (TBSA) went from 30% [20–45] before, to 35% [25–46] ($p = 0.013$) after the period of ketamine restriction. There was no difference in terms of severity of illness with a median [IQR] Simplified Acute Physiology Score (SAPS) II of 32 [20–46] and 31 [18–43], respectively ($p = 0.497$). The total amount of ketamine infused during the intensive care unit stay dropped from a median [IQR] of 14 g [1.8–50 g] before, to 1.5 g [0.3–3.5 g] ($p < 0.001$) after we introduced the restrictions. A total of 151 (54%) and 33 (53%) ($p = 0.963$) patients developed BAC, as previously defined,[7] during the 2 periods, respectively. Median [IQR] maximum alkaline phosphatase (ALP) levels during intensive care unit stay were 1.7× the upper limit of normal (ULN) [0.9–3.5] and 1.9× the ULN [1.1–2.6] during the 2 periods, respectively ($p = 0.845$). The number of patients with an ALP level ≥10× the ULN decreased after ketamine use restriction from 19 (6.7%) patients to 0 (0%) patients ($p = 0.031$) (Fig. 1).

Altogether, our data suggest that ketamine may contribute to the progression of BAC to the most severe cholangitis-type diseases. Ketamine use restriction did not prevent BAC in our unit but prevented the development of the most severe cases of cholestasis. Ketamine-associated DILI and its relationship with outcome is currently being further explored by our group. We think, as suggested by Dr Meunier and colleagues and French regulations, that ketamine-related liver toxicity should be explored in critically ill patients and its use should probably be restricted in patients with severe burn injury.

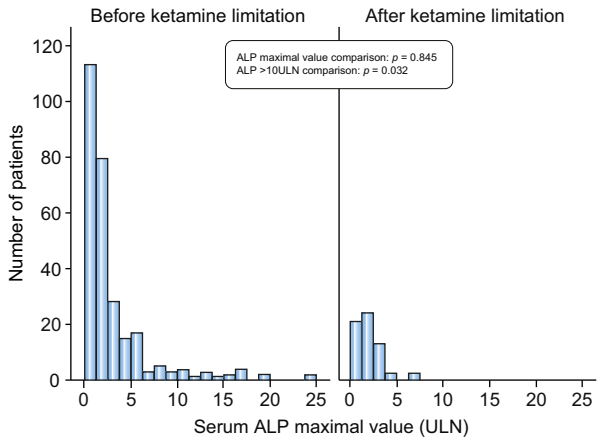


**Fig. 1. Serum ALP maximal value during ICU according to the period of ketamine prescription.** The ALP maximal value comparison was performed with the Mann-Whitney *U* test. The comparison of patients with ALP >10× ULN was performed with the Fisher's exact test. ALP, alkaline phosphatase; ICU, intensive care unit; ULN, upper limit of normal.

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## Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

ML designed the study, analyzed the data, drafted the manuscript and approved the final version. CdT and KH collected the data, analyzed the data, drafted the manuscript and approved the final version. VM and ML designed the study, analyzed the data, drafted the manuscript and approved the final version.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.09.006.

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