

"Predictors of poor outcomes in patients with wild mushroom-induced acute liver injury"

02 January 2017

Dear Editor,

We are grateful for the opportunity to revise our paper and deeply appreciate your generous review about our article. The responses to your comments and the changes made in the manuscript are highlighted in yellow.

Thank you.

Sincerely,

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Reviewer (No. 00011373)'s Comments to Author:

Death rate of the cohort studied of 93 cases of Death rate of the cohort studied of 93 cases of 10.7% is in agreement with findings of studies of similar groups liver transplantation. Authors showed in this study that total bilirubin >5 mg/dL concentration and aPTT >50 sec at day three, correlated with fatal outcomes in patients with wild mushroom induced acute liver injury. These two, could be used as indicators to prescribe liver transplantation. It will be relevant if authors discuss that within the 30 species of most poisonous mushrooms which of them are present in the geographic region of patients

Response:

Thank you for your comment. We have added the sentence in the discussion about poisonous mushrooms in South-Korea.

“Poisoning of toxic mushrooms can be divided into seven main categories: amatoxin, gyromitrin, coprine, muscarine, ibotenic acid-muscimol, psilocybin-psilocin and gastrointestinal irritants.[1, 2] In Korea, the vast majority of toxic mushroom ingestions were the amatoxin -containing mushrooms such as *Amanita abrupta* Peck, *Amanita castanopsidis* Hongo, *Amanita subjunquillea* S. Imai, *Amanita verna* (Bull.) Lam., *Amanita virosa* (Fr.) Bertill., *Conocybe filaris* (Fr.) Kühner, *Galerina calyptrata* P.D. Orton, *Galerina helvoliceps* (Berk. & M.A. Curtis) Singer.[2, 3] “

1 Jo W-S, Hossain M, Park S-C. Toxicological profiles of poisonous, edible, and medicinal mushrooms. *Mycobiology* 2014; 42(3): 215-220

2 Sohn CH. Type and treatment of toxic mushroom poisoning in Korea. *Journal of the Korean Medical Association* 2015; 58(9): 818-824

3 Seok S, Kim Y, Kim W, Suh J, Jeong M, Lim K, Sohn C, Lee Y. *Encyclopedia of poisonous mushrooms*. 2011

Reviewer (No. 00503536)'s Comments to Author:

The manuscript written by Kim et al. analyzed the possible predictors of poor outcomes in patients with mushroom-induced acute liver injury. They found that all patients with total bilirubin >5 mg/dL or aPTT >50 sec on day 3 died and those could be the good predictors. The data are important because patients with poor predictors of outcomes could be the candidate for liver transplantation. However, there are some concerns that need to be addressed. Major points 1. It is unclear why only aPTT but not PT is the predictor for poor outcome of the patients. Although the authors discuss on that point, more descriptions including the mechanism for elevated aPTT in those patients are needed. Moreover, the statistical analysis should be re-considered. 2. Only total bilirubin levels are analyzed, but the ratio of indirect bilirubin /direct bilirubin could be another possible predictors.

Response:

Thank you for your comment. We totally agree with your concern about the mechanism for elevated aPTT is unclear. However, a recent study shows that aPTT reflects failure of coagulation as a multi-organ dysfunction in critically ill patients with acute liver injuries and acute liver failure better than INR. Stravitz et al. noted monitoring the reaction time by thromboelastography or the aPTT might be more appropriate to assess bleeding risks in patients with ALI and ALF than the INR. [1] We have added this sentence in the discussion.

1 Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, Ibrahim A, Lee WM, Sanyal AJ. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. J Hepatol 2012; 56: 129-136 [PMID: 21703173 DOI: 10.1016/j.jhep.2011.04.]

We have analyzed ratio of indirect/direct bilirubin. As you pointed out, indirect/direct bilirubin (2.45 ± 1.39 vs. 0.99 ± 0.45 , $p < 0.01$) ratio was also significantly higher in non-survivors than in survivors. Logistic regression analysis showed that indirect/direct bilirubin ratio (OR: 0.14, 95% CI: 0.02-0.94) was significantly associated with mortality. We added these results in the abstract and results.