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Editorial

Early prediction of encephalopathy in hospitalized patients with severe acute liver disease: The narrow window of opportunity for transplant-free survival ☆

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Transplant-free survival, clearly the most suitable outcome for any patient hospitalized (inpatient) with a life-threatening acute liver disease (ALD), is unfortunately uncommon among inpatients with acute liver failure (ALF) not due to poisoning (paracetamol, mushroom poisoning) (non-P) (non-P ALF). Despite some recent improvements, transplant-free survival rates of these patients, who were often in a good condition before the onset of the causal ALD, remain low: 21% [1] to 39% [2] in those with grade 3–4 hepatic encephalopathy (HE), and 28% [3] to 67% [2] in those with grade 1–2 HE at admission to the liver unit. Even when IV *N*-acetylcysteine (NAC) is given to patients with ALF not due to paracetamol with grade 1–2 HE the survival rate increases significantly, but not above 52% [4]. In fact, the transplant-free survival rate remains above 80% only when, at admission to the liver unit, inpatients with non-P ALD present with severe coagulopathy but without HE [5], a condition often referred to as "severe ALD", "severe acute hepatitis" or "severe hepatic insufficiency" [6]. The survival rate of such patients still remains >80% even when patients at very low lethal risk such as those with acute hepatitis type A, are not considered [5].

These five previous studies [1–5] indicate that preservation of transplant-free survival of inpatients with non-P ALD is closely related to the ability to recognize early, during an often narrow window of opportunity [7], those at increased risk of short-term development of HE. As in Elinav's study [5], it is therefore logical to raise the question: "How to predict the short-term occurrence of HE in patients with ALD early enough in the course of the disease?". Among the three previously published studies attempting to answer this question [5,8,9], the only prospective one was restricted to patients with paracetamol overdose [8]. In this issue of the Journal, Takikawa and coworkers, from Japan, report the results of a 13-year prospective study that aimed to predict HE for inpatients with non-P ALD [10]: (a) HE was predicted with 100% sensitivity and 69% specificity, or 62% sensitivity and 93% specificity, when taking cut-off values of HE-developing probability >20% or >50%, respectively; (b) the HE-predictive model included four of the five variables used in the King's College criteria (KCC) established to determine short-term fatality rate >80% in British patients with non-P ALF [11], namely patient's age, the cause of ALD, serum total bilirubin and prothrombin (PT) ratio (% of control); (c) finally, HE was predicted from 1 to 25 days prior to its onset and half the inpatients with HE were admitted to the liver unit more than 5 days before its onset.

Several features support the credibility of the model developed by Takikawa et al. First, important methodological requirements for this type of study [11] were

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Abbreviations: ALD, acute liver disease; ALF, acute liver failure; non-P, not due to poisoning; HE, hepatic encephalopathy; IV, intravenous; NAC, *N*-acetylcysteine; KCC, King's College criteria; PT, prothrombin; LT, liver transplantation.

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fulfilled. Three independent, consecutive groups of symptomatic ALD inpatients, all without HE, were evaluated: the first group allowed to establish the criteria (PT ratio ⩽80% of control) for registration in the two others, the second group gave rise to the development of the HE-prediction model, and the third group was used to validate this model. Second, the emergence in the HE-prediction model of four of the five variables used in the KCC [11] is the cornerstone of the model. Since KCC are used worldwide as criteria for liver transplantation (LT) in ALF patients, as initially proposed [11], they are universally regarded as robust criteria of life-threatening liver dysfunction [12] and it makes sense that a set of four among their five variables was found prospectively to predict HE for non-P ALD inpatients. Third, the current study confirms a previous one [13] in which the authors found similar results, but with lower sensitivity and specificity of the model than those reported in this study [10].

The main value of Takikawa's current study is the demonstration that the difficult task of predicting short-term occurrence of HE for inpatients with severe non-P ALD is feasible, even with an annual incidence of two HE cases (validation group) [10]. The authors acknowledge that their results require country-specific studies in order to be validated outside Japan. We support this view and think that hepatologists now have an ethical duty to perform such prospective protracted studies: a population-based surveillance study yielded a 3.3 per million annual incidence of ALF not due to paracetamol in the United States in 2001–2004 [14] and, in their validation group, Takikawa et al. reported a 6.5% HE prevalence, 8/124 inpatients over 4 years. Although seven of these eight inpatients died, future prospective studies would be beneficial because they would help both to reduce the unacceptably high prevalence of patients admitted to the liver unit with grade 3–4 HE, 27% [3] to 81% [2], and to increase low transplant-free survival rates [1–3]. Early detection of inpatients with HE-threatened ALD and their early transfer to a liver unit, ideally close to LT facilities, will not only enable to correct possible aggravating cofactors in some patients [15], but also to try to protect the still undestroyed liver tissue with drug(s) therapy delivered over a sufficient period of time. Since early IV NAC infusion improved significantly transplant-free survival of non-acetaminophen ALF patients admitted to liver unit with grade 1–2 HE [4], it may be anticipated that IV NAC infusion will be at least as effective in patients without HE. Other drugs, some of them risky in patients with altered liver function, may be potentially liver- or life-saving if administered as early as possible to severe non-P ALD inpatients without HE: antiviral therapy in acute flare-up of type B hepatitis [16] (protocolized in Takikawa's study), IV acyclovir in patients with ALD due to necrotizing herpesviruses [17,18], D-penicillamine in uncommon cases of rapidly progressing acute forms of Wilson's disease [6] and heparin-based anticoagulation in patients with acute forms of Budd–Chiari syndrome [19]. Corticosteroids, recommended in patients with severe acute auto-immune hepatitis without HE [20], may be associated with a high risk of sepsis [21]. It could be argued that all these treatments could be initiated and supervised in medical wards other than liver units and the patients could be transferred to these units only when further deterioration of liver function is observed. We disagree with this wait-and-see strategy which, too often, ends with admission to the liver unit of aggravated ALD inpatients with established HE. Moreover, when the patient's condition deteriorates after a few days despite medical management in liver unit, LT may be considered in parallel to the unfavourable course and will be more easily decided, as reported in patients with *Amanita phalloides* poisoning [22].

Considering results when cut-off value of HE-developing probability is 50%, the HE-predicting model by Takikawa et al. has intrinsic drawbacks despite 91% accuracy. Half the patients in the validation group were admitted to the liver unit less than 5 days before HE, an interval sometimes too short to obtain the full efficacy of some drugs used to support the acutely injured liver. Moreover, although maximal sensitivity should be privileged to reduce the rate of admissions to the liver unit after the onset of HE [13], the sensitivity of the model was only 62%. Several ways for improving sensitivity are to be considered. Whereas the HE-model was based on a single determination of the PT ratio (% of control), its decrease over time might be demonstrated by serial dosages (even several times a day) as reported for individual coagulation factors [5]. Although the interval between the onset of jaundice and HE exceeding 7 days in patients with non-P ALF has a pejorative prognostic value [11], it remains to be demonstrated whether time duration of jaundice at evaluation, together with persistently decreased PT ratio, might be associated with increased risk of HE in patients with non-P ALD. Finally, decreasing the cut-off value from 50% to 20% increases the sensitivity up to 100%, but reduces specificity to 69% (Fig. 4 in [10]). However, the use of the model may be modulated according to the accepted risk of overtransfer to liver units of some patients who will recover without HE. The extra cost of such overtransfers should be well compensated by the avoidance of deaths or life-saving LTs in other patients.

Despite the above criticisms, several data contained in Takikawa's study should allow to improve the indications for urgent transfer of non-P ALD inpatients to a liver unit. Age >50 years and unfavourable etiologies (Fig. 2 in [10]) are are clearly related to an increased risk of short-term occurrence of HE in the Japanese inpatients. Initial PT ratio was <50% in 7/8 non-P ALD Japanese inpatients who developed HE (Fig. 5 in [10]) and, thus, could be set as a discriminatory level below which high