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Hepatorenal syndrome, MELD score and liver transplantation: An evolving issue with relevant implications for clinical practice

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Summary

Hepatorenal syndrome (HRS) is a severe complication of cirrhosis that is associated with poor survival. A rapid diagnosis of HRS and a prompt initiation of the treatment with terlipressin and albumin are mandatory because this leads to an improvement of prognosis.

This review covers the predictive value of HRS on 3-month mortality beyond the MELD score and its consequential impact on the prioritization policy to liver transplantation (LT). Moreover, it analyzes the impact of the response to pharmacological treatment on the MELD score, its possible delaying effect on the timing of LT, and suggests a way of overcoming the paradoxical effect of terlipressin and albumin on the priority to LT in responders.

Finally, the review discusses the appropriate use of combined liver–kidney transplantation (CLKT) in patients with HRS who do not respond to treatment with terlipressin and albumin.

Introduction

Hepatorenal syndrome (HRS) is a functional renal failure that often occurs in patients with cirrhosis and ascites [1–3]. HRS develops as a consequence of a severe reduction of effective circulating volume due to both extreme splanchnic arterial vasodilatation and a reduction of cardiac output. There are two different types of HRS. Type 1 HRS, which is often precipitated by a bacterial infection, especially spontaneous bacterial peritonitis, is characterized by a rapidly progressive impairment of renal function. Despite its functional origin, the prognosis of type 1 HRS is very poor. Type 2 HRS is characterized by a stable or slowly progressive renal failure so that its main clinical consequence is not acute renal failure, but refractory ascites and its impact on prognosis is less negative [1–3]. New types of treatment such as vasoconstrictors plus albumin [4–7], transjugular porto-systemic shunt [8], and the molecular adsorbent recirculating system [9], which were introduced in the past 10 years, are effective in improving renal function in patients with HRS. In particular, treatment with terlipressin plus albumin, which can also improve survival in patients with HRS, has brought about a change in attitude towards the management of this severe complication in patients with advanced cirrhosis [10–12]. The effects on survival are strongly related to the amelioration of renal function as a result of this treatment [10,11]. Consequently, survival is significantly longer in responders compared with non-responders. The non-response to treatment with terlipressin and albumin can be predicted by: (a) a high baseline value of total serum bilirubin [14], (b) a high baseline value of serum creatinine [15], and (c) a low response to treatment in terms of mean arterial pressure [14]. The finding of a predictive role for baseline serum creatinine provides an important clinical concept in order to optimize the results of the treatment: the early treatment of type 1 HRS with terlipressin and albumin enhances the chances of response. Translated into clinical practice, this means that the diagnosis of type 1 HRS should be performed within a short time frame, ideally 24–48 h, following the currently accepted guidelines [13], and treatment with terlipressin and albumin should be started as soon as the diagnosis is made [16]. Further incoming controlled clinical trials comparing terlipressin given by intravenous boluses, with terlipressin administered by continuous intravenous infusion, will provide additional information on another possible way of improving the efficacy of this treatment [17]. Secondly, the combination of pharmacological therapy with non-pharmacological therapies should be investigated, particularly in severe cases that have a low probability of response to pharmacological therapy alone. In this regard, a recent study showed that the combination of terlipressin and albumin and an extracorporeal liver support system using fractionated plasma separation and adsorption may improve survival in patients with type 1 HRS [18]. However, since this observation was made with a subanalysis of a larger study,

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Abbreviations: HRS, hepatorenal syndrome; RRT, renal replacement therapy; ARF, acute renal failure; CKD, chronic kidney dysfunction; NGAL, neutrophil gelatinase-associated lipocalin; MDRD, modification of diet in renal disease; CLKT, combined liver–kidney transplantation.

specific studies assessing this strategy in a specific population of patients with type 1 HRS should be performed. Meanwhile, liver transplantation (LT) is considered the treatment of choice for patients with cirrhosis and HRS because it "allows for both the liver disease and associated renal failure to be cured". In the perspective of LT in patients with HRS, some observations should be made on whether to consider differently the positions of responders *vs.* non-responders to pharmacological treatment of HRS.

The risk of 3-month mortality in patients with HRS and the MELD score

The MELD score incorporates three simple laboratory parameters (serum creatinine, bilirubin, and international normalized ratio for prothrombin time) and stratifies patients according to the severity of the disease in an objective and continuous ranking scale. The MELD-based liver graft allocation policy has led to a reduction in new registrations to waiting lists and mortality, to shorter waiting times, and to an increase in transplants, without altering overall graft and patient survival rates after transplantation. The MELD score succeeds in defining the 3-month death risk of patients with non-malignant end stage liver disease. It has proved to be a reliable tool for prioritizing these patients in the LT waiting list and it has contributed to optimize the allocation of grafts according to a "sickest first" policy [19]. Nevertheless, there are conditions that are not properly considered by the MELD score, either because they are not sufficiently "perceived" and weighted by the variables included in the score, or because their short-term risk is progression beyond the limit of transplant suitability, rather than death [20–22]. HRS can be included in the first category of such conditions. In actual fact, it has been observed that patients with HRS have worse survival expectancy than other populations of patients with cirrhosis with an equal MELD score. Indeed, for any given value of MELD or MELD-Na score, patients with HRS had shorter survival expectancy than patients with chronic liver disease who were candidates for LT [23]. More recently, it has been observed that not only MELD score and serum sodium concentration, but also the presence of hepatic encephalopathy and the phenotype of renal failure are associated with 3-month survival [24]. Specifically, concerning the cause of renal failure, it has been observed that patients with hypovolemia-related renal failure, and generally patients with HRS, have a much worse prognosis than patients with renal failure due to parenchymal nephropathy. This means that the same abnormal value of serum creatinine may correspond to a different clinical outcome, depending on the cause of renal impairment. Thus, a patient with HRS should receive a priority to LT that is not based only on the MELD score, but that also takes into account HRS, as it is the poorest predictor of 3-month survival among the different causes of renal failure in cirrhosis. This is not provided by the policy of "exceptions to the MELD score" that are currently used in several Western countries such as Italy [20], France [21], and the US [22]. According to what has been recently suggested as essential to justify any proposal for an "exception to MELD", here we are dealing with a problem of mortality and not only of quality of life. Evidence-based data can be used to substantiate our proposal, to give additional priority to patients with HRS, making sure the subjective elements are removed or at least minimized, and keeping the system of transplant allocation fair and transparent [25].

Response to terlipressin and albumin and MELD score: implications for LT

Improvement of renal function by means of terlipressin and albumin has been defined either as a reduction of serum creatinine below 133 μmol/L at the end of treatment (complete response) or as a reduction in serum creatinine greater than 50% of the pre-treatment value but with an end-of-treatment value equal to or greater than 133 μmol/L (partial response) [10,26]. As previously reported, in patients with type 1 HRS responding to treatment with terlipressin and albumin, the survival rate improved [10,11]. Moreover, the treatment almost normalized the outcome after LT in terms of survival, rate of renal failure, and need for renal replacement therapy (RRT) after LT [27]. Nevertheless, with the MELD score-based allocation system, these patients may not get the priority to LT they need. This risk is not only related to the limitations of MELD or MELD-Na scores in predicting the 3-month mortality in patients with type 1 HRS, but also to the effect of treatment on specific components of the MELD (serum creatinine) and MELD-Na (serum creatinine and serum sodium concentration) scores. It has been clearly shown that treatment with terlipressin and albumin reduces the MELD score and negatively affects the position of patients on the waiting list. It also points to the fact that this problem cannot be solved by considering the MELD-Na score, since hyponatremia is also improved by the treatment. The extreme example of this paradoxical situation is represented by patients with continuous recurrence of type 1 HRS, which require long-term treatment with terlipressin and albumin [28,29]. These patients probably have the highest priority to LT, but are at risk of remaining on the waiting list for months simply because their MELD and MELD-Na scores are reduced by the treatment. For this reason, we put forward a proposal to resolve this paradoxical situation by highlighting two different clinical scenarios: (a) the patient who responds to terlipressin and albumin and then maintains an adequate renal function, (b) the patient with continuous recurrence of type 1 HRS who, therefore, requires a continuous treatment of type 1 HRS. For reasons of clarity, we define continuous recurrence of type 1 HRS as a relapse of type 1 HRS more than once within 72 h after treatment discontinuation [29]. Since it has been stated that 14 days is the maximum time required to treat an episode of type 1 HRS in partial responders [2], we consider the administration of terlipressin and albumin for more than 30 days as a "long term" treatment, because it covers more than two subsequent episodes of type 1 HRS. In the first patient, we proposed to use the baseline MELD or MELD-Na score for the definition of priority in the waiting list to LT. This is basically the score calculated with the highest serum creatinine value and the lowest value of serum sodium concentration just before starting treatment with terlipressin and albumin, without taking into account the subsequent effects of treatment on these values. It could be argued that this proposal does not take into consideration that among the responders there are patients with a survival longer than 6 months. However, survival at 3 months in responders was about 60%, a value which was lower than the one predicted by their baseline MELD score [30]. In the second patient, we propose to include treatment with

terlipressin and albumin in the calculation of MELD score, as it is already provided for RRT. This differential proposal moves from the observation that, although to date the prognostic impact of continuous recurrence of type 1 HRS has never been evaluated, it is not unreasonable to speculate that it is even worse than that related to a single episode of HRS. This is why we want to ensure the patient with continuous recurrence of type 1 HRS, the highest possible impact of serum creatinine on their MELD or MELD-Na score. We think that this approach addresses and solves the problem of the priority to LT in responders to pharmacological treatment of type 1 HRS, enabling us to go ahead along the road of objectivity and transparency with respect to the policy of allocating organs, which has begun with the introduction of MELD. The proposed exceptions to the MELD score would prevent unequal treatment in these patients from nation to nation, between different transplant centers in the same country and between different patients belonging to the same center, which often occurs when the decision-making process is entrusted to a gentleman's agreement between different transplant centers, or by a case discussion within the same center. Of course, we realize that the applicability of our proposal has some limitations. Particularly, in relation to our first patient, it requires a system of organ allocation based on a timely update of the MELD score as it happens in the US, Italy, and Spain. On the contrary, where the MELD updating is mandatory on a monthly basis as in Euro Transplant, or on a quarterly basis as in France, our proposal is likely to be unnecessary, since these time periods assure a reasonable chance to this patient to be transplanted on time despite creatinine improvement. Concerning our second patient, we realized that in some countries, patients with type 1 HRS do not receive pharmacological treatment and are placed on RRT, therefore receiving *de facto* a higher priority to LT. Nevertheless, we are confident that the growing need of a timely update of the priorities on waiting list in the sickest patients on the one hand, and the progressive spread of the pharmacological therapy for HRS on the other hand, gradually will give more meaning and relevance to our proposal.

At this point someone may wonder: what about patients with type 2 HRS? We realize that the severity of prognosis is not fully expressed by the MELD score of patients with type 2 HRS either [24]. Nevertheless, the discussion of allocation priorities to LT for these patients according to their response to treatment with terlipressin and albumin is a very difficult task, due to the following reasons: (a) the prognostic value of HRS is quite different in patients with type 1 and type 2 HRS, (b) there are currently insufficient data on the impact of terlipressin and albumin on clinical outcomes in patients with type 2 HRS [24]. Nevertheless, taking into account that a percent of patients and type 2 HRS, mainly those with a serum creatinine >2 mg/dl [24,31], are treated with terlipressin and albumin in clinical practice, we suggest to maintain the baseline MELD or MELD-Na score in the allocation of priority to LT in those who will respond to treatment. The rate of recurrence of type 2 HRS after treatment discontinuation is high [31]. The recurrence can meet the criteria of type 2 as well as type 1 HRS in these patients [31]. It is far from our intentions to suggest that the repeated recurrence of type 2 HRS after discontinuation of pharmacological treatment could imply the necessity of giving an equal value to treatment with terlipressin and albumin and to RRT in the calculation of MELD score. However, we think that a further option to assure a priority to be transplanted within 3 months seems acceptable for patients with type 2 HRS in case of continuous recurrence of type 2 HRS after the treatment discontinuation. We propose either to consider their highest MELD or MELD-Na score over time or to add some extra points to their highest MELD score over time deriving them from a specific prognostic formula for the estimation of 3-month mortality which was proposed for patients with HRS [24].

Non-response to treatment with terlipressin and albumin: implications for LT

In the perspective of LT, the main problem in non-responders to terlipressin and albumin is not to assure them the right priority to LT, being their baseline MELD and MELD-Na unaffected by treatment, but rather to obtain the best result in terms of survival and recovery of renal function after LT and to avoid futility. In patients with type 1 HRS, a progressive increase in the urinary excretion of biomarkers of tubular damage, among which γ-glutamyltranspeptidase (Fig. 1), was observed in non-responders to vasoconstrictors and albumin [5]. This preliminary observation suggests the possibility that a progression from type 1 HRS to acute tubular necrosis can occur in these patients. If this observation is confirmed by clinical studies based on renal biopsies or new biomarkers of renal tubular damage, it will certainly have relevant consequences in the perspective of LT [32], since we are potentially moving from a phenotype of ARF, which can be completely reversed by LT alone, to a phenotype of ARF, which cannot recover after LT alone. In only one study, comparing the impact of LT between responders and non-responders to terlipressin and albumin, it has been observed that LT offered a clear 6-month survival benefit to patients with HRS-1, regardless of the therapy they received for HRS and whether or not they achieved HRS reversal before LT [29]. In relation to the recovery of renal function after LT, in one recent retrospective study, the HRS treatment with midodrine plus octreotide and albumin was not associated with an additional benefit on glomerular filtration rate after LT [33]. Nevertheless, nowadays most of the data we can discuss on this specific topic are related to observations made in patients with type 1 HRS who did not receive treatment with vasoconstrictors and albumin. These data indicate that the percentage of patients who will recover renal function after LT ranges from 58% to 94% [34,35]. Several factors may contribute

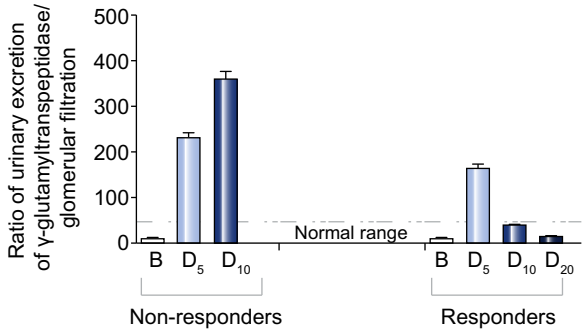

Fig. 1. Dynamic behavior of the ratio of urinary excretion of γ-glutamyltranspeptidase to glomerular filtration rate in patients with type 1 HRS according to the response to pharmacological treatment. Data from Ref. [5]. B, baseline; D, day after the initiation of treatment; the area under the dotted line represents the normal range for this parameter in our laboratory. No response was defined by a decrease in pretreatment peak serum creatinine less than 50%.

Table 1. UNOS recommendations for combined liver–kidney transplantation (CLKT) in 2006 [36] and 2007 [37].

UNOS recommendations in 2006	UNOS recommendations in 2007
Patients with CKD a measured CrCl [or preferentially an iothalamate clearance] of ≤30 ml/min	Patients with ESRD
Patients with AKI and/or HRS on dialysis for ≥6 wk. CLKT was not recommended in patients with AKI not requiring dialysis	Patients with CKD with GFR ≤30 ml/min
Patients with prolonged AKI with kidney biopsy showing fixed renal damage	Patients with AKI including HRS with creatinine ≥2 mg/dl and dialysis ≥8 wk
	Patients with evidence of CKD and kidney biopsy demonstrating >30% glomerulosclerosis or 30% fibrosis

CKD, chronic kidney disease; CrCl, creatinine clearance; ESRD, End Stage Renal disease; AKI, acute kidney injury; HRS, hepatorenal syndrome.

to the persistence of an impairment of renal function after LT, such as intraoperative factors and postoperative factors, which include overall calcineurin inhibitors used for immunosuppression after LT. Nevertheless, in 2006, Marik *et al.* showed that HRS resolved in 16 out of 28 patients after LT, when the mean duration of HRS prior to LT was <6 weeks [34]. In 2009, Xu *et al.* showed that when the mean interval between the onset of type 1 HRS and LT was <4 weeks, HRS resolved in 30 out of 32 patients, with eight patients dying during the first month after LT, and eight patients receiving post-LT RRT [35]. Although these observations are not specifically coming from non-responders to treatment with terlipressin and albumin, they suggest that if the time elapsed between the onset of type 1 HRS and LT is within 4 and 6 weeks, ARF is resolved in many of the patients by LT alone, regardless of whether or not they needed RRT in the pre-transplant setting. Consequently, while we await further studies on the new biomarkers of renal damage, the time between the onset of type 1 HRS and LT and the severity of renal impairment are the only criteria we can use in the decision-making process on whether to perform LT alone or combined liver–kidney transplantation (CLKT) in non-responders to terlipressin and albumin. For these reasons, it was considered appropriate to move from the first two sets of recommendations for CLKT in 2006 [36] (Table 1) and 2007 [37] respectively, to the current ones which were introduced in 2009 [38]. In the most recent recommendations (Table 2), two criteria can be considered as being tailored to patients with type 1 HRS who are non-responders to terlipressin and albumin: (a) sustained ARF requiring dialysis for 6 weeks or more (defined as dialysis at least twice a week for 6 consecutive weeks) or (b) sustained ARF not requiring dialysis with a GFR ⩽25 ml/min for 6 weeks or more measured at least once a week by MDRD6 formula or directly by means of inulin or other markers [36]. Based on the current limited knowledge on the evolution of type 1 HRS in non-responders to terlipressin and albumin, this seems to be a good balance between the need to avoid the development of CKD after LT in these patients on the one hand, and, the requests for CLKT, which have been already expanded in the MELD era, on the other hand.

ment may improve LT rates and post-LT outcomes in transplant candidates with type 1 HRS. Nevertheless, in order to optimize the results of pharmacological treatment, responders should receive the right priority in the waiting list, taking into account not only the specific value of HRS *per se* on 3-month mortality beyond the MELD score, but also considering that the effect of terlipressin and albumin in lowering serum creatinine can reduce the baseline MELD score in these patients and therefore delay the timing of LT. The paradoxical effect of treatment in patients with type 1 HRS who respond to terlipressin and albumin can be avoided either by continuing to consider the baseline MELD, or by considering the pharmacological treatment of HRS as dialysis, in the calculation of the MELD score (key points).

Key Points

- In order to optimize the results of the pharmacological treatment of HRS, responders should receive the right priority in the waiting list, taking into account not only the specific value of HRS *per se* on three-month mortality beyond the MELD score, but also considering that the pharmacological treatment of HRS can reduce the baseline MELD score in these patients
- The paradoxical effect of treatment in patients with type 1 HRS who respond to terlipressin and albumin can be avoided either by continuing to consider the baseline MELD, or, in case of continuous recurrence of HRS by considering the pharmacological treatment of HRS as dialysis in the calculation of the MELD score
- The baseline MELD should be maintained also in patients with severe type 2 HRS who responded to the pharmacological treatment. A further option to assure a priority should be given to patients with type 2 HRS in case of repeated recurrences of HRS after the discontinuation of the treatment, taking into account their highest MELD-Na score over time
- The applicability of these proposals has some limitations, particularly in relation to the variability of the allocation systems worldwide

Conclusions

HRS is an extremely severe complication of cirrhosis, with a deep negative impact on prognosis in patients who are not treated with terlipressin and albumin, or in patients who do not respond to this pharmacological therapy. A prompt diagnosis and treatment may improve LT rates and post-LT outcomes in transplant candidates with type 1 HRS. Nevertheless, in order to optimize the results of pharmacological treatment, responders should receive the right priority in the waiting list, taking into account not only the specific value of HRS *per se* on 3-month mortality beyond the MELD score, but also considering that the effect of terlipressin and albumin in lowering serum creatinine can reduce the baseline MELD score in these patients and therefore delay the timing of LT. The paradoxical effect of treatment in patients with type 1 HRS who respond to terlipressin and albumin can be avoided either by continuing to consider the baseline MELD, or by considering the pharmacological treatment of HRS as dialysis, in the calculation of the MELD score (key points).

With regard to non-responders to the pharmacological treatment, some data show a possible evolution of ARF from the HRS phenotype to an ATN phenotype with a consequential loss of the potential reversibility of ARF after LT alone. While waiting

Table 2. Current UNOS recommendations for combined liver–kidney transplantation (CLKT) [38].

a) CKD requiring dialysis
b) CKD not requiring dialysis: documentation of both GFR ≤30 ml/min [by MDRD6 or iothalamate measurement] and proteinuria [>3 g protein per day with 24 h protein measurement or urine protein/creatinine ratio >3] is required
c) Sustained AKI requiring dialysis: documentation of dialysis for 6 wk or more [defined as dialysis at least twice a week for 6 consecutive weeks] is required
d) Sustained AKI not requiring dialysis: documentation of a GFR ≤25 ml/min for 6 wk or more by MDRD6 or direct measurement [iothalamate or iohexol] is required at least once a week
e) Sustained AKI: patients may also qualify for CLKT listing with a combination of time in categories (c) and (d) above for a total of 6 wk
f) Metabolic disease

CKD, chronic kidney disease; GFR, glomerular filtration rate; MDRD6, modification of diet in renal disease formula 6; AKI, acute kidney injury.

for further confirmation of these data, the current indications to CKLD elaborated by the International transplant community seem to represent a good balance in order to avoid development of CKD after LT in these patients, without further increasing the requirements for CLKT.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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