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REVIEW ARTICLE

Model for end-stage liver disease score and MELD exceptions: 15 years later

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Abstract The model for end-stage liver disease (MELD) score has been used as an objective scale of disease severity for management of patients with end-stage liver disease; it currently serves as the basis of an urgency-based organ-allocation policy in several countries. Implementation of the MELD score led to a reduction in waiting-list registration and waiting-list mortality and an increase in the number of deceased-donor transplants without adversely affecting long-term outcomes after liver transplantation (LT). The MELD score has been used for management of non-transplant patients with chronic liver disease. MELD exceptions serve as a mechanism to advance the needs of subsets of patients with liver disease not adequately addressed by MELD-based organ allocation. Several models have been proposed to refine and improve the MELD score as the environment within which it operates continues to evolve toward transplantation for sicker patients. The MELD score continues to serve and be used as a template to improve upon as an objective gauge of disease severity and as a metric enabling optimization of allocation of scarce donor organs for LT.

Keywords Organ allocation · Prognosis · Survival · Hepatopulmonary syndrome · Portopulmonary hypertension · Asia

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Abbreviations

LT	Liver transplantation
MELD	Model for end-stage liver disease
INR	International normalized ratio
HCC	Hepatocellular carcinoma
HCV	Chronic viral hepatitis C
TIPS	Transjugular intrahepatic portosystemic shunt
c statistic	Concordance statistic
CTP	Child–Turcotte–Pugh

Introduction

Fifteen years ago, the model for end-stage liver disease (MELD) score was proposed as an objective measure of short-term mortality among cirrhotics undergoing transjugular intrahepatic portosystemic shunt (TIPS) placement [1]. Subsequently, the MELD score was rapidly accepted into the common vernacular of physicians worldwide for assessment of liver disease. In addition, in several countries, it has been adopted as a marker of medical urgency, leading to its current use for organ allocation. This review addresses development of the MELD score, its current applications and shortcomings, and proposed modifications. "MELD exceptions" as they pertain to organ allocation are also discussed.

Development of the MELD score

In the early 1990s in the United States, livers were allocated on the basis of a combination of blood type, time on the liver transplantation (LT) waiting list, and location of the patient (intensive-care unit, hospital, or outpatient),

which served as a surrogate for disease severity. Given that intensive-care-unit placement was subjective, a new system incorporating the Child–Turcotte–Pugh (CTP) score as an index of liver disease severity and prognosis was introduced in 1998. Elements of the CTP score, namely ascites and encephalopathy, were fallible to subjective assessment and affected by extraneous factors (e.g. diuretics). Other disadvantages included ceiling effects for variables (e.g. bilirubin and albumin) necessitating time on the waiting list as a common tiebreaker. In studies that correlated waiting time and risk of mortality, waiting time was a poor metric for disease severity [2]. CTP components also lacked statistical validity (e.g., equal weights for all elements, for example hyperbilirubinemia versus grade II hepatic encephalopathy). Under the system, waiting-list mortality and waiting time continued to increase [3–5] and a more equitable and efficient system that reduced the emphasis on waiting time and set allocation priorities on the basis of the severity of the liver disease and the risk of mortality was desired [6].

In this context, the MELD score, a mathematical model based on serum creatinine, bilirubin, and INR was proposed to aid organ allocation. The MELD score, originally developed to predict survival after TIPS, was validated as a predictor of survival among cirrhotics awaiting LT [1, 7]. In a prospective investigation, MELD was an excellent predictor of three-month waiting-list mortality with a *c*-statistic of 0.83, implying that 83 % of the time the model correctly predicted for a pair of cirrhotics that the patient with the higher MELD score had higher short-term mortality and hence was more likely to benefit from early LT [8]. Incorporation of the etiology of liver disease and individual complications of portal hypertension did not provide further prognostic information [7, 8]. Several changes were introduced to the score when used for organ allocation, including lower bounds for serum creatinine and bilirubin, an international normalized ratio (INR) fixed at 1, to avoid negative scores, and an upper bound of serum creatinine fixed at 4 mg/dL, including for patients on hemodialysis [9].

Impact of the MELD score

In the US, the MELD score was used for organ allocation beginning in February 2002. The initial effect was a reduction in waiting-list registration (12 %), a reduction in death on the waiting list (3.5 %), a decrease in the median waiting time (656–416 days), and an increase in the number of patients transplanted within 30 days of listing without a diminution in post-transplant survival [10]. Over time, despite transplants for sicker patients (higher MELD scores), there was no appreciable decrease in survival after LT [5, 11–15]. Between 2002 and 2008, the number of waiting-list candidates decreased by 3.4 % and annual dropout from the waiting list remained stationary [16]. Waiting time also decreased, with a larger proportion of candidates receiving transplants within 30 days (23 % 2001 to 37 % in 2008) [11, 17]. Between 1998 and 2007, adjusted one-year graft survival improved from 79.5 % to 85.6 % and patient survival from 85.4 to 89.4 %.

In subsequent years, several other countries adopted the MELD score, leading to a reduction in waiting-list registration and waiting-list mortality and to an increase in deceased donor transplants [18–20]. In Brazil, in an-intent-to-treat analysis of mortality assessed from the time of listing, survival was higher in the post MELD era than in the pre MELD era (53 vs. 43 % for five-year survival and 44 vs. 41 % for 10-year survival) [21]. In the Eurotransplant countries MELD-based organ allocation was implemented in December 2006. There was a significant reduction in waiting-list mortality across the Eurotransplant area (20–10 %) [22].

The MELD score, as an objective scale of disease severity, was also helpful for management of non-transplant patients with chronic liver disease. The MELD score is a predictor of long-term survival for patients with decompensated cirrhosis [23]. Application of the MELD score for persons with chronic liver disease has included prognosis and treatment of variceal bleeding, infection, surgical resection of HCC, placement of TIPS, and management of renal failure [8, 24–26]. The MELD score is a predictor of non-transplant surgical mortality among patients with cirrhosis [27, 28]. The MELD score can also be used to predict the risk of mortality for patients without cirrhosis. The MELD score, as opposed to the discriminant function, is useful for predicting short-term mortality for patients with acute alcoholic hepatitis [29]. Among patients with non-acetaminophen-induced fulminant hepatic failure, the MELD score was a significant predictor of mortality [25]. MELD score can also be used to predict hepatic dysfunction among patients with heart failure. Among ambulatory patients with heart failure, an increasing MELD score was associated with poor survival after one year and the need for a heart transplant [30]. It was independently predictive of poor outcomes after placement of left ventricular-assist devices in subjects with advanced heart failure [31].

Advantages and disadvantages of the MELD score

Strengths of the MELD score include that it is an objective metric utilizing a continuous scale, enabling ranking of patients on the basis of disease severity. It incorporates laboratory data that are easily available and reproducible. Its validity as a robust mathematical model for assessment of mortality risk among patients with end-stage liver

disease has been shown in a multitude of studies [8]. The MELD score has been shown to be superior to clinical judgment in identifying patients at risk of mortality [32]. Several caveats of the MELD system are investigated in the following sections.

Components of the MELD score Concerns about the components of the MELD score focus on whether they are truly objective and appropriately reflect the severity of liver disease. Serum bilirubin has a linear relationship with 90-day mortality, irrespective of inter-laboratory variability in its measurement [33]. Further, although total bilirubin is used and may be theoretically advantageous for patients with indirect hyperbilirubinemia (e.g. hemolysis) it is less likely to be in the range that would prompt significant alteration in the MELD score; further unpublished data suggests that it is not superior to use of total bilirubin.

Serum creatinine in the MELD score serves as an indirect marker of the severity of the liver disease and is an independent predictor of survival [34–37]. Issues with its use are threefold. First, serum creatinine as a surrogate may be suboptimal among cirrhotic patients [13, 38, 39]. For subjects who are malnourished or have decreased muscle mass (e.g. females), the severity of liver disease may be underestimated. True, measured glomerular filtration rate (GFR, e.g., by iothalamate clearance measurement) is better than creatinine and mathematical equations containing creatinine for assessing prognosis [38, 39]. A multivariable model that incorporates calculated GFR and/or serum sodium is superior to the MELD score [13]. Second, incorporation of serum creatinine does not take into account inherent renal dysfunction *independent* of liver disease. As an example, a diabetic cirrhotic with chronic kidney disease would be afforded significant MELD points in the absence of decompensated cirrhosis. Third, measurement of serum creatinine may be skewed by the assay used. For patients with high serum bilirubin (>25 mg/dL), serum creatinine can be overestimated by use of the traditional colorimetric alkaline picric Jaffe method as compared with enzymatic methods, leading to imprecise calculation of the MELD score [8, 40].

The INR has a linear relationship with increasing mortality until an INR of approximately 3, after which a plateau is observed. There is variability in assays, depending on the reagent and/or measurement technique used in the laboratory for calculation of prothrombin time and INR, and may be suboptimum for cirrhotics [41–44]. In contrast, if calibration is performed by use of standards derived for liver disease patients, inter-assay and inter-laboratory variability can be substantially reduced [45].

However, potential barriers include the need for two separate determinants of INR (for liver and non-liver patients), cost of standardization, implementation, and monitoring [42]. If a high MELD score is mostly driven by an artificially high INR, the true MELD may be quite low (e.g. less than 15), making transplantation less beneficial to the patient [46]. Heuman et al. [47] examined a model without INR ("MELD-XI") for LT candidates on stable oral anticoagulation. The model was still less accurate than MELD, suggesting that, even for those patients, INR somehow carries prognostic information. There remains a need for a more accurate measure of coagulopathy amongst cirrhotics [48].

MELD score and organ allocation Over the last decade, since the MELD score has been used as the basis of organ allocation, several suppositions have arisen. The MELD score was created for a carefully screened population without acute, reversible complications (e.g. infection). Hence, it may not accurately capture the risk of mortality for acutely decompensated cirrhotic patients [8]. Further, pre-transplant patient status in general and the MELD score in particular has limited ability to predict post-transplant mortality. Several other factors that may affect and determine outcomes and survival include donor characteristics, transplant factors, geographic factors (center, region, country), and random post-operative complications.

Waiting list Subjects undergoing LT are globally sicker in the current era than when the MELD score was first established. According to the latest annual report of the Scientific Registry of Transplant Recipients (SRTR), compared with 2002, candidates on the waiting list in 2012 have a higher MELD score at transplant (mean MELD > 30, 34 vs. 14.6 %), are older (age > 65 years, 14.6 vs. 7.6 %), and have more co-morbidities, for example obesity (32 vs. 26 %), portal vein thrombosis (9.9 vs. 2.8 %), previous abdominal surgery (43 vs. 36 %), and spontaneous bacterial peritonitis (9.1 vs. 7.3 %). [49] Despite this, patient survival within the first 2–3 years did not differ from that in the pre MELD era [50, 51]. Management of patients on the waiting list is becoming more difficult. The number of patients removed from the list for being too sick for transplant has also increased, and in some regions is close to the incidence of death on the waiting list. Geography is important with regard to when patients receive a transplant across a region or country. MELD or disease severity required at transplant is affected not only by the region but also by the transplant center [52–54]. As subjects wait longer, end-stage liver disease candidates with a MELD score >40 are at twice the risk of status 1A candidates [55]. There is also a significant increase in mean MELD score at the time of organ allocation in Europe. In the Eurotransplant region, there was a 25 % increase in the number of high MELD recipients (≥30 points) in recent years. In Germany this was as high as 43 %.

One of the repercussions of having sicker patients on the waiting list is the financial cost. Axelrod et al. assessed the variation of costs for patients awaiting transplantation in the US, and observed notable wide regional variation in cost for a particular MELD score. There was an exponential increase in cost (tenfold) going from a MELD score of 20 ($2,000) to a MELD score of 30 ($23,000) [56]. Hence, initial improvements in the system for incorporation of the MELD score have been partially offset by some of the tangible challenges faced by the current system.

Renal function Given the emphasis on renal dysfunction in the MELD score, more subjects now have renal insufficiency than previously. Since introduction of the MELD score, kidney transplantation, preoperative creatinine, and the number of patients requiring preoperative hemodialysis have increased [50, 51]. Although the number of patients with renal dysfunction at the time of LT increased (26.1 % in 2002 to 29.8 % in 2008) [16] implementation of the MELD allocation system was not associated with increased mortality or the occurrence of stage 3 of 4 chronic kidney disease in the first two years after LT [57, 58]. However, the number of persons needing simultaneous liver and kidney transplants has dramatically increased from 2 to 8 % over the last decade [49]. The risk of *long*-term post-transplant end-stage renal disease, a significant predictor of post-transplant mortality, was 15 % higher in the MELD era. Part of this is driven by incorporation of serum creatinine in the MELD score, but part of it is also driven by sicker patients being transplanted and the increased prevalence of unrecognized chronic kidney disease. That is not well recognized. Further, non-MELD factors affecting this increase include a history of re-transplantation, older donor age, receipt of a donation after cardiac death (DCD), elevated serum sodium, diabetes, hepatitis C, and African–American race. Hence there is inferential evidence that other factors besides the MELD score are probably also causative [59].

Gender Females are more likely to die or become too sick for a transplant, and are less likely to receive a transplant. Female gender is associated with an approximately 15 % greater risk of death on the waiting list and a 12 % decrease in the probability of receiving a transplant [60–62]. Greater mortality among females on the waiting list may be multifactorial. Serum creatinine may be decreased (because of lower muscle mass) and the smaller body size of females may reduce the chance of a female with a competitive MELD score receiving a transplant. Females also present with worse overall hepatic dysfunction, increasing the urgency for LT. Including a better measure of renal dysfunction, for example estimated GFR, more accurately accounts for differences in the risk of death between genders. Use of eGFR as defined by the MDRD equation conferred a 15 % survival advantage to females [60, 62, 63]. Gender disparity is further enhanced because survival of females would be expected to be better (not equivalent), because of the greater prevalence of specific diagnoses with excellent post-transplant outcomes (e.g. autoimmune hepatitis or cholestatic disease). However, this purported advantage may be offset by females undergoing LT for fulminant hepatic failure [64, 65].

MELD exceptions

A high *c*-statistic associated with the MELD score (0.83-0.87 in recent reports) implies it is an excellent predictor of short-term mortality. Conversely, approximately 15 % of the time a MELD-based organ allocation incorrectly classifies which patient needs a transplant more urgently. Second, there are some rare manifestations of liver disease (e.g. portopulmonary hypertension) associated with a high risk of mortality without transplant, for whom disease severity is not adequately captured by the MELD score [5]. Third, although initial derivations of the MELD score de-emphasized the incremental benefit of addition of complications of liver disease (e.g. refractory ascites or recurrent cholangitis), a system was desired whereby physicians could appeal for assignment of MELD points on a case-to-case basis. Finally, on the basis of studies indicating that for some small cancers (HCC and hilar cholangiocarcinoma) livers could be safely transplanted with acceptable post-transplant outcomes, a system was sought whereby additional MELD points could be assigned to selected cancer patients (most of whom have preserved synthetic function and a lower MELD) and would, therefore, be competitive to receive a transplant.

Hence, a system of MELD exceptions was created. Some were *standard MELD exceptions* whereby an initial MELD score would be automatically assigned (22–28 points) if manifestation-specific criteria were met (Table 1). Further, additional points would be assigned every three months equivalent to those subjects with an equal risk of mortality within three months (or a risk of tumor progression, if applicable). This would enable timely transplantation for these subjects, as long as listing criteria were still met. In addition, *symptom based MELD exceptions* were allowed whereby special cases could be appealed to the regional review board (e.g. for recurrent cholangitis) and assignment of initial points and upgrades would be at the board's discretion. Table 1 lists some of the MELD exceptions and criteria in the US, and in Germany in the Eurotransplant region.

Between 2002 and 2008, MELD exceptions on the waiting list increased from 382 to 890. As the incidence of HCC in the US continues to rise, the number of LT candidates receiving the standard exception score for HCC has

Table 1 Selection MELD exception criteria

	USA	Germany
Hilar cholangiocarcinoma	Initial 22	Initial 10 %
	Upgrade 10 %	Upgrade 10 %
Hepatocellular carcinoma	Initial 22	Initial 15 %
		Upgrade 10 %
Cystic fibrosis	Initial 22	Initial 10 %
	Upgrade 10 %	Upgrade 10 %
Familial amyloid polyneuropathy	Initial 22	Initial 15 %
	Upgrade 10 %	Upgrade 10 %
Hepatic artery thrombosis	Status 1 40 (within 14 days)	
Hepatoblastoma	Status 1b (pediatric)	Initial 30
		Urgent after 30 days if no LTx
Hepatopulmonary syndrome	Initial 22	Initial 15 %
	Upgrade 10 % $PaO_2 < 60$	Upgrade 10 %
Hereditary hemorrhagic telangiectasia	Appeal	Initial 15 %
		Upgrade 10 %
		ALF: MELD 40
Hepatic hemangioendothelioma	Appeal	Initial 15 %
		Upgrade 10 %
Portopulmonary Hypertension	Initial 22	Initial 25 %
	Upgrade 10 %	Upgrade 10 %
Primary hyperoxaluria	Initial 28	Initial 10 %
	Upgrade 10 %	Upgrade 10 %
Polycystic liver disease	Appeal	Initial 10 %
		Upgrade 10 %
Primary sclerosing cholangitis	Appeal on symptoms	Initial 15 %[a]
		Upgrade 10 %
Biliary sepsis/secondary sclerosing cholangitis	Appeal	Variable[b]

Selected MELD exception criteria in the United States and Germany. Definitions for meeting exception criteria for the aforementioned indications are specific and vary by country. Details are given in the UNOS/Organ Procurement and Transplantation network policies (www.unos.org) and Eurotransplant liver allocation system (www.eurotransplant.org)

[a] PSC (need 2/3): two spontaneously occurring septic episodes within six months (not because of intervention, not treated by intervention), documented development of dominant bile duct stenosis, BMI reduction >10 % within 12 months

[b] Biliary sepsis, SSC: two spontaneously occurring septic episodes within six months (not because of intervention, not treated by intervention), septicemia despite antibiotic therapy, can only be treated by LT and can be because of complication of liver transplantation, bile duct necrosis, diffuse bile duct damage, and/or vanishing bile duct syndrome

also been increasing [16, 66–69] (see below). The most common indications for MELD score exceptions included HCC (19 %) followed by complications of portal hypertension (7.5 %), hepatopulmonary syndrome or portopulmonary hypertension (1.3 %), and inborn metabolic disorders [70].

Several issues have, however, arisen with the advent of MELD exceptions. First, there is wide regional and geographic variation in the use of MELD exceptions. There are also disparate criteria for MELD exceptions across countries that perform deceased donor LT [71]. Although, by design, exception candidates have a lower incidence of removal for death or clinical deterioration, there is a higher than expected rate of transplantation with potential for undue effect on others waiting LT with high biological MELD scores (discussed in the section on "Hepatocellular carcinoma", below). Second, there is debate whether non-standardized exceptions given to some manifestations, for example complications of primary sclerosing cholangitis or portopulmonary hypertension, are appropriately used and whether they are even justified [72, 73]. In a recent analysis of patients given transplants for portopulmonary hypertension, only 47 % of waiting-list candidates met the standardized exception criteria. There was an increased risk

of death, irrespective of whether or not subjects met hemodynamic criteria [72]. In an analogous evaluation of listing practices for hepatopulmonary syndrome, the hazard ratio for post-transplant mortality was 1.58 for those with a PaO_2 of less than 44 mmHg, suggesting need for refinement of criteria on the basis of which patients with HPS should be given a transplant [74]. Finally, there is concern that other appropriate considerations, for example worsening malnutrition or hyponatremia, are not considered among the MELD exceptions.

Hepatocellular carcinoma

Driven partially by the excellent survival of small HCCs that met the Milan criteria, exception points are granted to subjects with HCC. Interval points are granted every three months, in parallel with the risk of tumor progression. Over the last decade several point systems have been investigated (earlier 29 points were awarded) with current standardized initial MELD exceptions of 22 points for stage 2 tumors (>2 cm) as long as the Milan criteria are met [75].

However, there has been a palpable effect on the dynamics of the waiting list after incorporation of such a policy. By design, subjects receiving exception points have lower waiting list mortality. However, there has been a dramatic increase in the number of subjects with HCC. Hence, even though it was expected that exception candidates may be a minority of the patients listed and hence would not affect the outcome of subjects without exception, this is not observed. The percentage of HCC MELD exceptions is the strongest independent predictor of regional MELD score at transplant. There has been an increase over time in the number of subjects receiving exception points for HCC. Non-exception candidates wait 180 % longer for transplants than MELD exception candidates [70, 76]. As expected, the number of people that drop out of the waiting list is much higher for those who are non-exception candidates (22 %) than for those who are HCC exception (10 %) or non-HCC exception (11.3 %). The number of non-exception candidates receiving transplants is lower (45 %) than for HCC exception (72 %) and non-HCC exception (71 %) candidates. Waiting-list deaths are also lower (HCC 4.5 % vs. non-HCC 24 %). Hence increased waiting time affects HCC patients less than non-HCC patients [77]. Several solutions have been proposed, including a combination of reducing the initial MELD exception points, static versus dynamic number of points assigned on the waiting list, incorporation of tumor biology and risk of drop out, and incorporation of waiting time after initial therapy for HCC on the waiting list [69, 78].

Table 2 Model for end-stage liver disease (MELD) score and its proposed modifications

MELD score [7]

MELD score = $3.8 \times \log_e$(bilirubin mg/dL) + $11.2 \times \log_e$ (INR) + $9.6 \times \log_e$ (creatinine mg/dL) + 6.4

MELD Na [83]

MELDNa = MELD − Na − [0.025 × MELD × (140 − Na)] + 140, where the serum sodium concentration (Na) is bound between 125 and 140 mmol/L

ReFit MELD [82]

ReFit MELD = $4.082 \times \log_e$ (bilirubin) + $8.485 \times \log_e$ (creatinine) + $10.671 \times \mathrm{Log}_e$ (INR) + 7.432

bilirubin = bilirubin bounded below by 1 mg/dL

creatinine = creatinine capped by 0.8 mg/dL below and 3 mg/dL above

INR = INR bounded by 1 below and 3 above. Renal replacement therapy = 3 mg/dL

ReFit MELDNa [82]

ReFit MELDNa = $4.258 \times \log_e$ (bilirubin) + $6.792 \times \log_e$ (creatinine) + $8.290 \times \log_e$ (INR) + $0.652 \times (140 - \mathrm{Na}) - 0.194 \times (140 - \mathrm{Na}) \times$ bilirubin# + 6.327

bilirubin = bilirubin bounded below by 1 mg/dL

creatinine = creatinine capped by 0.8 mg/dL below and 3 mg/dL above

INR = INR bounded by 1 below and 3 above. Renal replacement therapy = 3 mg/dL

bilirubin# bounded below by 1 mg/dL and above by 20 mg/dL

UKELD [84]

UKELD = $5 \times [1.5 \times \log_e$(INR) + $0.3 \times$ loge(creatinine, μmol/l) + $0.6 \times$ loge(bilirubin, μmol/l) − $13 \times \log_e$(serum sodium, mmol/l) + 70]

RE-weighted MELD [81]

Re-weighted MELD = $1.266 \log_e(1 +$ creatinine, mg/dL) + $0.939 \log_e(1 +$ bilirubin, mg/dL) + $1.658 \log_e(1 +$ INR)

No set upper and lower limit bounds on the coefficients of each of the components

Conclusions and future directions

The MELD score is an important contribution to hepatology because it accurately gauges the severity of liver disease and forms the cornerstone of an organ-allocation system based on medical urgency. It has become part of the hepatologist's vocabulary inasmuch that a MELD score conveys a succinct picture of the health status of a patient with end-stage liver disease. The overall issue is that the MELD score still resides and operates under a variety of factors that are independent of disease severity, and are rapidly changing. By design, it should be continually evolving; it is a working model and has served as a template for further refinement to achieve the objective of equitable distribution of a scarce resource [79, 80]. In fact, several new versions of the MELD score have been proposed that focus on either re-weighting the MELD components or adding other pertinent variables (e.g. serum sodium) [81–84] (Table 2). Other applications of these updated models are awaited.

Variation in the delivery of healthcare in different regions, centers, and countries is commonplace; given the rich data relating to liver transplantation that are publicly available, this variation is *more* recognized in LT but may not be of *significantly* greater magnitude. Controversies about the use of MELD exception points will always be present. Exception candidates, by definition, will always have lower waiting list mortality, and that in itself should not be construed as being unfair. The more important issue is that the probability of receipt of LT is much higher than that for similarly matched patients without exception points and this needs to be revised [85].

Compliance with ethical requirements and Conflict of interest All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all the patients included in this study. Sumeet Asrani and Patrick Kamath declare that they have no conflict of interest.

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