Comparison of the ability of the PDD-ICG clearance test, CTP, MELD, and MELD-Na to predict short-term and medium-term mortality in patients with decompensated hepatitis B cirrhosis

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Objective Various methods, including the indocyanine green (ICG) clearance test, the Child–Turcotte–Pugh score (CTP), model for end-stage liver disease (MELD), and MELD combined with serum sodium concentration (MELD-Na), have been used widely in liver function evaluation in patients with end-stage liver disease. In this study, we compared the ability of these methods to predict mortality in patients with decompensated hepatitis B cirrhosis.

Methods A total of 98 patients with decompensated hepatitis B cirrhosis were included in this study and followed up for 12 months. The ICG-derived measurements (ICG-PDR, ICG-R_{15}, EHBF), CTP, MELD, and MELD-Na were obtained within 2 days after patients' admission and patients' survival at 1, 3, 6, and 12 months was recorded. Receiver operating curve was used to evaluate the ability of these methods to predict mortality in these patients with decompensated hepatitis B cirrhosis.

Results At 1 month, 3 months, 6 months and 12 months, the cumulative number of deaths and liver transplant recipients was 12 (12.2%), 17 (17.3%), 21 (21.4%) and 25 (25.5%), respectively. The ICG-derived measurements, CTP, MELD, and MELD-Na of nonsurvivors were significantly different compared with that in survivors. All methods yielded viable values in predicting short-term and medium-term prognosis for patients with decompensated hepatitis B cirrhosis, with most area under the curve exceeding 0.8. Moreover, the ICG-derived measurements showed a significant correlation with that of CTP, MELD, and MELD-Na.

Conclusion All four methods, ICG clearance test, CTP, MELD, and MELD-Na, provided reliable prediction of mortality in patients with decompensated hepatitis B cirrhosis for both short-term and medium-term prognosis. Eur J Gastroenterol Hepatol 28:444–448

Introduction

In China, hepatitis B virus is the major cause of end-stage liver disease and liver cirrhosis. Decompensated cirrhosis is a major cause of mortality in hepatitis B patients, leading to various complications, including portal hypertension, gastrointestinal variceal bleeding, ascites and hepatic encephalopathy, and others. Despite the availability of a few therapeutic options [1], patients with decompensated liver cirrhosis show significant differences in terms of survival and morbidity. A simple and reliable prognostic method is therefore needed to determine the mortality risk for these patients, and accordingly stratify and help guide the clinician to make appropriate therapeutic decisions on the basis of the predictive outcomes.

The indocyanine green (ICG) clearance test was proposed as a quantitative liver function test five decades ago [2]. As a water-soluble dye, ICG is absorbed entirely by hepatocytes without becoming involved in biotransformation, and is almost entirely excreted into the bile secretion without any toxic side effects on the human body [2]. Given these advantages, ICG has been used widely in perioperation liver function evaluation or as a prognostic indicator in critically ill and/or patients with end-stage liver disease [3–5]. A couple of measurements derived from the ICG clearance test, including the plasma disappearance rate of indocyanine green (ICG-PDR), the retention rate of indocyanine green 15 min after administration (ICG-R_{15}), and estimated hepatic blood flow (EHBF), are also commonly used in liver function evaluation both clinically as well as in research studies [3,6].

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Another test to determine the severity of liver cirrhosis, the Child–Turcotte–Pugh score (CTP), is performed by calculating serum bilirubin and albumin, prothrombin time, hepatic encephalopathy, and ascites [7]. It has been used more frequently and widely in clinic because of its simplicity. The third test, the model for end-stage liver disease (MELD), is determined by three routine laboratory test results: bilirubin, international normalized ratio (INR), and creatinine, and is by far the most commonly used method worldwide in the evaluation of patients with end-stage liver disease for transplantation [8]. As the serum sodium (Na) level is considered to be strongly associated with mortality, Biggins *et al.* [9] originally proposed MELD combined with serum sodium concentration (MELD-Na) as a predictive method in patients on the transplant waiting list because of end-stage liver disease.

Although all four methods, ICG clearance test, CTP, MELD, and MELD-Na, are being used to a certain extent clinically, it remains unclear as to which is the most reliable method to predict prognosis in patients with liver cirrhosis. To date, there are no data on the comparison of all four approaches in evaluating and predicting prognosis for patients with decompensated hepatitis B cirrhosis.

This study aimed to compare the short-term and medium-term predictive significance and capacity of the ICG clearance test, CTP, MELD, and MELD-Na in patients with decompensated hepatitis B cirrhosis.

Methods

Patients

This was a prospective cohort study. From January 2011 to August 2012, 98 patients with decompensated hepatitis B liver cirrhosis hospitalized at Beijing Youan Hospital, Capital Medical University, were enrolled in this study. The diagnosis of decompensated hepatitis B cirrhosis was made on the basis of clinical, biochemical, ultrasonic, histological, radiological, and endoscopic findings and results. The patients excluded from this study were those with other types of hepatitis virus infection (HAV, HCV, HDV, or HEV), hepatocellular carcinoma, previous liver transplantation, and patients not fulfilling the ICG test manufacturer's recommendation, hyperthyroidism, and iodine allergy. Survival was evaluated at 1, 3, 6, and 12 months, respectively, by direct phone call and/or assessment of medical records. Patients who died or accepted liver transplantation during this period were categorized into the nonsurvival group for this study. The cumulative number of deaths at 1, 3, 6, and 12 months was 9, 14, 18, and 21, respectively; for liver transplantation, the cumulative number at 1, 3, and 6 months was 3; and at 12 months, the cumulative number of liver transplantations was 4. More detailed information has been provided in Supplementary part, Supplemental digital content 1, *http://links.lww.com/EJGH/A63*.

This study was approved by the ethics committee of Beijing Youan Hospital, Capital Medical University. All enrolled patients signed a written consent.

Methods

The ICG clearance test was carried out using a Pulse Dye Densito-Graph Analyzer (DDG-3300K; Nihon-Kohden, Tokyo, Japan) noninvasively. Within 10 s after injecting the ICG (0.5 mg/kg; Jishi Pharmaceutical, Shenyang, China) into the median cubital vein, plasma ICG concentrations were monitored using a probe attached to the patients' nose, with ICG-PDR, ICG-R_{15}, and EHBF subsequently assessed by a computer. CTP was calculated as described previously by Pugh *et al.* [7]. MELD was determined using the formulation $3.78 \times \text{Ln}$ (bilirubin mg/dl) $+ 11.2 \times \text{Ln}$ (INR) $+ 9.57 \times \text{Ln}$ (creatinine mg/dl) $+ 6.43$ [10]. The count of MELD-Na was performed in accordance with Biggins *et al.* [9] using MELD $+1.59 \times$ [135-Na (mmol/l)]. Measurements of routine laboratory parameters were performed on the next morning of admission and the ICG clearance test was carried out within 2 days.

Statistical analysis

All statistical analyses were carried out using SPSS21.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables were presented as mean with SD and categorical variables were presented as count with percentage; P up to 0.05 was considered statistically significant. Comparisons for continuous variables were performed using Student's t-test or the Mann–Whitney U-test where appropriate; χ^2 testing was performed for categorical data. To assess the predictive value of prognostic parameters, receiver operating curve analysis was carried out, and the area under the ROC curve (AUROC), sensitivity, specificity, and the best cut-off point were calculated. Pearson's correlation test was structured to evaluate the correlation between ICG-derived parameters and other indicators.

Results

Clinical characteristics of the participants

The clinical characteristics of the participants are described in Table 1. The mean age of the patients was 48.0 years, and 88.8% were men (87). The mean ICG-derived parameters ICG-PDR, ICG-R_{15}, and EHBF were 7.0%/min, 39.6%, and 0.4 l/min, respectively. The mean CTP, MELD, and MELD-Na were 8.9, 12.5, and 13.0, respectively.

Table 1. Characteristics of the participants

	Participants ($n = 98$)
Male sex [n (%)]	87 (88.8)
Age	48.0 ± 10.2
Aspartate aminotransferase (U/l)	159.8 ± 224.1
Bilirubin (μmol/l)	124.1 ± 168.3
Albumin (g/l)	31.3 ± 4.5
Creatinine (μmol/l)	67.8 ± 15.4
Sodium (mmol/l)	138.0 ± 3.1
Hemoglobin (g/l)	111.7 ± 23.5
International normalized ratio	1.5 ± 0.4
CTP	8.9 ± 2.1
MELD	12.5 ± 6.0
MELD-Na	13.0 ± 6.6
ICG-PDR (%/min)	7.0 ± 3.6
ICG-R_{15} (%)	39.6 ± 17.0
EHBF (l/min)	0.4 ± 0.2

CTP, Child–Turcotte–Pugh; EHBF, estimated hepatic blood flow; ICG-PDR, plasma disappearance rate of indocyanine green; ICG-R_{15}, the retention rate of indocyanine green 15 min after administration; MELD, the model for end-stage liver disease; MELD-Na, MELD combined with serum sodium concentration.

Comparison between the survival group and the nonsurvival group

A total of 12 (12.2%), 17 (17.3%), 21 (21.4%), and 25 (25.5%) patients died or accepted liver transplantation within 1, 3, 6, and 12 months, respectively. CTP, MELD, MELD-Na, and ICG-R_{15} of nonsurvivors were all significantly higher compared with survivors during any phase of the follow-up ($P < 0.001$), whereas ICG-PDR and EHBF of the nonsurvivors were significantly lower than those of the survivors ($P < 0.001$) (Table 2).

Predictive significance and capacity of the four methods

The prognostic significance of ICG-derived parameters, CTP, MELD, and MELD-Na calculated for 1-, 3-, 6-, and 12-month survival is summarized in Table 3. All methods showed excellent accuracies in predicting mortality, and the AUC of CTP, MELD, and MELD-Na even exceeded 0.9 for short-term evaluation. Moreover, the prognostic value of CTP and MELD was consistently better than that of other methods, for example at 12 months, the AUC of CTP and MELD was 0.880 and 0.838, whereas the AUC of MELD-Na, ICG-PDR, ICG-R_{15}, and EHBF was 0.834, 0.831, 0.831, and 0.757, respectively. However, no significant difference was found between all four methods.

Correlation between ICG-derived measurements and CTP, MELD, and MELD-Na

All ICG-derived measurements showed a significant correlation with CTP, MELD, and MELD-Na. Positive correlations were observed between ICG-R_{15} and CTP, MELD, and MELD-Na ($r = 0.642$, 0.613, 0.608), and negative correlations were found between ICG-PDR and CTP, MELD, MELD-Na ($r = -0.642$, -0.613, -0.608), and between EHBF and CTP, MELD, and MELD-Na ($r = -0.612$, -0.541, -0.550) (Table 4).

Discussion

In this study, we found that the ICG clearance test, CTP, MELD, and MELD-Na all showed excellent predictive significance and capacity in short-term and medium-term mortality evaluation in patients with decompensated hepatitis B cirrhosis, including 1, 3, 6, or 12 months. In addition, the predictive capacity of CTP and MELD, although lacking significance among them, seemed superior to that of MELD-Na and ICG. ICG-derived measurements, especially ICG-PDR and ICG-R_{15}, showed a significant correlation with CTP, MELD, and MELD-Na. Of great interest, ICG-PDR and ICG-R_{15} shared the same

Table 2. Comparison between survival group and nonsurvival group at 1-, 3-, 6- and 12-month follow-up

	Mean	SD	Mean	SD	*T* / *Z*	*d.f.*	*P*
	Survivors ($n = 86$)		Nonsurvivors ($n = 12$)			Statistics	
1 month							
CTP	8.5	1.8	12.3	1.2	5.2	[a]	< 0.001
MELD	11.1	4.5	22.9	5.0	5.0	[a]	< 0.001
MELD-Na	11.4	4.9	24.4	6.7	5.0	[a]	< 0.001
ICG-PDR (%/min)	7.4	3.6	3.6	0.7	−4.3	[a]	< 0.001
ICG-R_{15}(%)	37.0	16.3	58.6	6.1	−8.7	96	< 0.001
EHBF (l/min)	0.4	0.2	0.2	0.1	6.8	96	< 0.001
	Survivors ($n = 81$)		Nonsurvivors ($n = 17$)			Statistics	
3 month							
CTP	8.4	1.7	11.5	1.8	5.2	[a]	< 0.001
MELD	10.7	3.9	21.2	6.8	5.3	[a]	< 0.001
MELD-Na	11.0	4.4	22.5	7.4	5.2	[a]	< 0.001
ICG-PDR (%/min)	7.6	3.6	4.0	1.6	−4.6	[a]	< 0.001
ICG-R_{15}(%)	36.2	16.1	56.0	10.5	−6.4	96	< 0.001
EHBF (l/min)	0.4	0.2	0.2	0.1	5.9	96	< 0.001
	Survivors ($n = 77$)		Nonsurvivors ($n = 21$)			Statistics	
6 month							
CTP	8.3	1.8	11.1	1.8	5.2	[a]	< 0.001
MELD	10.7	3.8	19.6	7.2	5.1	[a]	< 0.001
MELD-Na	10.9	4.3	20.8	7.9	5.1	[a]	< 0.001
ICG-PDR (%/min)	7.6	3.6	4.5	2.1	−4.2	[a]	< 0.001
ICG-R_{15}(%)	36.0	16.2	52.9	12.8	−4.4	96	< 0.001
EHBF (l/min)	0.4	0.2	0.3	0.1	5.1	96	< 0.001
	Survivors ($n = 73$)		Nonsurvivors ($n = 25$)			Statistics	
12 month							
CTP	8.2	1.7	11.1	1.8	5.7	[a]	< 0.001
MELD	10.5	3.7	18.6	7.2	5.0	[a]	< 0.001
MELD-Na	10.7	4.3	19.6	7.9	5.0	[a]	< 0.001
ICG-PDR (%/min)	7.8	3.6	4.4	2.0	−4.9	[a]	< 0.001
ICG-R_{15}(%)	34.9	15.7	53.5	12.7	−5.4	96	< 0.001
EHBF (l/min)	0.4	0.2	0.3	0.1	4.9	96	< 0.001

CTP, Child–Turcotte–Pugh; EHBF, estimated hepatic blood flow; ICG-PDR, plasma disappearance rate of indocyanine green; ICG-R_{15}, the retention rate of indocyanine green 15 min after administration; MELD, the model for end-stage liver disease; MELD-Na, MELD combined with serum sodium concentration.
[a]Mann–Whitney *U*-test

Table 3. Predictive value of prognostic parameters calculated for 1-, 3-, 6-, and 12-month survival

	AUC	95% CI	Cut-off	Sensitivity	Specificity	*P*
1 month						
CTP	0.960	0.924–0.996	10.5	100.0	89.5	<0.001
MELD	0.950	0.889–1.0	21.0	83.3	97.7	<0.001
MELD-Na	0.946	0.884–1.0	22.0	83.3	96.5	<0.001
ICG-PDR (%/min)	0.885	0.820–0.950	4.7	100.0	79.1	<0.001
ICG-R_{15} (%)	0.885	0.820–0.950	49.45	100.0	79.1	<0.001
EHBF (l/min)	0.822	0.736–0.907	0.2805	91.7	70.9	<0.001
3 months						
CTP	0.897	0.800–0.994	10.5	88.2	92.6	<0.001
MELD	0.909	0.794–1.0	15.5	88.2	85.2	<0.001
MELD-Na	0.903	0.791–1.0	16.5	88.2	88.9	<0.001
ICG-PDR (%/min)	0.854	0.761–0.947	4.45	82.4	84.0	<0.001
ICG-R_{15} (%)	0.854	0.761–0.947	51.3	82.4	84.0	<0.001
EHBF (l/min)	0.801	0.706–0.897	0.265	76.5	80.2	<0.001
6 months						
CTP	0.869	0.777–0.962	9.5	85.7	77.9	<0.001
MELD	0.864	0.752–0.976	12.5	81.0	75.3	<0.001
MELD-Na	0.861	0.752–0.971	16.5	76.2	89.6	<0.001
ICG-PDR (%/min)	0.803	0.698–0.908	5.75	90.5	63.6	<0.001
ICG-R_{15} (%)	0.803	0.698–0.908	42.2	90.5	63.6	<0.001
EHBF (l/min)	0.761	0.659–0.864	0.265	67.7	80.5	<0.001
12 months						
CTP	0.880	0.798–0.962	10.5	68.0	94.5	<0.001
MELD	0.838	0.729–0.946	15.5	72.0	87.7	<0.001
MELD-Na	0.834	0.727–0.941	15.5	72.0	87.7	<0.001
ICG-PDR (%/min)	0.831	0.738–0.924	5.45	84.0	72.6	<0.001
ICG-R_{15} (%)	0.831	0.738–0.924	44.15	84.0	72.6	<0.001
EHBF (l/min)	0.757	0.652–0.862	0.265	64.0	82.2	<0.001

AUC, area under the curve; CI, confidence interval; CTP, Child–Turcotte–Pugh; EHBF, estimated hepatic blood flow; ICG-PDR, plasma disappearance rate of indocyanine green; ICG-R_{15}, the retention rate of indocyanine green 15 min after administration; MELD, the model for end-stage liver disease; MELD-Na, MELD combined with serum sodium concentration.

Table 4. Correlation between ICG-derived parameters and CTP, MELD, and MELD-Na

	CTP		MELD		MELD-Na	
	r	*P*	*r*	*P*	*r*	*P*
ICG-PDR	−0.642	<0.001	−0.613	<0.001	−0.608	<0.001
ICG-R_{15}	0.642	<0.001	0.613	<0.001	0.608	<0.001
EHBF	−0.612	<0.001	−0.541	<0.001	−0.550	<0.001

CTP, Child–Turcotte–Pugh; EHBF, estimated hepatic blood flow; ICG-PDR, plasma disappearance rate of indocyanine green; ICG-R_{15}, the retention rate of indocyanine green 15 min after administration; MELD, the model for end-stage liver disease; MELD-Na, MELD combined with serum sodium concentration.

correlation coefficients and CTP had the closest relationship with ICG. To our knowledge, this is the first report to make a comparison of the four prognostic methods in mortality evaluation in patients with decompensated hepatitis B liver cirrhosis.

Cirrhosis is the final stage of chronic HBV infection, inevitably presented with decompensation in the end, with associated worse clinical outcome. Consistent with a previous study of patients with liver cirrhosis [11], about a quarter of patients with decompensated hepatitis B liver cirrhosis died within 1 year in the present study. To reduce the mortality, it is crucial to recognize those patients with a potential poor prognosis, and then prioritize and treat them accordingly in an appropriate and timely manner.

Previous methods of ICG measurement include spectrophotometry and a fiberoptic-based reference technique, which are invasive and sophisticated [12,13]. In the past two decades, the development of pulse dye densitometry (PDD) has enabled the measurement of ICG to become noninvasive, more efficient, and practicable, even for use at bedside, while maintaining a good correlation of the PDD method with the previous ones [14]. In this study, the PDD-ICG clearance test showed a good relationship with CTP, MELD, and MELD-Na, respectively, and can identify those patients with liver cirrhosis who potentially have a poor prognosis. The relationship between the ICG-derived measurement and MELD was also observed by Sheng *et al.* [15]; a significant correlation with MELD ($r = -0.892$ and 0.804) was suggested with ICG-PDR and ICG-R_{15}. Considering independence of routine clinical indexes and avoiding blood sample drawn, PDD-ICG can be used as an alternative method to evaluate the prognosis of short-term and medium-term mortality of patients with decompensated hepatitis B liver cirrhosis.

To our knowledge, although predictive significance comparisons among the PDD-ICG clearance test, CTP, MELD, and MELD-Na have not been reported before, some comparisons between selective means have been performed in several studies. In 2006, Cholongitas *et al.* [16] summarized the papers on comparing the prognosis significance of CTP and MELD in patients with end-stage liver disease awaiting transplantation, and concluded that MELD was not more reliable than CTP, which is in agreement with our findings. However, in 753 primary liver transplant candidates, Biggins *et al.* [9] reported that MELD-Na was a more reliable predictor than MELD of death within 6 months. On the other hand, Feng *et al.* [17] found that the AUC of ICG-R_{15} was markedly higher than that of MELD (0.793 vs. 0.776) in 69 patients with acute liver failure. The discrepancies among these studies may be because of the differences in the etiology and pathophysiology of liver disease in participants of each study.

Although promising results were obtained in our study, these methods still have some application limitations. First, CTP is relatively restricted because of the subjective nature of hepatic encephalopathy and ascites severity, and albumin level may be affected by supplementation and prothrombin time variation from one laboratory to another [18,19]. In addition, the limited values, ranging from 5 to 15 score, make it obviously imprecise. Second, the predictive value of MELD and MELD-Na might be devalued in some situations. Malabsorption of vitamin K secondary to cholestasis can increase INR, whereas starving and infection can cause an increase of bilirubin; however, diuretic use can aggregate creatinine [20,21]. Finally, ICG can be altered with hepatic blood flow and bile excretory function [22]. To optimize these methods, a new approach was established by some researchers, which incorporated these methods and measurement together. The new approach appeared to achieve a better result, for example the combination of MELD and the ICG-derived measurement, either in liver transplant recipients or in patients with liver cirrhosis, is a more reliable predictor than either of them alone for outcome [23,24]. We will further increase the number of patients for study to construct a combined model that might be able to perfectly evaluate the prognosis of patients with decompensated hepatitis B cirrhosis. Dynamic monitoring of the change of the ICG clearance test, CTP, MELD, and MELD-Na during disease progression and exploration of their roles in diagnosis could be another research focus in a future study.

In conclusion, our findings have confirmed that the PDD-ICG clearance test, CTP, MELD, and MELD-Na all provide reliable predictions of short-term and medium-term mortality in patients with decompensated hepatitis B cirrhosis, which can help to prioritize the patient and guide the clinician for appropriate treatment.

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Conflicts of interest

There are no conflicts of interest.

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