

Received: 2017.10.28
Accepted: 2018.05.03
Published: 2018.06.01

Predictive Value of Indocyanine Green Plasma Disappearance Rate on Liver Function and Complications After Liver Transplantation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACEG **Yan Sun**
BCD **Lixin Yu**
BCF **Yihe Liu**

Department of Organ Transplantation, Tianjin First Central Hospital, Tianjin, P.R. China

Corresponding Author: Yan Sun, e-mail: smallforsize@yeah.net
Source of support: Departmental sources

Background: The aim of this study was to investigate the correlation between indocyanine green plasma disappearance rate (ICG-PDR) and allograft function as well as postoperative complications after liver transplantation.

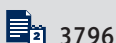
Material/Methods: In this prospective study, 115 cases of adult liver transplantation performed from 1 June 2016 to 1 December 2016 were enrolled. These 115 patients were divided into a group of PDR <18%/min (50 cases) and a group of PDR ≥18%/min (65 cases). The rates of liver recovery, postoperative complications, and survival were compared between these 2 groups.

Result: Among the total of 115 patients, 111 patients recovered well and were discharged, whereas 4 patients died during the first month after the operation. Between the 2 groups, significant differences were observed in terms of the model for end-stage liver disease (MELD) score, intraoperative bleeding volume, and the level of hemoglobin (Hb), pre-albumin (PA) and total bilirubin (TB) the first week after the operation. Overall, the incidence of hepatic arterial complications and pneumonia was much higher in the PDR<18%/min group (P<0.05).

Conclusions: The early postoperative value of ICG-PDR was closely related to graft function and could act as a good predictor for the incidence of postoperative arterial complications.

MeSH Keywords: **Liver Function Tests • Liver Transplantation • Survival Analysis**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/907783>



Background

Liver transplantation (LT) is a major surgical option to treat a wide range of medical disorders [1]. Liver donation from deceased citizens has become the major source of livers used for transplantation. However, almost all liver donors died from certain diseases, and some donors had critical diseases and deteriorating organ functions, including that of the liver. These factors significantly affect the post-transplant recovery of graft functions [2]. Clinically, it remains a main challenge to find a rapid and accurate approach to evaluate the function of transplanted livers and to predict the incidence of post-transplant complications [3]. Although the current assessment systems for liver functions, such as CHILD-PUGH scores and MELD scores, are commonly used to discover late-stage liver diseases prior to liver transplantation, they lack the sensitivity and specificity needed for such applications [4]. Therefore, within the first 90 days after liver transplantation, artery complications, biliary strictures, and infectious complications are frequently seen. In addition, some severe complications such as PVT and HAT can lead to significant morbidity [5]. Therefore, the early detection of these complications is crucial for proper responses. Unfortunately, no simple and specific tool of diagnosis is available to spot these complications early on, thus making it necessary to conduct repeated liver function tests, Doppler ultrasound, and other examinations within the first 72–96 h after the operation [6]. Furthermore, in the arterial reconstruction following liver transplantation, complications such as aneurysms, steal syndromes, occlusions, and stenoses are frequently observed. In particular, stenoses can occur in the graft artery or in the recipient artery within the anastomotic region [7], and are often caused by technical issues. For example, stenoses following anastomosis can be caused by the bending and twisting of excessively long graft arteries. In addition, preservation injury and technical errors could trigger early thrombosis and occlusions in the graft artery, thus causing high resistance to peripheral vascular perfusion [8].

The indocyanine green (ICG) clearance test, which is based on the flow of liver perfusion and the metabolism of hepatocytes, measures the reserve of hepatic functions. The ICG clearance test has been widely employed to evaluate the prognosis among patients with chronic hepatic diseases and liver failure. However, the ICG test is seldom used in China for post-liver transplant assessment [9]. Nevertheless, the plasma retention rate and plasma disappearance rate of ICG (ICG-PDR) are some ICG-related indicators that can be measured following the intravenous administration of ICG [11]. Among these indicators, the most frequently used one, ICG-PDR, is used for the experimental and clinical evaluation of liver functions, and its normal value ranges from 18% to 25%/min [12]. In addition, the measurement of ICG-PDR has been shown to be a reliable indicator of liver functions [13,14]. Several recent studies have

demonstrated the role of ICG-PDR in predicting early and serious complications after liver transplantation [14–16]. Although other observational approaches may be utilized while early graft functions are sufficient, ICG-PDR is particularly suited as a direct and quick way to evaluate graft quality when early interventions are required to enhance graft functions [17].

In the present study, the data from 115 patients who underwent liver transplantation between 1 June 2016 and 1 December 2016 were analyzed to investigate the role of ICG-PDR in evaluating post-transplant liver functions and prognosis.

Material and Methods

Patient data and grouping

Patient data: a total of 115 liver transplant recipients (82 males and 33 females) with an average age of 50.0 years were included. Among these patients, the primary diseases in 57 patients were HBV-related diseases (HBV-related cirrhosis, HBV infection combined with primary hepatocellular carcinoma or chronic/acute liver failure). There were also 10 patients with HCV-related diseases (HCV-related cirrhosis, HCV infection combined with primary hepatocellular carcinoma), 19 with cryptogenic cirrhosis, 10 with alcoholic liver cirrhosis, 4 with autoimmune liver diseases, 4 with primary biliary cirrhosis, 3 with primary sclerosing cholangitis, 3 with hepatolithiasis, 1 with post-hepatectomy liver failure, 1 with post-liver transplantation biliary complication, 1 with hepatic adenomatous hyperplasia combined with cell canceration, 1 with hepatolenticular degeneration, and 1 with a non-alcoholic fatty liver disease. In terms of the score for end-stage liver disease (MELD score) prior to liver transplantation, 37 recipients had a score of ≤ 10 , 52 recipients had a score between 11 and 20, 22 recipients had a score between 21 and 30, and 4 recipients had a score of > 30 . The study protocol was approved by the institute's Ethics Committee on 10 October 2015 (No. 201500213).

Grouping: the subjects were divided into 2 groups according to their ICG-PDR results: the group of ICG-PDR $< 18\%$ /min (50 cases) and the group of ICG-PDR $\geq 18\%$ /min (65 cases). The preoperative data of the 2 groups are summarized in Table 1. In this article, ICG-PDR is hereinafter referred to as PDR.

Methods of operation

Among the 115 liver recipients, 105 patients received the classical whole-liver transplantation without veno-venous bypass, while 5 recipients underwent living donor liver transplantation using a right-lobe graft and a piggyback technique, and 5 recipients underwent right-lobe split liver transplantation. The intraoperative data of all recipients are summarized in Table 2.

Table 1. Comparison of general data between the two groups.

Group	n	Age	Male (cases)	HBV-related diseases as the primary disease (cases)	Pre-operative MELD score
PDR <18%/min group	50	50.7±12.2	38	28	16 (11–21)
PDR ≥18%/min group	65	49.5±15.9	44	29	12 (8–16.3)
Z/ χ^2 value		0.462	0.953	1.465	3.238
P value		0.645	0.329	0.226	<0.001

Table 2. Comparison of operation data between the two groups.

Group	n	Spilt LT /LDLT (cases)	GRWR (%)	Warm Ischemia time of the liver graft (min)	Cold Ischemia time of the liver graft	Operation Duration (h)	Anhepatic Phase (min)	Intraoperative Blood Loss (ml)
PDR <18%/min group	50	5	1.6±0.45	1 (1–2)	4 (3–7.5)	7.8 (6.8–9.5)	44.9±12.1	1800 (1000–3000)
PDR ≥18%/min group	65	5	1.8±0.42	1 (1–2)	3.6 (3–5.3)	7.2 (6.5–9.1)	42.6±11.4	1500 (950–2400)
Z/ χ^2 value		0.19	0.553	1.254	1.817	1.057	1.997	
P value		0.663	0.58	0.21	0.414	0.293	0.046	

Postoperative management

Immunosuppressive regimen: 20 mg Basiliximab in conjunction with 10 mg/kg methylprednisolone was given intraoperatively to induce immunity. Postoperatively, an anti-rejection regimen (tacrolimus + methylprednisolone + MMF + basiliximab) was employed. The second dose of basiliximab (20 mg) was given on Day 4 after the operation, while the oral administration (or via a gastric tube) of tacrolimus started at 36–48 h after the operation, with an initial dose of 0.6–0.8mg·kg⁻¹·d⁻¹ (split into 2 administrations per day). The blood concentration of tacrolimus during the early period after transplantation was maintained at 8–10 µg/L. If a patient was exposed to the risk of serious infection, the dosing regimen would be adjusted to a tacrolimus-based regimen containing 2 or 3 drugs, while the dose of immunosuppressant would be reduced. When such a dosing regimen was used, the blood concentration of tacrolimus should be maintained at 3–6 µg/L, while the liver functions are kept under close monitoring at the same time. In case of suspected clinical rejection, the immunosuppressive regimen should be adjusted according to the pathological results of liver biopsy.

Infection prevention: Due to the use of a large dose of immunosuppressant during the early period after transplantation, intravenous administration of broad-spectrum antibiotics was given routinely for the first 5 days after transplantation. In general, third-generation cephalosporins or piperacillin/tazobactam containing enzyme inhibitors were selected. During the

administration of antibiotics, the blood concentration of procalcitonin was evaluated to prevent bacterial infection. If the body temperature and blood concentration of procalcitonin in a recipient remained normal on Day 5 after the transplantation, the use of broad-spectrum antibiotics was discontinued. However, if a patient showed signs of fever, a series of tests (including blood procalcitonin test, C-reactive protein test, sputum smear and culture, routine ascites test and culture, blood culture, fungal glucan test, cytomegalovirus PCR, chest CR, and chest + abdomen CT) was conducted according to the clinical manifestation of the patient, so as to switch to a more reasonable anti-infection treatment.

Prevention of vascular complications: Bedside ultrasonography of the liver was conducted every day within the first week after the transplantation, so as to monitor the blood flow in portal vein, portal artery, and the vein in the transplanted liver. In case of any suspected vascular complications, contrast-enhanced ultrasonography, contrast-enhanced CT, or interventional angiography were conducted to obtain a definite diagnosis, followed by necessary treatments. If an anti-coagulation treatment was needed, a continuous venous infusion of heparin or argatroban was usually given to maintain the activated partial thromboplastin time at 1.5–2.0 times the upper limit of the normal value.

PDR test: PDR tests were given on Day 2 after the operation. The setting of PDR test was as follows: 0.5 mg/kg ICG (25 mg/ampoule, Liaoning TianYi Biological Pharmaceutical Co., Ltd.) was

injected via the peripheral or the central vein, and PDR was measured using the LiMON module on a PiCCO₂ Hemodynamic Monitor (PULSION MEDICAL SYSTEMS SE, Germany). Only the patients with a body weight greater than 20 kg were eligible for the PDR test. In addition, the PDR test was not given to those exhibiting unstable hemodynamic conditions. The frequency of the PDR testing depended on the length of a patient's stay in the ICU. In general, the PDR test was conducted once a day on Day 2, Day 3, and Day 4 after the operation. If the patient was held in the ICU for more than 1 week, the PDR test would be conducted again on Day 8 after the operation. Among the 115 patients, 52 patients received 2 tests, 45 patients received 3 tests, and 18 patients received 4 tests. The PDR data of each patient were recorded and we calculated their individual values.

Conventional Laboratory Tests conducted postoperatively:

During the stay in the ICU, routine blood tests and liver function tests were conducted daily within the first week after the transplantation. Hemoglobin (Hb), alanine aminotransferase (ALT), total bilirubin (TB), and pre-albumin (PA) values were recorded every day for each patient to calculate their own average values. In Months 1, 3, and 6 after the transplantation, the liver functions of the patients were reviewed and their ALT and TB values were recorded.

Discharge and follow-up visit: In general, the recipients were transferred to regular wards on Days 2–4 after the transplantation if their condition remained stable. The patients showing steady recovery were discharged from the hospital about 1 month after the operation. In the first year after the operation, the patients were followed up once every 1–2 months for routine blood and liver function tests, blood tacrolimus concentration measurement, and abdominal vascular ultrasonography. In case of any suspected vascular/biliary/infectious complications or organ rejection, the patient would be diagnosed and treated accordingly. Overall, the median postoperative follow-up lasted 8.5 months (range, 6–12 months).

Statistical analysis

SPSS (Version 18.0) statistical software was used for data analysis. The quantitative data are expressed as median (Q1, Q3) or mean \pm standard deviation, while the qualitative data are expressed as ratios (%). The *t* test or non-parametric test was used for inter-group comparison of quantitative data, while the chi-square test or Fisher's exact test was used for inter-group comparison of qualitative data. The log-rank test was used to compare the survival rates. The significance level was set at 0.05, and any difference with a *P* value of <0.05 was considered as statistically significant.

Results

General data and surgical conditions of patients

Among the 115 recipients, 50 were in the PDR <18%/min group, while the other 65 were in the PDR \geq 18%/min group. The patients in the PDR <18%/min group had significantly higher pre-operative MELD scores (16 vs. 12, *P*<0.001, Table 1) and intraoperative blood loss (1800 mL vs. 1500 mL, *P*=0.046, Table 2). In addition, there was no significant difference between the 2 groups in terms of gender, age, primary disease, surgical method, weight of liver graft, body weight of the recipient, warm and cold ischemia time of the liver graft, operational duration, and the duration of intraoperative anhepatic phase (*P*>0.05, Tables 1, 2).

General laboratory indicators after transplantation

Within the first week after the operation, the patients in the PDR <18%/min group had significantly lower values of Hb (93.4 vs. 103.1, *P*=0.002) and PA (2.01 vs. 2.24, *P*=0.05) and a significantly higher value of TB (46.4 vs. 30.7, *P*<0.001). However, no significant difference was found between the 2 groups in terms of ALT value at 1 week after the operation. Similarly, no significant difference was found between the 2 groups in terms of ALT and TB values at Months 1, 3, and 6 after the operation (*P*>0.05, Table 3).

Comparisons of postoperative complications

Among the 115 liver graft recipients, there were 6 cases of arterial complications (5.2%), 12 cases of portal vein complications (10.4%), 1 case of outflow obstruction (0.87%), and 20 cases of bile duct complications (17.4%) after transplantation. In the PDR<18%/min group, the incidence of arterial complications within 6 months after the transplantation was significantly higher than in the PDR \geq 18%/min group (8% vs. 3.1%, *P*=0.041, Table 4, Figure 1). However, no significant difference was found between the 2 groups in terms of portal vein complications, outflow obstruction, biliary complications, and organ rejection. In addition, the PDR <18%/min group had a higher incidence of postoperative infections such as pneumonia, abdominal infections, septicemia, and cytomegalovirus infection within 6 months after the operation, although only the incidence of pneumonia was significantly different between the 2 groups (34% vs. 15.4%, *P*=0.02, Table 4, Figure 2).

Survival analysis

By 1 June 2017, the median follow-up time for all these patients was 8.5 months (range, 6–12 months). In particular, 111 of the 115 recipients were discharged from the hospital, while 4 died within 1 month after the operation. Among the deaths,

Table 3. Comparison of postoperative routine laboratory indicators between the two groups.

Group	n	Mean Hb in week 1 (g/L)	Mean PA in week 1 (g/L)	Mean ALT in week 1 (U/L)	Mean TB in week 1 (μmol/L)	Mean ALT in month 1 (U/L)
PDR <18% min group	50	93.4±13.4	2.01±0.57	252.1 (92.3–469.7)	46.4 (30.0–88.6)	21 (14.7–38.9)
PDR ≥18% min group	65	103.1±17.9	2.24±0.66	225.4 (131.7–320.6)	30.7 (20.7–45.2)	23 (13.0–47)
Z/χ ² value		3.194	1.978	0.666	4.051	0.247
P value		0.002	0.05	0.506	<0.001	0.805

Group	Mean TB in month 1 (μmol/L)	Mean ALT in month 3 (U/L)	Mean TB in month 3 (μmol/L)	Mean ALT in month 6 (U/L)	Mean TB in month 6 (μmol/L)
PDR <18% min group	16.0 (9.3–23.5)	21 (15.0–29.0)	10.7 (7.9–17)	23.4 (16.0–25)	15.6 (14.0–27.0)
PDR ≥18% min group	12.5 (9–21)	28.8 (14.9–40)	11 (8–20)	20.5 (13.7–39)	16.8 (13.5–35)
Z/χ ² value	1.382	0.675	0.284	0.712	1.321
P value	0.167	0.5	0.776	0.65	0.425

Table 4. Comparison of postoperative complications between the two groups.

Group	n	Incidence rate of hepatic arterial complications (%)	Incidence rate of portal vein complications (%)	Incidence rate of outflow obstruction (%)	Incidence rate of bile duct complications (%)	Incidence rate of rejection (%)
PDR <18% min group	50	8 (4/50)	10 (5/50)	2 (1/50)	22 (11/50)	4 (2/50)
PDR ≥18% min group	65	3.1 (2/65)	10.8 (7/65)	0 (0/65)	10.8 (7/65)	7.7 (5/65)
Z/χ ² value		2.11	0.018	1.311	3.364	0.183
P value		0.041	0.894	0.435	0.067	0.669

Group	Incidence rate of pneumonia (%)	Incidence rate of septicemia (%)	Incidence rate of abdominal infections (%)	Incidence rate of biliary tract infections (%)	Incidence rate of cytomegalovirus infection (%)	Mortality
PDR <18% min group	34 (17/50)	14 (7/50)	22 (11/50)	20 (10/50)	8 (4/50)	6 (3/50)
PDR ≥18% min group	15.4 (10/65)	3.1 (2/65)	16.9 (11/65)	9.2 (6/65)	4.6 (3/65)	1.5 (1/65)
Z/χ ² value	5.451	3.283	0.471	2.736	0.129	0.61
P value	0.02	0.07	0.493	0.098	0.791	0.436

3 were in the PDR <18%/min group: 1 who died of intestinal fistula combined with infectious shock on Day 30, 1 who died of ruptured hepatic artery combined with hemorrhagic shock on Day 10, and 1 who died of aspergillus-induced pneumonia combined with respiratory failure on Day 6. The 1 death in the PDR ≥18%/min group was caused by abdominal infection combined with infectious shock on Day 18 after the operation. The 3-month and 6-month survival rates of the PDR <18%/min group were both 94% (47/50), as compared to 98.5% (64/65)

in the PDR ≥18%/min group, showing no significant difference in terms of survival between these 2 groups (Table 4, Figure 3).

Discussion

ICG is a bluish-green fluorescent dye of low toxicity and mild adverse effects. After intravenous injection, ICG is taken up by liver cells from blood circulation and excreted into the biliary

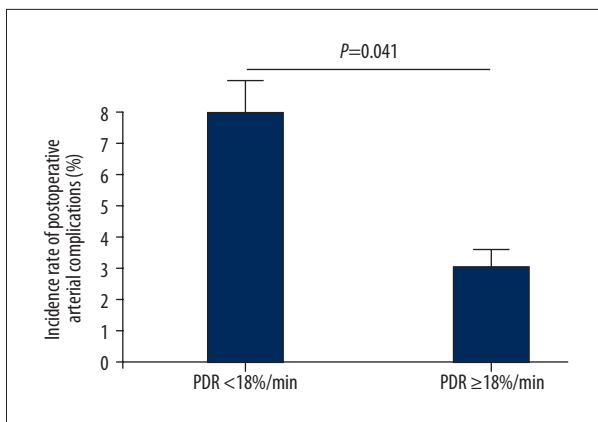


Figure 1. Comparison of the incidence rates of postoperative arterial complications between the 2 groups.

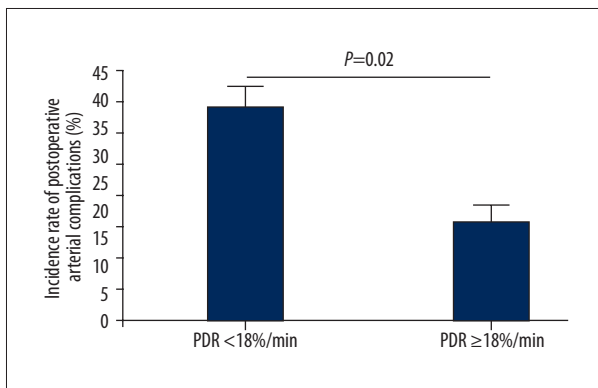


Figure 2. Comparison of the incidence rates of postoperative pneumonia between the 2 groups.

tract without entering the enterohepatic circulation [18]. Therefore, the excretion rate of ICG is closely related to liver perfusion, the physiological function of hepatocytes, and the total number of reactive liver cells, and hence can be used as a tool to evaluate the functional reserve in the liver [14]. In addition, the ICG test has a relatively higher sensitivity and specificity than other conventional tests of liver functions [19]. In particular, the measurement of PDR with densitometry was first reported in 1967, although this method required repeated blood sampling and hence resulted in greater trauma [20]. At present, pulse spectrophotometry can be used to conduct non-invasive and bedside PDR measurements within a few minutes, and thus is widely used in clinical applications [21]. So far, PDR testing has been used to carry out liver function assessment for patients with chronic liver diseases, cirrhosis, or liver failure. In addition, the PDR test can be used to monitor liver functions in patients who have undergone liver transplantation or to guide hepatectomy [14,19]. Finally, since the performance of liver perfusion is related to the performance of whole-body perfusion, the PDR test is also frequently used in the prognostic evaluation for patients with sepsis and abdominal hypertension [18].

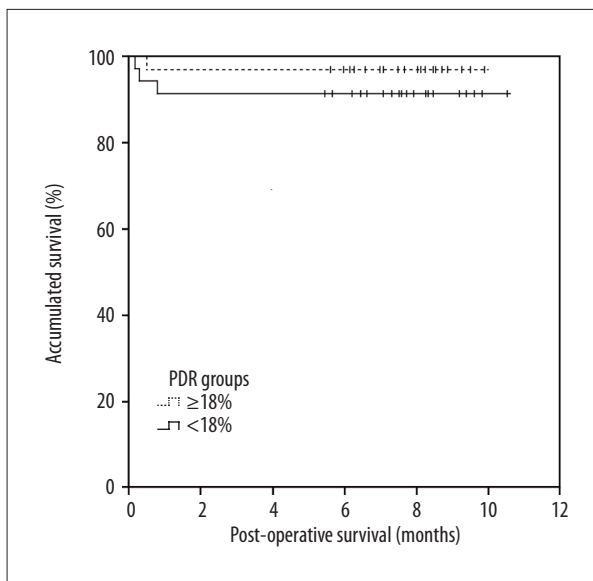


Figure 3. Post-transplant survival curve. Cumulative survival rate PDR group $\geq 18\%$ and $<18\%$, $\geq 18\%$ --- Censored, and $<18\%$ --- Censored.

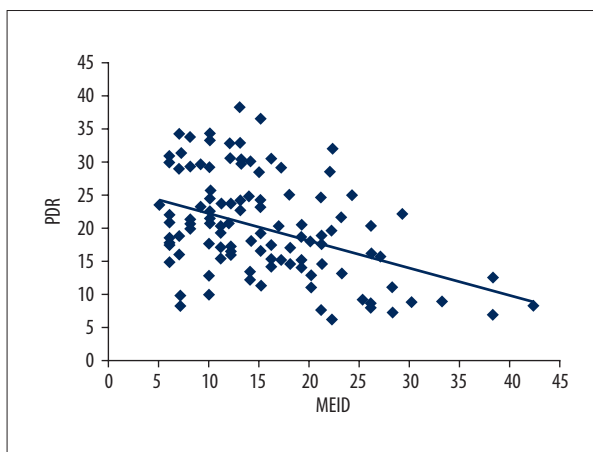


Figure 4. Correlation between MELD Score and ICG-PDR ($r=-0.424$, $P<0.001$).

Interestingly, PDR tests performed in the very early stage after transplantation may overestimate liver functions in those patients who later develop vascular complications. In fact, we have shown that the initial value of PDR_{r60} was still high in patients with arterial thrombosis, although such values eventually decreased [22]. Nevertheless, we suggest combining both time frames for PDR determination during the early diagnosis of SGD.

Intraoperative monitoring of liver functions via PDR measurement is a simple, non-invasive, and inexpensive way to predict the likelihood of early postoperative complications in patients undergoing liver transplantation [13]. For example, when a PDR value is above 23.5 min^{-1} , it can be used to indicate the

adequacy of initial graft functions, whereas a PDR value lower than this cut-off point triggers a warning for liver graft functions and quality, thus calling for immediate interventions to prevent the development of postoperative complications [23].

The results of the present study showed that the value of PDR measured in the early post-transplant period was negatively correlated with the pre-operative MELD score ($r=-0.424$, $P<0.001$, Figure 4). The calculation of MELD score was mainly based on the measurement of International Normalized Ratio for Prothrombin Time (INR), total bilirubin (TB), and serum creatinine (Cr) [24]. An elevated level of INR indicates coagulation malfunction and an increased risk of bleeding, which can lead to increased intraoperative blood loss and increased blood circulation instability. Since the malfunction of coagulation causes hypotension and hepatic hypo-perfusion, it can be detected by the PDR measurements. Secondly, the postoperative decline in bilirubin values tend to be slower in patients with a relatively high preoperative level of bilirubin [25]. In addition, bilirubin can competitively inhibit the uptake of ICG; therefore, an elevated level of bilirubin can lower PDR. It has been shown that patients with a higher preoperative MELD score have shorter expected survival and slower recovery of postoperative liver functions. In the present study, we found that the early postoperative PDR was negatively and linearly correlated with the preoperative MELD score, consistent with the findings of a previous study [26]. In addition, our study showed significant differences in terms of intraoperative blood loss and postoperative hemoglobin volume between the 2 groups. Since the increase in intraoperative blood loss can lead to a decreased blood volume, it can reduce the oxygen-carrying capacity of red blood cells and cause poor organ/tissue perfusion. Therefore, patients with increased bleeding risk or decreased hemoglobin would show a lower reserve of liver functions. In addition, our results also showed that the $PDR \geq 18\%/min$ group had a significantly higher level of pre-albumin as compared with the $PDR < 18\%/min$ group. As a protein synthesized in the liver and with a half-life of about 12 h, pre-albumin is a more sensitive index than albumin to reflect the synthetic function of the liver. In terms of the conventional indexes for liver functions (i.e., ALT and TB), only the mean value of TB between the 2 groups showed a significant difference in Week 1 after the operation, although the difference was gone by Month 3 and Month 6 after the operation. This may be because the PDR value measured within 2 weeks after the operation was highly associated with the TB level in the early post-transplant period, but as time went on, the indexes of liver functions in the 2 groups gradually converged by 3 months after the operation, suggesting that the early monitoring of PDR more accurately reflects hepatic recovery in the early post-transplant period. In some previous studies, Olmedilla et al. also found that a PCR level of $<10-13\%/min$ in the early post-transplant period was related to graft dysfunction [14,27,28]. In another

study, conducted by Tian et al., 62 patients underwent PCR tests within 2 weeks following liver transplantation and the results showed a significant correlation among the levels of total bilirubin, pre-albumin, and albumin measured at different time points; therefore, the authors treated the declined value of PDR as an independent risk factor of graft dysfunction during the early post-transplant period [29,30]. It should be noted that PDR is affected by the volume of hepatic blood flow and the ability of the liver to eliminate ICG. As low cardiac output is the main cause for systemic hemodynamics, local hepatic problems (e.g., hepatic arterial thrombosis and abdominal hypertension) are common factors resulting in a decreased volume of hepatic blood flow [25]. Levesque et al. studied 14 liver transplant patients who showed undetectable hepatic arterial blood flow under ultrasonography during the early post-transplant period. In 7 of the patients, hepatic artery thrombosis (HAT) was confirmed by CT and the PDR in the HAT group was significantly lower than that in the non-HAT group ($5.8 \pm 4.3\%/min$ vs. $15.6 \pm 3.5\%/min$, $p=0.0009$). In addition, a significant increase in PDR was observed in the HAT group after the patients received revascularization treatments (from $5.8 \pm 4.3\%/min$ to $15.6 \pm 3.5\%/min$, $p=0.006$). Hence, it was reasonable to conclude that PDR was a sensitive indicator to reflect the functional reserve in the liver. Among the 115 liver graft recipients enrolled in the present study, only 6 recipients showed severe complications of the hepatic artery, which included 3 cases of HAT and 3 cases of ruptured hepatic artery. Two of these 6 patients died of massive hemorrhage caused by their ruptured hepatic artery, while the liver functions in the other 4 patients gradually returned to normal. Interestingly, 2 of these 6 patients showed normal PDR profiles during the early postoperative period and both achieved early recovery of liver functions. However, on Day 18 after the operation, 1 of these 2 patients died of hepatic artery rupture caused by severe abdominal infection and septicemia, while the other patient experienced acute HAT on Day 16. The arterial complications of these 2 patients were both caused by acute factors, although their PDR was not re-evaluated due to the rapid progression of their diseases. Therefore, it seems that the statistical analysis of PDR acquired within 2 weeks after the operation may not accurately predict the possibility of arterial complications.

According to the results of this study, the incidence of arterial complications and pneumonia in the $PDR < 18\%/min$ group was significantly higher than that in the $PDR \geq 18\%/min$ group. Since the patients in the $PDR < 18\%/min$ group had relatively higher preoperative MELD scores, larger volumes of intraoperative bleeding, higher degrees of postoperative anemia, relatively slower recovery of liver graft functions, and relatively longer durations of ICU stay, the higher incidence of postoperative pneumonia in this group is not unexpected. In addition, it was found that the incidences of abdominal infection,

septicemia, biliary tract infection, and cytomegalovirus infection in the PDR <18%/min group was all higher than that in the PDR ≥18%/min group, although the differences were all statistically insignificant. These various types of infections may all lead to hemodynamic changes due to their effect on microcirculation, thus resulting in decreased efficacy of liver perfusion.

From the present study, we found that the PDR values measured during the early post-transplant period were closely correlated with the early liver graft functions. In addition, the PDR <18%/min group was associated with a significantly higher incidence of arterial complications. We believe that the early monitoring of postoperative PDR, in conjunction with conventional examinations (e.g., ultrasonography), could help to predict the occurrence of arterial complications [31,32]. Moreover, the results of this study showed that, at 1 year after transplantation, the incidence of biliary complications, organ rejection, sepsis, abdominal infection, bile duct infection, and cytomegalovirus

infection was quite different between the 2 groups, although these differences were not statistically significant. Nevertheless, it remains unclear whether the early monitoring of PDR could truly predict the long-term prognosis of liver transplantation. Therefore, further studies employing longer follow-up durations and larger sample sizes are required.

Conclusions

We demonstrated that the early postoperative value of ICG-PDR was closely related to graft function and might be novel biomarker to predict the risk of postoperative arterial complications.

Conflict of interest

None.

References:

- Murray KF, Carithers RL Jr.: AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology*, 2005; 41: 1407–32
- Ashokkumar C, Soltys K, Mazariegos G et al: Predicting cellular rejection with a cell-based assay: Preclinical evaluation in children. *Transplantation*, 2017; 101: 131–40
- Hassanain M, Simoneau E, Madkhali A et al: Post-transplant liver function score as an early surrogate marker of long-term outcome. *Ann Transplant*, 2015; 20: 198–205
- Garutti I, Sanz J, Olmedilla L et al: Extravascular lung water and pulmonary vascular permeability index measured at the end of surgery are independent predictors of prolonged mechanical ventilation in patients undergoing liver transplantation. *Anesth Analg*, 2015; 121: 736–45
- Busuttill RW, Farmer DG, Yersiz H et al: Analysis of long-term outcomes of 3200 liver transplantations over two decades: A single-center experience. *Ann Surg*, 2005; 241: 905–16; discussion 916–18
- Escorsell A, Mas A, Fernandez J, Garcia-Valdecasas JC: Limitations of use of the noninvasive clearance of indocyanine green as a prognostic indicator of graft function in liver transplantation. *Transplant Proc*, 2012; 44: 1539–41
- Perilli V, Avolio AW, Sollazzi L et al: Pulmonary gas exchange during orthotopic liver transplantation. *Br J Anaesth*, 1994; 73: 695–96
- Battaglia SE, Pretto JJ, Irving LB et al: Resolution of gas exchange abnormalities and intrapulmonary shunting following liver transplantation. *Hepatology*, 1997; 25: 1228–32
- Sheng QS, Lang R, He Q et al: Indocyanine green clearance test and model for end-stage liver disease score of patients with liver cirrhosis. *Hepatobiliary Pancreat Dis Int*, 2009; 8: 46–49
- Chijiwa K, Mizuta A, Ueda J et al: Relation of biliary bile acid output to hepatic adenosine triphosphate level and biliary indocyanine green excretion in humans. *World J Surg*, 2002; 26: 457–61
- Tsubono T, Todo S, Jabbour N et al: Indocyanine green elimination test in orthotopic liver recipients. *Hepatology*, 1996; 24: 1165–71
- Plevris JN, Jalan R, Bzeizi KI et al: Indocyanine green clearance reflects reperfusion injury following liver transplantation and is an early predictor of graft function. *J Hepatol*, 1999; 30: 142–48
- Caesar J, Shaldon S, Chiandussi L et al: The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin Sci*, 1961; 21: 43–57
- Levesque E, Saliba F, Benhamida S et al: Plasma disappearance rate of indocyanine green: A tool to evaluate early graft outcome after liver transplantation. *Liver Transpl*, 2009; 15: 1358–64
- Lock JF, Schwabauer E, Martus P et al: Early diagnosis of primary nonfunction and indication for reoperation after liver transplantation. *Liver Transpl*, 2010; 16: 172–80
- Jalan R, Plevris JN, Jalan AR et al: A pilot study of indocyanine green clearance as an early predictor of graft function. *Transplantation*, 1994; 58: 196–200
- Maring JK, Klompmaaker JJ, Zwaveling JH et al: Poor initial graft function after orthotopic liver transplantation: can it be predicted and does it affect outcome? An analysis of 125 adult primary transplantations. *Clin Transplant*, 1997; 11: 373–79
- Inal MT, Memis D, Kargi M, Sut N: Prognostic value of indocyanine green elimination assessed with LiMON in septic patients. *J Crit Care*, 2009; 24: 329–34
- de Liguori Carino N, O'Reilly DA, Dajani K et al: Perioperative use of the LiMON method of indocyanine green elimination measurement for the prediction and early detection of post-hepatectomy liver failure. *Eur J Surg Oncol*, 2009; 35: 957–62
- Eryilmaz HB, Memis D, Sezer A, Inal MT: The effects of different insufflation pressures on liver functions assessed with LiMON on patients undergoing laparoscopic cholecystectomy. *ScientificWorldJournal*, 2012; 2012: 172575
- Kaulen SA, Hubner C, Mieth J et al: [Indocyanine green elimination for the evaluation of liver function: Prognostic value in patients with community-acquired sepsis]. *Med Klin Intensivmed Notfmed*, 2014; 109: 531–40 [in German]
- Chen GH, Fu BS, Cai CJ et al: A single-center experience of retransplantation for liver transplant recipients with a failing graft. *Transplant Proc*, 2008; 40: 1485–87
- Deschenes M, Belle SH, Krom RA et al: Early allograft dysfunction after liver transplantation: a definition and predictors of outcome. National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. *Transplantation*, 1998; 66: 302–10
- Li J, Lei B, Nie X et al: A comprehensive method for predicting fatal liver failure of patients with liver cancer resection. *Medicine*, 2015; 94: e784
- Vos JJ, Wietasch JK, Absalom AR et al: Green light for liver function monitoring using indocyanine green? An overview of current clinical applications. *Anaesthesia*, 2014; 69: 1364–76
- Levesque E, Hoti E, Azoulay D et al: Non-invasive ICG-clearance: a useful tool for the management of hepatic artery thrombosis following liver transplantation. *Clin Transplant*, 2011; 25: 297–301
- Olmedilla L, Perez-Pena JM, Ripoll C et al: Early noninvasive measurement of the indocyanine green plasma disappearance rate accurately predicts early graft dysfunction and mortality after deceased donor liver transplantation. *Liver Transpl*, 2009; 15: 1247–53

28. Schneider L, Spiegel M, Latanowicz S et al: Noninvasive indocyanine green plasma disappearance rate predicts early complications, graft failure or death after liver transplantation. *Hepatobiliary Pancreat Dis Int*, 2011; 10: 362–68
29. Feng HL, Li Q, Wang L et al: Indocyanine green clearance test combined with MELD score in predicting the short-term prognosis of patients with acute liver failure. *Hepatobiliary Pancreat Dis Int*, 2014; 13: 271–75
30. Yunhua T, Weiqiang J, Maogen C et al: The combination of indocyanine green clearance test and model for end-stage liver disease score predicts early graft outcome after liver transplantation. *J Clin Monit Comput*, 2018; 32(3): 471–79
31. Kim JM, Kwon CH, Joh JW et al: Can the model for end-stage liver disease score replace the indocyanine green clearance test in the selection of right hemihepatectomy in Child-Pugh class A? *Ann Surg Treat Res*, 2014; 86: 122–29
32. Stauber RE, Wagner D, Stadlbauer V et al: Evaluation of indocyanine green clearance and model for end-stage liver disease for estimation of short-term prognosis in decompensated cirrhosis. *Liver Int*, 2009; 29: 1516–20