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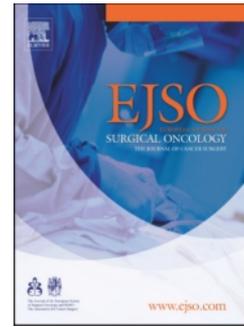
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Authors: N. deLiguori Carino, D.A. O'Reilly, K. Dajani, P. Ghaneh, G.J. Poston, A.V. Wu.



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# **Perioperative use of the LiMON method of indocyanine green elimination measurement for the prediction and early detection of post-hepatectomy liver failure.**

**Keywords:** liver resection, liver failure, indocyanine green, liver tumors

N de Liguori Carino, DA O'Reilly, K Dajani, P Ghaneh, GJ Poston, AV Wu.

Supra-Regional Hepatobiliary Unit, University Hospital Aintree, Liverpool, L9 7AL, UK

## **Correspondence and reprints:**

Nicola de Liguori Carino  
Supra-Regional Hepatobiliary Unit  
Directorate of General Surgery  
University Hospital Aintree  
Lower Lane, Liverpool  
L9 7AL, UK  
Tel: +44-151-5292740  
Fax: +44-151-5298547  
Email: Nicola.dlc@gmail.com

**Original article**

**ABSTRACT**

**Introduction:** A non-invasive liver function monitoring system, the LiMON®, has been developed that measures indocyanine green (ICG) elimination by pulse spectrophotometry. The aim was to assess the relationship between pre and post-operative ICG plasma disappearance rate (ICG PDR %/min) values and the onset of post-hepatectomy liver dysfunction.

**Methods:** 37 patients scheduled for major liver resections were selected. None had chronic liver disease. IGC PDR was measured preoperatively and on days 1, five and 10 postoperatively. On the same day, serum liver function tests were measured.

**Results:** The median preoperative and post-operative day 1 ICG PDR for the patients who developed liver dysfunction was significantly lower compared to the one of those who did not ( $p=0.044$ ,  $p=0.014$ ). Significant correlation was found between ICG PDR measurement taken on postoperative day 1 and bilirubin level on day 1 ( $p=0.002$ ), 5 ( $p<0.001$ ) and 10 ( $p= 0.001$ ). The same was true for ICG PDR on post-operative day 1 and albumin level on day 5 and 10 ( $p= 0.003$ ,  $p<0.001$ ).

**Discussion:** LiMON ICG PDR measured by pulse spectrophotometry is a quick, non-invasive and reliable liver function test in patients undergoing liver resection that aids in the prediction and early detection of post-hepatectomy liver dysfunction.

## INTRODUCTION

Liver resection is firmly established as the treatment of choice for operable primary and secondary liver tumours (1-7). Despite significant improvements in techniques of hepatic resection, anaesthetic interventions and peri-operative care, liver failure remains a serious but rare complication after major liver resection. (3, 8). A correct estimation of hepatic functional reserve is essential to prevent postoperative hepatic failure. So far, standard liver biochemistry tests have not been shown to be of predictive value. Future remnant functional liver volume after resection and preoperative Child-Pugh score in cirrhotic patients, are currently the most advocated methods (9-10).

Indocyanine green (ICG) clearance and ICG retention rate at 15 min (ICG R15) in patients with chronic liver disease are thought to reflect the degree of sinusoidal capillarization, intrahepatic portovenous shunt and alteration in liver blood flow (11-13) Thus ICG clearance test has been widely used to assess liver function reserve in patients with chronically reduced hepatic function (hepatitis, cirrhosis), evaluation of liver function in organ donors and recipients and critically ill patients. However, there are little data available in the literature on its use in the healthy liver and in the perioperative period for surgery on non-cirrhotic livers (14)

Recently, a non-invasive liver function monitoring system, the LiMON® (Pulsion Medical Systems, Munich, Germany), has been developed that measures indocyanine green (ICG) elimination by pulse spectrophotometry. This is a quick and non-expensive technique, that by intravenous injection of ICG-PULSION® dye, allows bedside assessment of the ICG plasma disappearance rate (ICG PDR %/min) and ICG R15(%/min).

The aim of this study was to assess the relationship between serial pre and post-operative ICG PDR(%/min) and R15(%/min) values and the onset of post-hepatectomy liver dysfunction.

## **METHODS**

### **Patients**

This study was conducted with the approval of the Local Research Ethics Committee. Between February 2006 and November 2007, thirty seven patients scheduled for major liver resections (three or more liver segments according to Couinaud's nomenclature) at the Hepato-Biliary Unit of our Institution, were selected for this study. Patients undergoing minor liver resection (up to 2 Couinaud segments, either separately or in contiguity) were not included in this study.

To minimize the influence of other variables on hepatic resection outcomes and focus on the application of the ICG test, patients with chronic liver disease or preoperatively deranged values of liver synthetic functions (INR and Albumin) were excluded from this study.

### **Liver resections**

Operations were performed under low central venous pressure anaesthesia (3-5 cm H<sub>2</sub>O)(15) Liver resections were performed anatomically according to Couinaud's liver segments. The liver was assessed by intraoperative ultrasonography. The hepatic parenchyma was dissected using either an ultrasonic surgical aspirator (CUSA Excel TM®, Radionics, Burlington, MA, USA) and argon beam plasma coagulation (APC) (Force GSU System®, Valleylab, Boulder, Colorado, USA) (AW, PG) or the crush-clamp technique with APC (GJP) according to the senior surgeon's preference. When needed, hepatic pedicle clamping was used with blood flow occlusion continued for 15 minutes, followed by a 10 minutes release period; this schedule was repeated until the liver parenchyma was resected.

**ICG Pulse Spectrophotometry (Indocyanine green test) and other liver function tests**

The LiMON® (Pulsion Medical Systems, Munich, Germany) method of measuring indocyanine green (ICG) elimination by pulse spectrophotometry was used. ICG Plasma Disappearance Rate (PDR %/min) and ICG Retention Rate after 15 minutes (R15 %/min) were measured in all patients instantaneously and non invasively by pulse spectrophotometry after injection of an intravenous bolus of 0.25 mg/kg of ICG-PULSION® dye dissolved in 5 ml of normal saline preoperatively and on days 1, five and 10 postoperatively. Measurements were performed while the cardiovascular circulation was stable. On the same day, serum total bilirubin( $\mu\text{mol/L}$ ), albumin( $\text{g/L}$ ), aspartate transaminase(AST)( $\text{iu/L}$ ), alkaline phosphatase( $\text{iu/L}$ ) and INR level were also measured. Complications and outcome were recorded.

**Study endpoints**

Primary study endpoint was to assess the correlation between perioperative ICG PDR(%/min) and the onset of postoperative liver dysfunction following major liver resection in the absence of liver cirrhosis or other chronic liver disease. Secondary study endpoint was to assess the correlation between perioperative ICG PDR and serum bilirubin, albumin, AST, alkaline phosphatase and INR as measured on consecutive days postoperatively in the same cohort of patients. Postoperative liver dysfunction was defined by any one of the following criteria: persistent hyperbilirubinemia (total bilirubin level over  $60\mu\text{mol/l}$ ), presence of ascites (postoperative drainage exceeding 500 ml/day, or detection of fluid by ultrasonography after the removal of the drains requiring diuretics), INR greater than 1.7 beyond postoperative day 7 and hepatic encephalopathy.(16)

### Statistical analysis

Continuous data were analysed using median, interquartile range and 95% CI with 2-tailed Mann-Whitney U testing for comparative analysis. Correlation between two continuous data sets was analysed using Spearman's rank correlation. Receiver Operating Characteristic (ROC) curves were used to analyse whether preoperative PDR or preoperative bilirubin conferred superior predictive information with regard to the development of postoperative liver failure. Positive predictive value, negative predictive value, sensitivity and specificity for predicting postoperative liver failure were calculated for preoperative PDR  $\leq 17.6\%$  and preoperative bilirubin  $\geq 17\ \mu\text{mol/l}$ , individually and in combination. Positive predictive value for liver failure represents the likelihood of predicting correctly a patient preoperatively who will develop liver failure following hepatic resection in the group analysed.

Because of the strong relationship between ICG PDR and ICG R15 (correlation  $-0.999$ ,  $p < 0.001$ ) similar models can be constructed that relate these two values to different variables. Therefore, only the ICG PDR data will be presented.

## RESULTS

### Surgery

All patients in the study underwent the planned liver resection. There were 26 male and eleven females with a median age of 67 years (range 39-77). Twenty seven patients had colorectal liver metastases, 4 cholangiocarcinoma, 4 hepatocellular carcinoma (HCC), 1 cutaneous melanoma metastases and one had a benign liver lesion (table 1). As for criteria selection none among the enrolled patients had a background clinical history of chronic liver disease.

Seventeen underwent formal right hemihepatectomy, nine right trisectionectomy, 6 left hemihepatectomy and five a combined procedure on the right and left lobes (table 1). Intermittent

hepatic pedicle clamping was used in 13 cases and the median operative blood loss was 617 ml (interquartile range 262.5 – 875 ml).

### **Postoperative complications and deaths**

Postoperative surgical complications were seen in seven cases: five had a bile leak (among whom one required treatment with ERCP), two had an intra-abdominal collection fluid that didn't require drainage. Liver dysfunction occurred in six patients and in two of these it was fatal. Among all liver dysfunction patients, five presented with hyperbilirubinemia and four with low albumin level (< 29 g/l) after postoperative day seven. Ascites occurred in only one case and encephalopathy in two.

The first of two patients who suffered fatal liver failure, this occurred after a right hemihepatectomy for colorectal liver metastases. The onset of clinical signs did not present until postoperative day five, with a high bilirubin level, while encephalopathy and ascites occurred after postoperative day ten. Patient died of multiorgan failure on postoperative day 28. The second case occurred after a right trisectionectomy with resection of segment I and portal vein reconstruction for hilar cholangiocarcinoma. On postoperative day 2, the patient became encephalopathic due to acute liver failure, eventually dying from multiorgan failure two days later. The bilirubin level remained below 40 $\mu$ mol/l.

The symptoms and signs in the others four patients with liver dysfunction improved during the second and third week and eventually they were well enough to be discharged. In none of the resected histopathological specimens were there features of chronic hepatitis, liver fibrosis or cirrhosis.

**ICG PDR**

The median (interquartile range) preoperative PDR for the six patients who developed liver dysfunction was significantly lower, 15.45 (11.63 – 17.48), compared to the patients who did not, which was 19.5 (16.3 – 26.4) (Mann-Whitney  $P=0.044$ ). A diagrammatical illustration of this relationship is given in figure 1. The Receiver Operating Characteristic (ROC) curve is a plot of true positive rate (sensitivity) against the false positive rate (specificity) for the different possible cut-off points of a diagnostic test. When a ROC curve was constructed that correlated preoperative PDR and bilirubin to development of postoperative liver dysfunction, an optimal cut-off value for preoperative PDR was established at 17.6 ( $P = 0.005$ ) (Figure 2). The 2x2 contingency table with positive and negative predictive values (PPV, NPV), sensitivity and specificity for each of preoperative PDR and bilirubin are shown in Table 2. A high risk group of patients with a preoperative PDR of less than 17.6 and a bilirubin greater than 17  $\mu\text{mol/L}$  was identified. When the predictive value of both preoperative PDR and bilirubin was combined the NPV was 90% and a PPV was 75% (Fisher  $P= 0.012$ ).

The median PDR value on postoperative day 1 for those patients who subsequently develop liver dysfunction was 6.75 (interquartile range 6.325 – 10.4). This was significantly lower than for those who did not have dysfunction, where the median value was 13.4 (interquartile range 9.875 – 20.475) (Mann-Whitney  $P=0.014$ ) (Figure 3).

Moreover it was found that PDR measurement taken on postoperative day 1 had a significant inverse correlation with bilirubin level on post operative day 1 ( $p=0.002$ ), day 5 ( $p=<0.001$ ) and day 10 ( $p= 0.001$ ). This, with a direct correlation, was also proven for postoperative day 1 PDR and albumin level as measured on postoperative day 5 ( $p= 0.003$ ) and day 10 ( $p=<0.001$ ).

When the other variables (AST, Alkaline Phosphate and INR), measured pre and post-operatively, were included in the regression analysis there was no evidence of any significant relationship with ICG PDR at any time.

## DISCUSSION

Hepatic functional reserve is one of the principal factors in the determination of a patient's ability to tolerate hepatic resection. Despite recent advances in surgery, liver failure after major hepatectomy remains a rare but serious complication. In a major systematic review of surgical resection to assess efficacy and safety for colorectal liver metastases (CRLM) the commonest specified causes of fatal complication was hepatic failure(17). Thus, assessment of liver function is critical in selecting patients for hepatic surgery.

This need for assessment has become all the greater in recent years as tremendous efforts have been made to expand the pool of suitable patients for potentially curative liver resection. Portal vein embolization induces atrophy of the liver to be resected and hypertrophy of the liver that will remain (i.e. increases the future liver remnant) (18). Similarly, two-stage hepatectomies in CRLM involve delayed re-hepatectomy after hypertrophy of the residual liver and may be used for large bilateral lesions in which a one stage resection of all the involved segments would lead to liver failure (19). Modern chemotherapeutic regimens combining 5-FU, folinic acid and oxaliplatin and/or irinotecan are associated with much higher response rates and can allow 10-30% of patients with initially unresectable CRLM to be successfully treated with liver surgery (20-23).

The clinical assessment of liver function has evolved from the original Child system, which was developed to relate liver cirrhosis and portal hypertension to portal systemic shunt surgery. The Child-Pugh modification provides refined predictions of risk, however it remains unreliable, particularly with regard to discriminating between good and poor risk Child-Pugh A patients (24). To overcome this limitation, various tests of clearance and tolerance, functional imaging and volumetric tests based on radiological imaging have been used to assess hepatic reserve (10). An ideal liver function test, that combines an accurate preoperative assessment of future liver remnant function with ease of performance, reproducibility and patient safety has yet to be developed.

Indocyanine green (ICG) is a tricarboyanine dye that binds to albumin and alpha-1 lipoproteins and is completely and exclusively removed from plasma by the liver and excreted into bile without intrahepatic conjugation or enterohepatic circulation. ICG Plasma Disappearance Rate (PDR %/min) and ICG Retention Rate after 15 minutes (R15 %/min) provide single tests of liver function. The LiMON® (Pulsion Medical Systems, Munich, Germany) method measures ICG elimination by pulse spectrophotometry. To date, this test has mainly been studied in patients undergoing liver resection for HCC, in studies from the Far East. Lam et al. have demonstrated that in selected patients with limited hepatic functional reserve, defined as an ICG retention value greater than 14%, postoperative and survival outcomes can be obtained comparable to those with better hepatic functional reserve, after major resection for HCC (25). Okochi et al. measured ICG by pulse spectrophotometry in a series of 22 patients, pre and post operatively. They showed a significant decrease in ICG clearance after surgery, related to the reduction in liver function. Lower values were obtained in five patients with prolonged jaundice (26). Perioperative real-time monitoring of ICG clearance was also assessed by Ohwada et al. in 75 patients also undergoing liver resection for HCC. ICG clearance was useful for evaluating the remnant liver functional reserve before, during and after liver resection. The estimated remnant ICG clearance was a significant predictor of liver failure (11). Early detection of liver failure has also been described by Sugimoto et al. in 51 patients undergoing hepatectomy. Although there were no differences between preoperative ICG clearance values in patients who developed liver failure, an ICG-K value  $< 0.07$  on postoperative day 1 had a sensitivity of 71.4% and a specificity of 95.5% for predicting liver failure (16).

By contrast, little is known about perioperative ICG values in a Western setting, where the majority of resections are for colorectal liver metastases and other primary or secondary tumours on a background of non-cirrhotic liver rather than cirrhosis-related HCC.

The present study has demonstrated that the median preoperative and post-operative day 1 ICG PDR of patients who developed post-operative liver dysfunction was significantly lower than in

those who did not developed dysfunction. In addition if established cut-off values for preoperative PDR and serum bilirubin were combined a high rate of sensitivity and specificity for prediction of post-resection liver dysfunction was achieved.

We have also shown a significant correlation between .postoperative day 1 ICG PDR and elevated bilirubin levels on this and subsequent days. The day 1 value for ICG PDR also correlated with serum albumin levels at post-operative days 5 and 10. Therefore the ICG PDR appears to have potential as a test for the prediction and early detection of post-hepatectomy liver dysfunction when compared with conventional liver function tests.

The LiMON's ICG test therefore provides important early information in the perioperative phase about which patients are at risk of developing liver failure, allowing aggressive remediable action to be taken, especially the provision of appropriate critical care beds and monitoring. Moreover, in an era where an increasing number of patients receive neoadjuvant chemotherapy for CRLM (27), with high risk of developing a degree of sinusoidal obstruction syndrome with associated complications following oxaliplatin (28, 29) and potentially lethal steatohepatitis following irinotecan (30), a correct estimation of hepatic functional reserve to guide hepatobiliary surgeons in tailoring the correct timing and extent of liver resection in individual patients is required.

In conclusion, the perioperative use of the LiMON® method of indocyanine green elimination measurement appears to be a useful tool for the prediction and early detection of post-hepatectomy liver dysfunction. Further validation of these data is needed.

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**Conflict of interest**

The authors state that they have no conflict of interest.

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Table 1 Patient demographic data

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Age (IQR)	67years (61 – 71)
Gender M : F	26 : 11
Pathology	
CRLM	27
HCC	4
Cholangiocarcinoma	4
Cutaneous Melanoma Mets	1
Benign Lesion	1
Type of Resection	
Right hemihepatectomy	17
Right trisectionectomy	9
Left hemihepatectomy	6
Combine procedure	5

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Table 2 Contingency table for predictive values of preoperative PDR and bilirubin in determining the development of liver failure following liver resection.

		Liver Failure	No Liver Failure	
Preoperative PDR %/min	≤ 17.6 %	5	11	PPV* = 31 % NPV *= 95% Sensitivity = 83 % Specificity = 62%  (Fishers P= 0.056)
	> 17.6 %	1	18	
Preoperative bilirubin μmol/l	Bilirubin >17	3	4	PPV = 43 % NPV = 90 % Sensitivity = 50 % Specificity = 87 %  (Fishers P= 0.073)
	Bilirubin <17	3	26	
Combined Preoperative bilirubin And PDR	PDR ≤17.6 + bilirubin >17	3	1	PPV = 75% NPV = 90% Sensitivity = 50% Specificity = 96%  (Fishers <b>P= 0.012</b> )
	Other combinations	3	27	

\*PPV, Positive predictive value; NPV, negative predictive value.

Figure 1: Box plot illustrating a significantly lower preoperative PDR in patients who subsequently develop liver dysfunction following resection

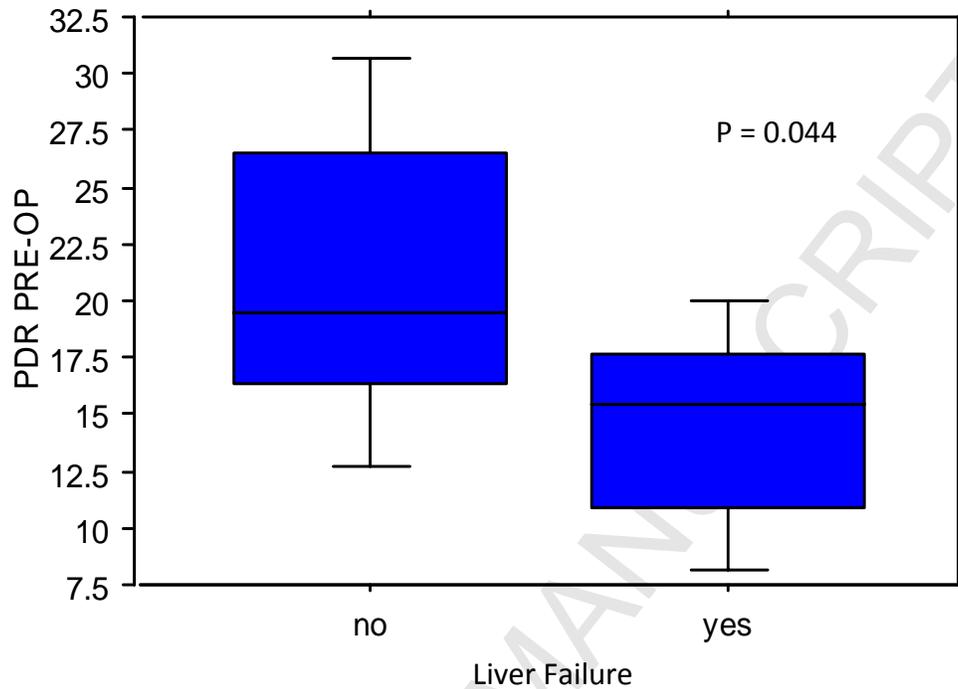


Fig 2: ROC curve that correlated preoperative PDR and bilirubin to development of postoperative liver dysfunction. 17.6 was an optimal cut-off value for preoperative PDR

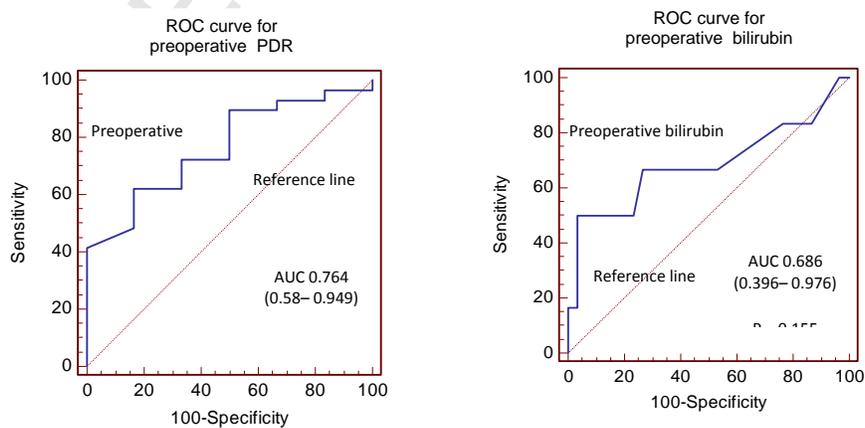


Figure 3 Box plot illustrating a significantly lower median PDR measured on postoperative day 1 in the group who develop liver dysfunction.

