Official journal
of the Spanish Society
of Chemotherapy

Revista Española de Quimioterapia
doi:10.37201/req/029.2024 - Advance Access published June 28, 2024

Original

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Use of noninvasive measurement of the indocyanine green plasma disappearance rate in patients with septic shock

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Article history
Received: 9 March 2024; Revision Requested: 1 May 2024; Revision Received: 25 May 2024;
Accepted: 29 May 2024; Published: 28 June 2024

ABSTRACT

Introduction. Our aim was to analyse the relation between serial values of the indocyanine green plasma disappearance rate (ICG-PDR) with hospital mortality in the first 48 hours of ICU admission in patients with septic shock.

Methods. A prospective observational study was carried out over 12 months of patients admitted to the ICU with septic shock. Each patient underwent noninvasive determination of ICG-PDR at 24 and 48 hours with the LiMON® module. Follow-up was performed until hospital discharge or exitus.

Results. 63 patients. Age 61.1±12.3 years. 60.3% men. SOFA score on admission 8.7±3.3, APACHE II score was 27.9±10.7 points. A total of 44.4% of patients died. The ICG-PDR values in the first 24 hours of ICU admission were lower in nonsurvivors: 10.5 (5.7-13.0)%/min vs. 15.9 (11.4-28.0)%/min, p <0.001. Furthermore, in nonsurvivors, there was no improvement in ICG-PDR between 24 h and 48 h, while in survivors, there was an increase of 25%: 15.9 (11.4-28.0)%/min and 20.9 (18.0-27.0)%/min, p=0.020. The silhouette measure of ICG-PDR cohesion and separation for the clusters analysed (nonsurvivors and survivors) was satisfactory (0.6). ICG-PDR<11.7%/min was related to in-hospital mortality, ICG-PDR> 18%/min to survival, and the interval between 11.7% and 18%/min covered a range of uncertainty. In the two-stage cluster, ICG-PDR, SOFA and APACHE II present satisfactory predictive scores 24 hours after patient admission.

Conclusions. ICG-PDR in our setting is a useful clinical prognostic tool and could optimise the decision tree in patients with septic shock.

Keywords: Indocyanine green; Septic shock; ICU

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Utilidad pronóstica de la medida no invasiva de la tasa de desaparición plasmática de verde de indocianina en pacientes con shock séptico

RESUMEN

Introducción. Nuestro objetivo fue analizar la relación de los valores seriados de la tasa de desaparición plasmática de verde de indocianina (ICG-PDR) con la mortalidad hospitalaria en las primeras 48 horas de ingreso en UCI en pacientes con shock séptico.

Métodos. Estudio observacional prospectivo durante 12 meses en pacientes de UCI con shock séptico. Cada paciente se sometió a la determinación no invasiva de ICG-PDR a las 24 y 48 horas con el módulo LiMON®. El seguimiento se realizó hasta el alta hospitalaria o el fallecimiento.

Resultados. 63 pacientes. Edad 61,1±12,3 años. 60,3% hombres. SOFA al ingreso 8,7±3,3, APACHE II 27,9±10,7 puntos. Un 44,4% de los pacientes falleció. Los valores de ICG-PDR en las primeras 24 horas de ingreso a la UCI fueron más bajos en los no supervivientes: 10,5 (5,7-13,0)%/min vs. 15,9 (11,4-28,0)%/min, p <0,001. Además, en los no supervivientes, no hubo mejora en ICG-PDR entre las 24 y 48 horas, mientras que en los supervivientes hubo un aumento del 25%: 15,9 (11,4-28,0)%/min y 20,9 (18,0-27,0)%/min, p=0,020. La medida de la silueta de la cohesión y separación de ICG-PDR para los grupos analizados (no supervivientes y supervivientes) fue satisfactoria (0,6). ICG-PDR<11,7%/min se relacionó con la mortalidad intrahospitalaria, ICG-PDR>18%/min con la supervivencia y el intervalo entre 11,7% y 18%/min abarcaba un rango de incertidumbre. En el clúster bietápico, ICG-PDR, SOFA y APACHE II presentan puntuaciones predictoras satisfactorias a las 24 horas del ingreso del paciente.

Conclusiones. ICG-PDR en nuestro entorno es una herramienta pronóstica clínica útil y podría optimizar el árbol de decisiones en pacientes con shock séptico.

Palabras clave: Verde de indocianina; Shock séptico; UCI

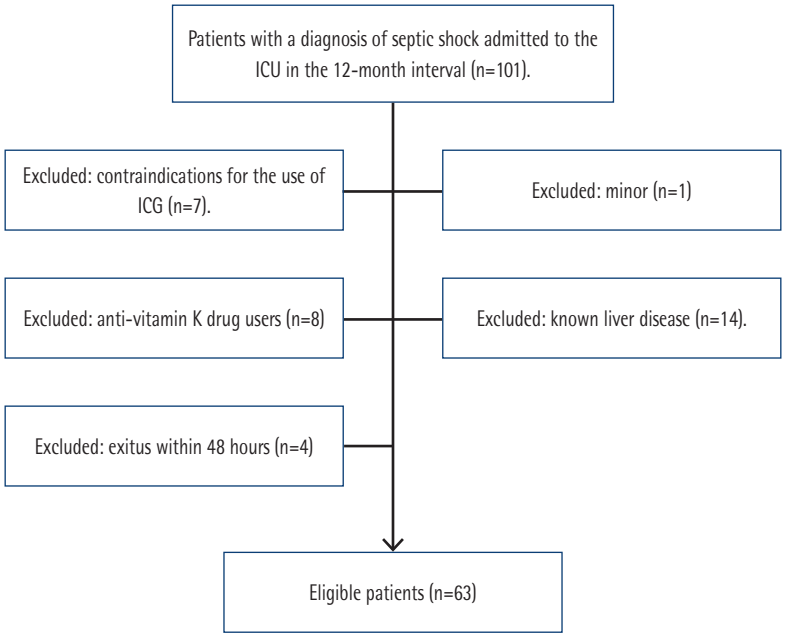

Figure 1 | **Flow diagram of patients included in the study.**

INTRODUCTION

In 35% of patients with sepsis or septic shock, without known previous liver disease, liver dysfunction occurs to a greater or lesser degree [1]. The causes of such functional alterations are diverse and include hypoxic liver injury, cholestatic dysfunction, sclerosing cholangitis in critical illness and drug-induced liver injury.

Liver dysfunction and acute liver failure of secondary causes are independent mortality factors in critically ill patients [2]. Therefore, the prognostic scales (SOFA, APACHE) applied in these patients incorporate different static tests of liver function and synthesis.

For years, dynamic function liver tests have been available to estimate liver functional reserve at the bedside in hepatectomised patients and in heterogeneous groups of critically ill patients. These tests are significantly superior to static tests as a predictor of mortality [2, 4-7]. The indocyanine green plasma disappearance rate (ICG-PDR) is currently the most widely used measure to assess hepatic functional reserve based on hepatic flow and hepatocyte metabolism.

Indocyanine green (ICG) is a water-soluble fluorescent dye with an absorption peak at 800 nm in blood plasma. When administered intravenously, it binds to plasma proteins (albumin and lipoproteins) its volume of distribution approximates the plasma volume. ICG is selectively absorbed by hepatocytes and is excreted unchanged in the bile without undergoing enterohepatic recirculation. The elimination of ICG from the blood depends on hepatic blood flow, the function of parenchymal cells, and biliary excretion [3].

ICG-PDR is the rate at which ICG disappears from plasma per unit time and is expressed in %/min. After intravenous administration of the dye, its ICG-PDR can be determined invasively and noninvasively (spectrophotometry). Its normal value is 18%/min, and values below 18% /min are associated with increased mortality and liver failure in critically ill patients [2, 8].

To date, few prospective studies have demonstrated the validity of the noninvasive ICG-PDR test for predicting mortality in patients with septic shock without known previous liver disease. The aim of the present study was to analyse whether serial values of the ICG-PDR obtained noninvasively in the first 48 hours of intensive care unit (ICU) admission in patients with septic shock are associated with mortality.

METHODS

We designed a prospective analytical observational study over a 12-month consecutive period (from May 30, 2019, to May 30, 2020) of all patients admitted to our 14-bed ICU with criteria of septic shock [9] (defined as lactate level>2 mmol/L and need for norepinephrine for mean arterial pressure >65 mmHg) with no history of previous known liver disease (Figure 1).

The main variable of the study is ICG-PDR at 24 and 48 hours, which has a normal value of 18%/min. Noninvasive de-

Table 1 Associations between hospital mortality and other parameters in patients with septic shock.

	Survivors N=35 (55.60%)	Non-survivors N=28 (44.40%)	p
Age (years)[1]	60 (50-65)	68 (56.5-71.75)	**0.022**
Gender			
Male	21(60.0)	17 (60.7)	0.580
Female	14 (40.0)	11 (39.3)	
Days of stay in Hospital[1]	19 (13-36)	17 (5.25-25.25)	0.113
Days of stay in ICU[1]	10 (6-14)	9 (4.25-16.75)	0.514
Days of mechanical ventilation[1]	4 (0-7)	8 (4- 16.75)	**0.003**
Focus			
Respiratory	16 (45.7)	10 (35.7)	0.294
Abdominal	13(46.4)	0.115	
Soft tissue	1 (3.6)	0.695	
Urologic	3 (10.7)	0.178	
Unknown	1 (3.6)	0.444	

[1]Median.

termination of ICG-PDR at 24 and 48 hours was performed at the bedside of each admitted patient with the LiMON® module. For each clinical variable recorded, the ICG-PDR values corresponding to the time of admission and the values obtained at 24 and 48 hours were recorded. Follow-up was performed in all cases until hospital discharge or death.

Protocol for administration of ICG. The technique was performed 24 hours after admission to the ICU (performed by the same physician following an agreed protocol). The patient is administered a single intravenous bolus of 0.25 to 0.50 mg of ICG diluted in water for injectable preparation per kilogram of body weight. The final dose of administration is indicated by the LiMON® monitor software based on prior knowledge of sex, age, height and weight. The total daily dose administered should be less than 5 mg/kg body weight.

The outcome variable was in-hospital mortality. Other clinical variables: 24 and 48 h values of ICG-PDR and validated scales predictive of mortality in the ICU: SOFA and APACHE II.

For the descriptive and inferential analysis, absolute frequency (N), relative frequency (%), mean values, median, standard deviation, and 25th, 50th and 75th percentiles were calculated. T tests: Chi-square, independent samples t test, U Mann-Whitney test for independent samples and Wilcoxon signed-rank test. A two-stage clustering was performed for the classification of the hospital mortality variable with different prognostic variables (ICG-PDR, SOFA, APACHE II). For analysis, we used IBM SPSS Statistics 22.

Informed consent for the administration of ICG was obtained from the patients/their families. The confidentiality of the data was guaranteed in accordance with ethical standards and current legislation concerning personal databases. The study protocol was approved by the Ethics Committee of the Hospital Universitario Virgen de Valme, Seville (protocol code 1438-N-19).

RESULTS

We analysed 63 critically ill patients (60.3% male); the age range was 61.1 ± 12.3 years. The mean hospital stay was 24.1±8.2 days and 11.8±4.8 days in the ICU. The SOFA score on admission was 8.7±3.3 and the APACHE II score was 27.9±10.7 points. All patients required sedation and connection to invasive mechanical ventilation.

Predictive capacity of ICG-PDR for overall mortality in patients with septic shock. A total of 28 patients (44.4%) died. Table 1 summarizes the epidemiological characteristics differentiated between survivors (S) and nonsurvivors (NS). The time course of different clinical variables during the first 48 hours of admission are shown in Table 2.

We observed that there were significant differences in ICG-PDR determinations between S and NS septic shock patients. The clearance rate was lower in NS than in S at 24 hours ($p<0.001$) and at 48 hours ($p<0.001$) (Table 3).

NS maintained low ICG-PDR values with no improvement between 24 and 48 hours: 10.5 (5.7-13.0) and 10.5 (3.9-13.6) %/min. However, in S, there was an increase of 25%: 15.9 (11.4-28.0) and 20.8 (18.0-27.0)%/min at 24 and 48 h, respectively (Table 4 and Figure 2).

The silhouette measure of ICG-PDR cohesion and separation for the clusters analysed (NS and S) was satisfactory

Table 2 **Time course of different clinical variables during the first 48 hours of admission in survivors and nonsurvivors.**

		Admission (0 h)	p	24 h	p	48 h	p
Mean arterial pressure (mmHg)	Survivors	60.0 (46.7-74.0)	0.347[2]	86.1 (78.8-93.3)	0.208[2]	93.0 (87.3-103.9)	**0.001[1]**
	Nonsurvivors	64.2 (59.2-77.4)		83.3 (71.7-92.5)		83.5 (72.3-93.5)	
Norepinephrine dosage (mcg/kg/min)	Survivors	0.7 (0.4-1.4)	0.923[2]	0.3 (0.2-0.7)	**<0.001[2]**	0.2 (0.1-0.5)	**<0.001[2]**
	Nonsurvivors	0.7 (0.3-1.9)		1.5 (0.6-2.5)		1.5 (0.4-3.2)	
PaO2/FiO2	Survivors	288.6 (167.0-411.1)	**0.017[2]**	397.5 (320.0-448.9)	**<0.001[2]**	382.8 (345.0-433.3)	**<0.001[2]**
	Nonsurvivors	131.1 (100.0-379.3)		125.1 (94.7-325.0)		171.8 (86.0-314.3)	
Urine Output (mL/kg/h)	Survivors	0.6 (0.4-0.9)	**0.048[2]**	0.9 (0.5-1.3)	**0.001[2]**	0.7 (0.6-1.1)	**0.002[2]**
	Nonsurvivors	0.4 (0-0.8)		0.5 (0.1-0.7)		0.5 (0-0.7)	
Creatinine (mg/dL)	Survivors	1.3 (1.0-1.9)	0.068[2]	1.3 (0.7-1.9)	**0.006[2]**	0.9 (0.7-1.6)	**<0.001[2]**
	Nonsurvivors	1.9 (1.1-2.9)		2.2 (1.5-3.0)		2.4 (1.4-4.1)	
Lactate (mmol/L)	Survivors	2.3 (1.1-3.7)	0.094[2]	1.6 (0.9-2.6)	**0.013[2]**	1.7 (0.9-2.1)	**<0.001[2]**
	Nonsurvivors	3.0 (2.1-4.3)		2.4 (1.7-4.5)		3.6 (2.1-7.7)	
Bilirubin (mg/dL)	Survivors	0.9 (0.4-2.3)	0.613[2]	0.7 (0.4-1.7)	0.105[2]	0.7 (0.3-1.3)	**0.036[2]**
	Nonsurvivors	1.0 (0.5-1.9)		1.2 (0.6-2.6)		1.3 (0.7-2.3)	
INR	Survivors	1.2 (1.1-1.2)	**<0.001[2]**	1.2 (1.1-1.3)	**<0.001[2]**	1.1 (1.1-1.2)	**<0.001[2]**
	Nonsurvivors	1.4 (1.2-1.6)		1.5 (1.3-1.8)		1.5 (1.3-1.8)	

[1]T Test; [2]U Mann-Whitney Test, INR: international normalized ratio.

(0.6003), and we proposed the ICG-PDR score for prognostic prediction in the sample of patients with septic shock: ICG-PDR<11.72%/min for in-hospital mortality and ICG-PDR>18%/min for survival. The interval between 11.7% and 18%/min covers a range of uncertainty. Optimal score ranges at 24 and 48 hours are shown in Figure 3.

Comparison of ICG-PDR with SOFA and APACHE II prognostic scores. All admitted patients were evaluated with the validated prognostic scores APACHE II at 24 hours and SOFA at admission and 24 and 48 hours (Table 3).

The silhouette measure of cohesion and separation for the clusters analysed in SOFA (0.5571) and APACHE II (0.7670) were adequate. In our sample of patients, SOFA scores above 11.02 points predicted mortality, while scores below 7.00 increased the probability of survival. APACHE II values higher than 31.04 points predict mortality. In the two-stage cluster, ICG-PDR, SOFA and APACHE II present satisfactory predictive scores 24 hours after patient admission.

We analysed the variability over time of ICG-PDR and SOFA to determine their intragroup behaviour in both S and NS patients.

As described in Table 3, the ICG-PDR in the S group had a statistically significant evolution over time, while in the NS group, the ICG-PDR values remained constant during the first 48 hours. The NS group presented similar values since admission; therefore, the ICG-PDR demonstrates little variability in serialisation (Figure 2). Nevertheless, there was statistically significant intragroup variability in SOFA scores in both the S and NS groups.

DISCUSSION

Septic shock patients acquire a life-threatening condition and should be promptly recognised and treated in an intensive care unit.

This study analyses the relationship between serial ICG-PDR measurements in the first 48 hours of ICU stay of patients with septic shock and in-hospital mortality. Our results show an association between the percentage of clearance, its time course and short-term mortality in septic shock.

The ICG-PDR has been demonstrated to be a dynamic test of liver function and has been proposed in numerous studies as an early prognostic predictor in critically ill patients with septic shock [2, 6, 10-13]. The noninvasive LiMON® method could be a noninvasive bedside prognostic tool for dynamic monitoring [14] in critically ill patients with septic shock in a manner comparable to SOFA and APACHE II [2, 10-13, 15].

We provide new proposals for optimal ranges of measures of the rate of plasma disappearance of indocyanine green that predict mortality or survival, considering that, to date, there is much heterogeneity among studies that propose multiple cut-off points, and there is currently no consensus on adjust-

Table 3 **Comparison of ICG-PDR determinations and SOFA and APACHE II scores in patients with septic shock.**

		Admission (0 h)	p	24 h	p	48 h	p
ICG-PDR[1] (%/min)	Survivors	-		15,9 (11,4-28,0)	**<0,001[2]**	20,8 (18,0-27,0)	**<0,001[3]**
	Non-Survivors	-		10,5 (5,7-13,0)		10,5 (3,9-13,6)	
SOFA[1]	Survivors	7,0 (6,0-11,0)	**0,164[3]**	7,0 (6,0-9,0)	**<0,001[3]**	5,0 (5,0-8,0)	**<0,001[3]**
	Non-Survivors	9,5 (7,0-11,0)		11,0 (8,3-12,8)		12,5 (11,0-20,8)	
APACHE II[1]	Survivors	-		19,0 (16,0-26,0)	**<0,001[2]**	-	
	Non-Survivors	-		35,5 (31,0-41,8)		-	

[1]Median; [2]T-test. [3]U Mann-Whitney test. ICG-PDR: indocyanine green plasma disappearance rate

ed figures to guide us in decision-making in these critically ill patients.

Predictive capacity of ICG-PDR for overall mortality in patients with septic shock. This study proposes the ICG-PDR obtained with noninvasive methods and in a safe manner to establish prognosis in a homogeneous cohort of patients diagnosed with septic shock. Although there are several authors who analyse this parameter, many are based on heterogeneous samples of critically ill patients (post-surgical, liver transplant, neurocritical and critically ill patients with multiple pathologies) [6].

If we compare our results with previous and similar publications that also focus their analysis exclusively on patients with septic shock [6, 10, 13, 15], it is reaffirmed that low values of early measured plasma green clearance are predictive of hospital mortality.

Kimura et al. (2001) [10] concluded that ICG-PDR was an early indicator of hepatocellular injury in septic shock and that low values during the first 24 to 120 hours correlated with poor prognosis.

Inal et al. (2009) [15] observed that ICG-PDR was significantly lower in NS (n=18) versus S (n=22) (12.1%±7.6%/min vs 21.2%±10.1%/min). There was 80% NS in the group with ICG-PDR less than 8%/min. Eighty-nine percent of patients who had an ICG-PDR greater than 24%/min survived. According to Kortgen et al. (2009) [16], an ICG-PDR less than 8%/min (AUC=0.81; p=0.006) predicts mortality with a sensitivity of 81% and a specificity of 70%.

Sakka et al. (2002) [12] demonstrated in 336 critically ill patients that small changes in ICG-PDR were associated with increased mortality. The lowest values collected in S were 16.7%±7.6%/min and in NS 8.0±6.7%/min.

Comparison of ICG-PDR with SOFA and APACHE II prognostic scores. The SOFA score is used as a key criterion in the diagnosis of sepsis syndrome and prognosis in patients with septic shock on admission [17]. We observed an association consistent with the literature [2] between mortality in patients with septic shock and an elevated APACHE II and SOFA score.

Lambden et al. [18] concluded that any scoring system that relies on the assessment of several clinical criteria or laboratory parameters, such as the SOFA score, may be subject to calculation variations, influenced by reliance on several laboratory samples, operator expertise or interobserver variability, and confounding factors that are not measured within the score.

Tallgren et al. [19] reported that the accuracy of the SOFA cardiovascular, renal, hematologic, and hepatic system assessment was 80%, while the respiratory and neurologic scores were correct in 75% and 70% of cases, respectively. This inconsistency meant that less than half of the SOFA scores agreed with the gold standard assessment.

Our study concludes that the variation in the serial measurement of the intragroup SOFA scale is statistically significant in both the S and NS groups in patients with septic shock. This reaffirms previous studies that modest changes in the SOFA score have a decisive influence on mortality [19, 20]. Nevertheless, we observed that ICG-PDR shows a constant evolution of values within nonsurvivors, which demonstrates that pathological values at 24 hours of admission can be valid for

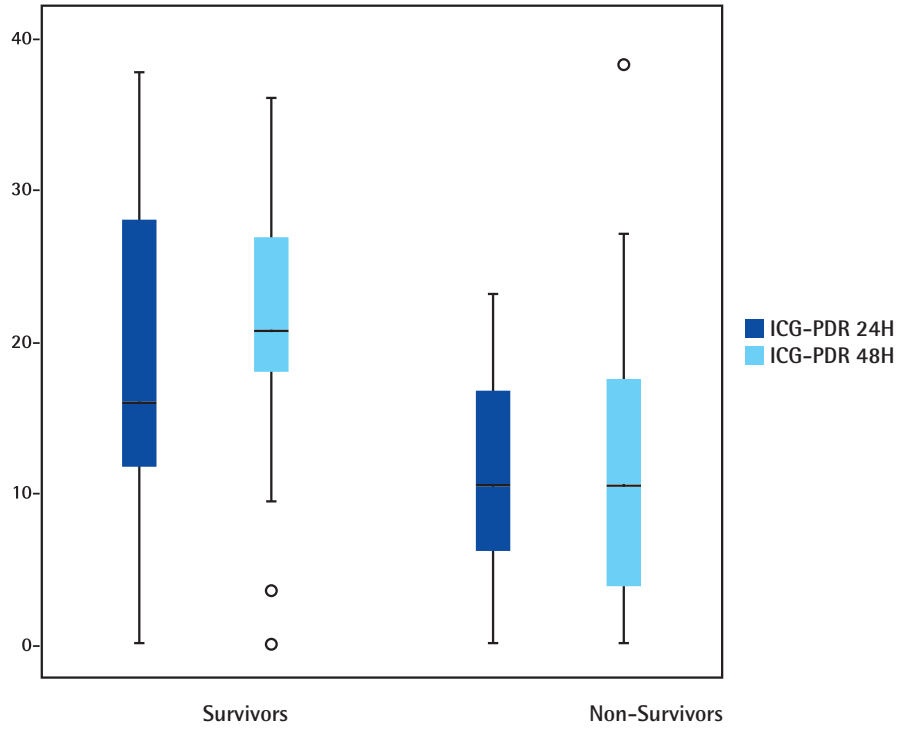

Figure 2 Box plot of the evolution of ICG-PDR (%/min) in the groups of survivors and nonsurvivors with septic shock.

ICG-PDR: indocyanine green plasma disappearance rate.

Table 4 Study of variability of ICG-PDR in patients with septic shock (24 hours-48 hours).

	Survivors	Non-Survivors
Variables	24-48 h	24-48 h
ICG-PDR (%/min)	**0,020**[1]	0,217[1]
SOFA	**<0,001**[1]	**<0,001**[1]

[1]Wilcoxon test. ICG-PDR: indocyanine green plasma disappearance rate.

predicting mortality, with little variability in the following determination.

It has been proposed that interoperator variability of the SOFA scale would decrease if the number of clinical criteria were reduced [19, 22]. Regarding this point, ICG provides benefits such as objective, noninvasive, immediate bedside measurement and prognostic value [6]. In addition, the ability to be a dynamic test with potential analysis of its temporal evolution is an advantage over scores such as APACHE II, which are determined only at 24 hours.

Clinical applicability. Our proposal to integrate ICG-PDR as a prognostic marker added to multimodal monitoring of septic shock together with validated scales such as SOFA and APACHE II is based on two theories taken from the literature. The first is that the treatment decision tree in patients depends on an accurate and consistent assessment of the SOFA score, which is also part of the definition of sepsis; therefore, low interoperator variability in the scores is essential [18]. Second, the European Medicines Agency accepted that in clinical trials in sepsis, a change in SOFA scores is a primary outcome of the study along with the reporting of mortality [23].

Limits of the study. Our study has some limitations. It was conducted in a single center with a small sample size of patients, which could limit the scope of our findings. We also excluded patients with pre-existing liver disease from our study, given that ICG-PDR is influenced by both hepatic blood flow and metabolic function. This exclusion may have impacted the initial values of ICG-PDR and consequently the accuracy of mortality prediction. Systematic studies that evaluate the validation of the ICG-PDR measure in these circumstances would be of great value. It would also be very useful to extend the study on the technical difficulties in the measurement of indocyanine green clearance during periods of tissue hypoperfusion in the first 6 hours of shock detection and treatment, which can alter the pulse wave and spectrophotometric measurement with digital clamp. In this sense, knowing the limitations may help to optimise this technique in the near future.

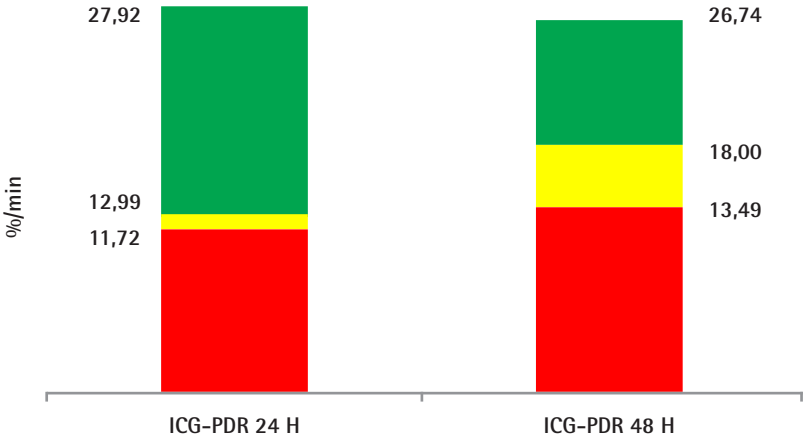

Figure 3 | **ICG-PDR score ranges (%/min) according to mortality or survival at 24 and 48 hours of admission in patients with septic shock.**

Red: mortality; green: survival; yellow: range of uncertainty. ICG-PDR: indocyanine green plasma disappearance rate.

CONCLUSIONS

ICG-PDR could be a useful clinical prognostic tool and could optimise the decision tree in patients with septic shock, in addition to clinical monitoring and validated prognostic scores. Further studies are necessary to design predictive models of ICG-PDR, appropriate to the clinical profile, that will allow us to improve patient care.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Macedonio Gutiérrez-Tello MD, Francisco Álvarez-Lerma MD, Antonio Lesmes-Serrano MD and Francisco Lucena-Calderón MD for their valuable guidance and support.

FUNDING

None to declare.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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