HHS Public Access

Author manuscript

*J Trauma Acute Care Surg*. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

*J Trauma Acute Care Surg*. 2019 May ; 86(5): 817–822. doi:10.1097/TA.0000000000002180.

# Clearance of Indocyanine Green in Severe Pediatric Burns

**Eva Carolina Diaz, M.D.**[1,4,5,6], **David Newcomb Herndon, M.D.**[2], **Mario Cleves, Ph.D.**[4,5,6], **Ronald P. Mlcak, Ph.D.**[2], **Asle Aarsland, M.D.**[1,3,*], and **Elisabet Børsheim, Ph.D.**[1,2,4,5,6,*]

[1]Former affiliation: Department of Surgery, University of Texas Medical Branch, Galveston, Texas; and Metabolism Unit, Shriners Hospitals for Children, Galveston, Texas.

[2]Department of Surgery, University of Texas Medical Branch, Galveston, Texas.

[3]Haukeland University Hospital, Bergen, Norway.

[4]Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas.

[5]Arkansas Children's Nutrition Center, Little Rock, Arkansas.

[6]Arkansas Children's Research Institute, Little Rock, Arkansas.

## Abstract

**Background:** Clearance of indocyanine green dye (ICGc) reflects sinusoidal perfusion and hepatocyte cell membrane function. Thus, ICGc is a reflection of the functional reserve of intact hepatocytes. The purpose of this study was to identify predictors of ICGc in severely burned children during the acute hospitalization and at the time of discharge from the ICU. A secondary aim was to determine the relationship between liver size and patient ICGc.

**Methods:** Twenty-six children (0.8 to 17 years old) with 35% or greater total body surface area burned (%TBSA-B) were included. Assessment of ICGc ($ml \cdot min^{-1} \cdot m^{-2}$) was done during the acute hospitalization (Median: 6 days after admission, Median: 14 days post-burn) and at the time of discharge from the ICU (Median: 19 days after admission, Median: 27 days post-burn). Age, TBSA-B, % third degree burns, inhalation injury, pre-existing chronic malnutrition, hematocrit, liver dysfunction, and time from burn injury were incorporated in multiple linear regressions as predictive variables of ICGc. Only variables with $p<0.05$ were retained in the final models.

**Results:** Time from injury and age were the strongest predictors of ICGc during the acute admission but not at the time of discharge from the ICU. Time from injury was negatively associated with ICGc, whereas age was positively associated. At the time of discharge from the ICU, ICGc was increased in proportion to the %TBSA-B, whereas inhalation injury and pre-

**Corresponding author:** Eva C. Diaz Fuentes. Address: 15 Children's Way, Slot 317, Little Rock, AR 72212. Phone: (501) 364-3056. Fax: (501) 364-3161 ecdiazfuentes@uams.edu.

AUTHOR CONTRIBUTION

A.A., D.N.H., E.B. conception and design of study.
A.A., R.P.M., D.N.H., E.B. data collection.
E.C.D.F., A.A. literature search.
E.C.D.F., A.A., M.C. data analysis.
E.C.D.F., A.A., E.B. data interpretation.
E.C.D.F. prepared manuscript.
E.C.D.F., D.N.H., M.C., R.P.M., A.A., E.B. critical revision of the manuscript.

*Co-senior authors

existing chronic malnutrition were associated with lower ICGc. There was no correlation between change-to-predicted liver length and ICGc.

**Conclusions:** The intrinsic ability of the liver to extract ICG from plasma was lower in younger burned patients during the acute admission, and in those with pre-existing chronic malnutrition and inhalation injury at the time of discharge from the ICU.

### Keywords

Indocyanine Green; burn injury; liver function

## Background

Following a major burn, the liver undergoes metabolic and morphologic adaptations. Increased glycolysis, glycogenolysis, and gluconeogenesis occur in response to elevated levels of stress hormones and energy requirements(1). Inflammatory and immunologic responses are also orchestrated by the liver in an attempt to preserve systemic homeostasis(2, 3)_ENREF_2. Although overt liver failure is infrequent in burn patients(4), _ENREF_4liver damage (as evidenced by decreased hepatic protein content, increased serum liver enzymes, and decreased synthesis of constitutive proteins) is a common finding(5, 6)_ENREF_2. In the pediatric population, liver enlargement develops immediately after burn injury and persist for at least a year post-trauma(5). Although liver cell proliferation occurs after burn injury(6), it is believed that liver enlargement is mainly due to intrahepatic edema, and in severe cases it may relate to fatty acid infiltration(7).

Static liver function tests are commonly used tools in the clinical setting. They provide information on hepatocellular integrity (aminotransferases), protein synthesis (albumin, coagulation factors), cholestasis (alkaline phosphatase, glutamyl transferase) and excretion (bilirubin). However, more complex functions such as liver clearance and metabolization capacity can only be assessed through dynamic liver function tests(8). Indocyanine green (ICG) is a fluorescent and infrared absorbing agent with a high hepatic extraction rate (70%). It does not undergo enterohepatic circulation and has negligible pharmacological effects(8, 9)_ENREF_9. Clearance of ICG dye (ICGc) is a dynamic liver function test that reflects both hepatic cell membrane function and sinusoidal perfusion. Therefore, ICGc is considered a good reflection of the functional reserve of intact hepatocytes(10).

To our knowledge, no study has used dynamic tests to assess liver function in severely burned children. Thus, the primary purpose of this study was to identify predictors of the clearance of ICG dye in severely burned children during the acute hospitalization and at the time of discharge from the ICU. A secondary aim was to determine the relationship between burn-induced changes in liver size and patient characteristics with the clearance of ICG.

## Methods

### Subjects

A post-hoc analysis was conducted on 26 severely burned children who underwent treatment at the Shriners Hospitals for Children – Galveston from 1999 to 2008. These children were

participants of several research projects with similar experimental design. Analyses were conducted on data from children for whom liver size and ICGc measurements were available after admission to the intensive care unit (~1 week) and at the time of discharge from the ICU (wounds 95% closed). Informed written consent was obtained from parents/guardians before enrollment, and assent/consent were obtained from children according to regulations. Experimental protocols were approved by the Institutional Review Board at the University of Texas Medical Branch.

## ICG infusion studies and estimation of ICGc

As part of their original research projects, children underwent 5-hour stable isotope infusion studies. A detailed description of this infusion protocol has been published elsewhere(11). ICGc was estimated from a constant infusion of the dye at 0.5 mg/min (1 ml/min) into the right femoral artery between hours 3 and 4 of the infusion study. ICG was first infused for 10 minutes in order to achieve a steady state(12). Then, blood was sampled at timed intervals from the contralateral femoral vein (FV). ICG concentrations were measured on a spectrophotometer at λ= 805nm (Spectronic 1001, Bausch and Lomb, Rochester, NY, USA). ICGc was calculated as the ratio of the infusion rate and the mean plasma dye absorbance over the sampling period.

$$ICGc(ml/min) = \frac{Absorbance\ in\ standard\ \times\ Dilution\ Factor \times Infusion\ Rate}{FV}$$

## Covariates

**Extent of the burn and inhalation injury—**Burn size and depth (% third degree) were clinically assessed. The Lund and Browder method(13) was used to estimate percent total body surface area burned (%TBSA). Inhalation injury was assessed with direct visualization of the airway using fiberoptic bronchoscopy.

**Pre-existing chronic malnutrition—**Chronic malnutrition at the time of the injury was assessed with the Center of Disease Control and Prevention (CDC) growth standards(14). Children with length/height-for-age below the 3$^{rd}$ percentile at the time of admission to the burn ICU were considered to have stunted growth, an indicator of chronic malnutrition(15).

**Liver size—**HP Sonos 100 CF echocardiogram (Hewlett-Packard Imaging Systems, Andover, MA, USA) with a 3.5 MHz transducer probe was used for this purpose. Liver length (cm) was measured with the patient in the recumbent position and the section level along the mid clavicular line was determined by simultaneous demonstration of the right kidney(16). The upper and lower points of the measurement of the liver span were marked and then measured from the sonographic image. All measurements were taken during breath holding (if possible) in older kids or during quiet breathing in younger patients.

**Liver failure—**Participants were considered to have liver failure if age <10 years and ICGc <195 mL·min$^{-1}$·m$^{-2}$, or if age ≥10 years old and ICGc <133 mL·min$^{-1}$·m$^{-2}$. These cutoff values are one standard deviation below reported mean values for healthy children(9).

**Other covariates—**Age at the time of the injury was determined from the participants' date of birth and burn date. Patients' hematocrit was measured on the day of the infusion study. Plasma volume, which decreases with increasing hematocrit concentration, regulates the amount of ICG-protein complexes available for hepatic dissociation. In consequence, an inverse correlation between hematocrit levels and ICGc may exist(17).

### Statistical analyses

Variables measured in the interval scale are summarized as medians and quartiles (Q1-Q3), whereas variables recorded in the ordinal or nominal scale are summarized as counts and percentages. The association between the clearance of ICG (dependent variable) with age, %TBSA burned, % third degree burned, inhalation injury, hematocrit, liver dysfunction, time from burn injury to ICGc measurement, and liver size (independent variables) was assessed using linear regression. Multiple linear regression was used to model ICGc (dependent variable) with patient characteristics simultaneously. The most parsimonious models were obtained using backward elimination. Only variables with $p<0.05$ were retained in the final model. Pearson's correlations were used to assess associations between absolute liver length (cm), liver length normalized to body weight (cm/kg), liver length normalized to body surface area ($cm/m^2$), and change to predicted liver length (%)(18) with age and normalized ICGc.

## RESULTS

Patient characteristics are presented in Table 1. Children's age ranged from 0.8 to 17 years, with a median age of 7 years. Ninety-six percent of the children were Hispanic and the median time from burn to ICGc measurements was14 and 27 days for the first and second study respectively. Forty-two of the participants suffered inhalation injury, whereas 26% (n=6) were chronically malnourished at the time of the injury. At the time of discharge from the ICU, liver ultrasound measurements were available for 22 children, thus results presented at this timepoint are based on a sample size of 22. A spaghetti plot depicting the trajectory of unadjusted ICGc ($ml \cdot min^{-1} \cdot m^{-2}$) between studied timepoints can be found as supplemental digital content (SDC, Figure 1).

### Multiple regression analyses

#### Clearance of ICG

**First study (Acute hospitalization, Table 2):** At the time of the first study, two children (8%) were considered to have liver failure. Among all the variables assessed, the time elapsed since burn injury was the strongest predictor of ICGc (Table 2). Time from burn injury was negatively associated with ICGc and accounted for 34% of the observed variance ($p=0.003$). Hematocrit was negatively associated with ICGc and explained 37% of the observed variance ($p=0.033$). Finally, age was positively associated with ICGc and explained 23% of the observed variance (Figure 1). For every year increase in age, ICGc increased by 29 $ml \cdot min^{-1} \cdot m^{-2}$ ($p=0.019$). Together, time from burn injury, hematocrit, and age explained 43% of the variance in in the clearance of ICG. Observed values of ICGc vs. age during the acute admission and at the time of discharge from the ICU can be found as SDC figures 2A and 2B, respectively.

**Second study (discharge from the ICU, Table 2):** At the time of discharge from the ICU (wounds 95% closed), %TBSA burned was the strongest predictor of ICGc accounting for 38% of the variance observed. For every 1% increase in %TBSA burned, ICGc increased by 14 $ml \cdot min^{-1} \cdot m^{-2}$ (Figure 2, $p$=0.003). Chronic malnutrition at the time of the injury was the second strongest predictor of ICGc and explained 32% of the observed variance ($p$=0.007). Chronic malnutrition was negatively associated with ICGc (Figure 3). Hematocrit ($p$=0.012) and inhalation injury ($p$=0.039) were negatively associated with ICGc and explained 29% and 21% of the observed variance, respectively. This final model explained 52% of the observed variance in ICGc at the time of discharge from the ICU. Observed values of ICGc vs. %TBSA, and observed ICGc values between patients with and without pre-existing malnutrition and inhalation injury, have been plotted as SDC Figures 3A, 3B and 3C, respectively.

### Correlations between liver size with patient characteristics and ICGc

Absolute liver length correlated with age (Figure 4A; $r^2$=0.59, $p$=0.001), weight ($r^2$=0.42, $p$=0.035), height ($r^2$=0.51, $p$=0.001), and body surface area ($r^2$=0.48, $p$=0.014). When normalized to body weight, liver length decreased with increasing age both during the acute phase of the injury ($r^2$=−0.76, $p$<.0001) and at the time of discharge from the ICU ($r^2$= −0.83, $p$<.0001;). When normalized to body surface area, liver length decreased with increasing age during the acute phase of the injury (Figure 4B, $r^2$=−0.68, $p$=0.0002) and also at the time of discharge from the burn unit ($r^2$=−0.84, $p$<.0001; not shown). Seventeen children (65%) during the acute hospitalization, and 19 (76%) at the time of discharge from the ICU had liver lengths above their age-predicted values. There was no correlation between change to predicted liver length (%) and normalized ICGc neither at the first (Figure 4C, $r^2$=0.06, $p$=0.755) nor the second studied timepoint (Figure 4D, $r^2$=0.07, $p$=737)

## DISCUSSION

The aim of the present study was to identify predictors of the clearance of ICG in severely burned children. The principal findings were that time from burn injury, age, chronic malnutrition, burn size, and inhalation injury independently affected ICGc. Finally, burn induced changes in liver length did not correlate with ICGc.

The hypermetabolic response triggered by the burn injury is characterized by mobilization of fuels and substrates needed to fulfill massive energetic demands and induce wound healing. Under these circumstances, the liver assumes a critical role in modulating endocrine, metabolic, immunologic, and inflammatory processes necessary for survival(19). Assessment of liver function in the context of severe burn injury has frequently been done with conventional (static) tests. Dynamic liver function tests are more advantageous in that they asses complex aspects of liver function, including hepatic clearance capacity(20).

ICG is an anionic dye with a high hepatic extraction rate thus its clearance is highly dependent on hepatic blood flow(21). ICG is extracted from plasma over the hepatocyte sinusoidal (baso-lateral) membrane, transported through the cell and finally excreted over the canalicular (apical) membrane(17). Because ICGc reflects sinusoidal perfusion and

hepatocyte cell membrane function, it is considered a measure of the functional reserve of intact hepatocytes(10, 20).

There is no agreement as to what constitutes liver failure in children when ICGc is used to measure liver function. Here, liver failure was defined as an ICGc below one standard deviation from the mean reported for healthy children(9). Based on this, 12% (n=3) of children had liver failure at the time of the first study. In contrast, Steinvall et al.(22) reported a much higher incidence (41%) of liver failure in severely burned adults when liver function was assessed using plasma disappearance rate of ICG. However, it is worth noting that in the latter study 35% of patients either had an underlying liver disease or were alcohol abusers at the time of the injury. It is known that liver disease, including alcohol induced liver injury affect the hepatic extraction of ICG(23). Thus, the unusually high incidence of liver failure reported for this particular group of adult patients could have been triggered and/or confounded by their preexisting liver disease.

In the present study, the number of days since the burn injury was negatively associated with ICGc when children were critically ill (first study), but no association was found when they were ready for discharge from the ICU (95% of wounds epithelialized). A great number of our patients come from referring facilities abroad hence transportation and appropriate level of care may be delayed. Children in this study had severe burns compromising 34 to 95% of the TBSA yet the time from burn injury to admission to our burn intensive care unit varied widely. The median time from burn to admission was 5 days, yet, it took some children >14 days to be admitted to our center. The authors believe this finding underscores the importance of initial care facilities and timely referral to burn centers in the clinical course of critically burned children.

A novel finding from this study was that normalized ICGc ($ml \cdot min^{-1} \cdot m^2$) in severely burned children increased linearly with increasing age during the acute hospitalization but not at the time of discharge from the ICU (Figure 1). Normalization of ICGc (ml/min) to body surface area (BSA) accounts for age-related differences in ICGc and allows an adequate comparison across different age-groups(9). In other words, no linear association between ICGc ($ml \cdot min^{-1} \cdot m^2$) and age should exist under normal physiological conditions. Thus, our results suggest that hepatic clearance capacity is lower in younger children during the most critical phase of the burn injury, but becomes comparable to that of older kids by the time of discharge from the ICU. Our finding supports previous reports of young age (<4 years) as a major determinant of outcomes in pediatric burns(24, 25). A limitation of our study, however, is that we did not account for sepsis or multiorgan failure, and this should be taken into consideration when interpreting our results.

The magnitude of cardiovascular, metabolic and inflammatory responses to burn injury relate to the extent of total body surface area burned(3, 26, 27). In this context, patients with larger burns have persistently greater energetic and metabolic demands than children with smaller burns. Thus, our finding of ICGc, and consequently liver blood flow, increasing in relation to the %TBSA burned at the time of discharge from the ICU agrees with the notion of burn size as a driver of the systemic response to burn trauma. Animal models of burn injury have shown that liver oxygen consumption not only increases in parallel with liver

blood flow but also occur in the context of an abnormally elevated β-hydroxybutyrate/acetoacetate ratio, indicating alterations in mitochondrial oxido-reduction state in the liver(28). Hence, the possibility that other metabolic mechanisms/disarrays intrinsic to the liver may be involved in our findings should be considered.

Another novel finding from our study was that pre-existing chronic malnutrition and inhalation injury were independently associated with lower hepatic clearance rate of ICG at the time of discharge from the ICU. Both pre-existing chronic malnutrition and inhalation injury increase mortality risk in burned patients(29, 30). The effects of inhalation injury on distant organs have been less studied. However, experiments of inhalation injury show a concomitant decrease in arterial oxygen saturation which may lead to distant organ hypoxia/ischemia(31). The present study does not allow assessment of mediating mechanism, but some possibilities could be considered. It is known that active transport processes on the basolateral pole of the hepatocyte are responsible for the extraction of ICG from plasma(17). These carrier systems have shown resilience to noxious stimuli in models of ischemia reperfusion injury in *ex vivo* experiments(10). In the latter study, hepatocytes responded to stress by overexpressing carrier proteins of ICG thus managing to preserve ICG uptake. Superimposition of aggravating factors, i.e., inhalation injury and malnutrition, to the burn injury may mitigate compensatory mechanisms resulting in disruption of ICG transport processes, or more simply, in greater loss of functional hepatic mass. Further studies characterizing the mechanisms and time course of our findings are warranted.

As expected, absolute liver length increased with increasing age whereas liver volume in relation to body weight was larger in younger kids(32). Despite younger kids having relatively larger livers, ICGc was lower among younger kids during the acute hospitalization, as previously discussed. Under physiological circumstances the functional parenchymal mass approximates liver size(9). In this group of children, liver length was above predicted values for 65% and 76% of children during acute hospitalization and at the time of discharge, respectively. Yet, normalized ICGc did not increase in relation to their change-to-predicted liver length (Figure 4). Given that ICGc is a reflection of hepatic functional parenchymal mass, our finding supports the notion that changes in liver size following a major burn are not mediated by increased cell proliferation but other mechanisms, e.g. hepatic edema formation and/or fatty acid infiltration(6).

Our results are strengthened by the longitudinal design of our study. A limitation could still be its small sample size. Also, the first measurement of ICGc was done ~14 days after the burn injury (~5 days after admission) when resuscitative efforts had taken place. Thus, this study does not report on the initial hepatocyte response to burn trauma. Finally, ICGc does not necessarily reflect biliary ICG excretion as previously shown in animal models of endotoxemia(33). Thus, the effects of burn injury on canalicular transport mechanisms and biliary excretion need to be further explored.

In conclusion, in this cohort of patients, delayed referral to a burn center and young age were associated with greater loss of functional hepatic mass, as evidenced by lower ICGc during the acute hospitalization. Thus, younger children and delayed admissions should be considered to be at higher risk for liver dysfunction during the critical period of the burn

injury. Pre-existing chronic malnutrition and inhalation injury were associated with lower ICGc at the time of discharge from the ICU. Future studies characterizing the time course, clinical implications and mechanisms of injury involved in these findings are necessary. Finally, ICGc does not increase in proportion to burn-induced changes in liver size corroborating the notion that liver enlargement is not mediated by hepatocyte proliferation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENT

The authors thank the children and their parents/caretakers for participating in this study. We thank the Clinical Research staff at the Shriners Hospitals for Children-Galveston (SHC-G) for support in screening, consenting and data collection. We thank the personnel in the Metabolism Unit, SHC-G for sample analyses.

**Conflict of interest and source of funding:** The authors have no conflict of interest to declare. NIH R01-HD049471, R01-GM056687, T32-GM008256, P50-GM060338 and Shriners of North America 84090, 84080, 71006, 71008, and 85310. ECD and EB are partly supported by funding from the Arkansas Biosciences Institute, the major research component of the Arkansas Tobacco Settlement Proceeds Act of 2000.

## REFERENCES

1. Gauglitz GG, Herndon DN, Jeschke MG. Insulin resistance postburn: underlying mechanisms and current therapeutic strategies. J Burn Care Res. 2008;29(5):683–94. [PubMed: 18695610]
2. Jeschke MG, Barrow RE, Herndon DN. Extended hypermetabolic response of the liver in severely burned pediatric patients. Arch Surg. 2004;139(6):641–7. [PubMed: 15197091]
3. Jeschke MG, Gauglitz GG, Kulp GA, Finnerty CC, Williams FN, Kraft R, Suman OE, Mlcak RP, Herndon DN. Long-term persistance of the pathophysiologic response to severe burn injury. PLoS One. 2011;6(7):e21245. [PubMed: 21789167]
4. Association AB. National Burn Repository Report. 2016.
5. Jeschke MG, Micak RP, Finnerty CC, Herndon DN. Changes in liver function and size after a severe thermal injury. Shock. 2007;28(2):172–7. [PubMed: 17529902]
6. Jeschke MG, Low JF, Spies M, Vita R, Hawkins HK, Herndon DN, Barrow RE. Cell proliferation, apoptosis, NF-kappaB expression, enzyme, protein, and weight changes in livers of burned rats. Am J Physiol Gastrointest Liver Physiol. 2001;280(6):G1314–20. [PubMed: 11352826]
7. Barrow RE, Mlcak R, Barrow LN, Hawkins HK. Increased liver weights in severely burned children: comparison of ultrasound and autopsy measurements. Burns. 2004;30(6):565–8. [PubMed: 15302422]
8. Sakka SG. Assessing liver function. Curr Opin Crit Care. 2007;13(2):207–14. [PubMed: 17327744]
9. Evans WE, Relling MV, de Graaf S, Rodman JH, Pieper JA, Christensen ML, Crom WR. Hepatic drug clearance in children: studies with indocyanine green as a model substrate. J Pharm Sci. 1989;78(6):452–6. [PubMed: 2760818]
10. Kortgen A, Paxian M, Werth M, Recknagel P, Rauchfuss F, Lupp A, Krenn CG, Muller D, Claus RA, Reinhart K, et al. Prospective assessment of hepatic function and mechanisms of dysfunction in the critically ill. Shock. 2009;32(4):358–65. [PubMed: 19197231]
11. Hart DW, Wolf SE, Chinkes DL, Gore DC, Mlcak RP, Beauford RB, Obeng MK, Lal S, Gold WF, Wolfe RR, et al. Determinants of skeletal muscle catabolism after severe burn. Ann Surg. 2000;232(4):455–65. [PubMed: 10998644]
12. Wolfe RR, Chinkes DL. Arterial-Venous Balance Technique to Measure Amino Acid Kinetics. Isotope Tracers in Metabolic Research Second ed 2005.
13. Hettiaratchy S, Papini R. Initial management of a major burn: II--assessment and resuscitation. BMJ. 2004;329(7457):101–3. [PubMed: 15242917]

14. Centers for Disease Control and Prevention, CDC. Clinical Growth Charts. [Accessed: 10–05–2018]. Available from: https://www.cdc.gov/growthcharts/clinical_charts.htm#Set2.
15. World Health Organization, WHO. Global Database on Child Growth and Malnutrtion 2017 [Accessed: 10–05–2018]. Available from: http://www.who.int/nutgrowthdb/about/introduction/en/index2.html.
16. Dittrich M, Milde S, Dinkel E, Baumann W, Weitzel D. Sonographic biometry of liver and spleen size in childhood. Pediatr Radiol. 1983;13(4):206–11. [PubMed: 6888991]
17. Ott P Hepatic elimination of indocyanine green with special reference to distribution kinetics and the influence of plasma protein binding. Pharmacol Toxicol. 1998;83 Suppl 2:1–48.
18. Konus OL, Ozdemir A, Akkaya A, Erbas G, Celik H, Isik S. Normal liver, spleen, and kidney dimensions in neonates, infants, and children: evaluation with sonography. AJR Am J Roentgenol. 1998;171(6):1693–8. [PubMed: 9843315]
19. Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? Mol Med. 2009;15(9–10):337–51. [PubMed: 19603107]
20. Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg. 2005;12(1):16–22. [PubMed: 15754094]
21. De Gasperi A, Mazza E, Prosperi M. Indocyanine green kinetics to assess liver function: Ready for a clinical dynamic assessment in major liver surgery? World J Hepatol. 2016;8(7):355–67. [PubMed: 26981173]
22. Steinvall I, Fredrikson M, Bak Z, Sjoberg F. Incidence of early burn-induced effects on liver function as reflected by the plasma disappearance rate of indocyanine green: A prospective descriptive cohort study. Burns. 2011.
23. Burns E, Triger DR, Tucker GT, Bax ND. Indocyanine green elimination in patients with liver disease and in normal subjects. Clin Sci (Lond). 1991;80(2):155–60. [PubMed: 1848168]
24. Rosanova MT, Stamboulian D, Lede R. Risk factors for mortality in burn children. Braz J Infect Dis. 2014;18(2):144–9. [PubMed: 24275369]
25. Thombs BD, Singh VA, Milner SM. Children under 4 years are at greater risk of mortality following acute burn injury: evidence from a national sample of 12,902 pediatric admissions. Shock. 2006;26(4):348–52. [PubMed: 16980880]
26. Wilmore DW, Aulick LH, Mason AD, Pruitt BA Jr. Influence of the burn wound on local and systemic responses to injury. Ann Surg. 1977;186(4):444–58. [PubMed: 907389]
27. Jeschke MG, Mlcak RP, Finnerty CC, Norbury WB, Gauglitz GG, Kulp GA, Herndon DN. Burn size determines the inflammatory and hypermetabolic response. Crit Care. 2007;11(4):R90. [PubMed: 17716366]
28. Yamaguchi Y, Yu YM, Zupke C, Yarmush DM, Berthiaume F, Tompkins RG, Yarmush ML. Effect of burn injury on glucose and nitrogen metabolism in the liver: preliminary studies in a perfused liver system. Surgery. 1997;121(3):295–303. [PubMed: 9092130]
29. Tredget EE, Shankowsky HA, Taerum TV, Moysa GL, Alton JD. The role of inhalation injury in burn trauma. A Canadian experience. Ann Surg. 1990;212(6):720–7. [PubMed: 2256764]
30. Grudziak J, Snock C, Mjuweni S, Gallaher J, Cairns B, Charles A. The effect of pre-existing malnutrition on pediatric burn mortality in a sub-Saharan African burn unit. Burns. 2017;43(7):1486–92. [PubMed: 28433345]
31. Traber DL, Linares HA, Herndon DN, Prien T. The pathophysiology of inhalation injury--a review. Burns Incl Therm Inj. 1988;14(5):357–64. [PubMed: 3067821]
32. Murry DJ, Crom WR, Reddick WE, Bhargava R, Evans WE. Liver volume as a determinant of drug clearance in children and adolescents. Drug Metab Dispos. 1995;23(10):1110–33. [PubMed: 8654200]
33. Stehr A, Ploner F, Traeger K, Theisen M, Zuelke C, Radermacher P, Matejovic M. Plasma disappearance of indocyanine green: a marker for excretory liver function? Intensive Care Med. 2005;31(12):1719–22. [PubMed: 16231068]

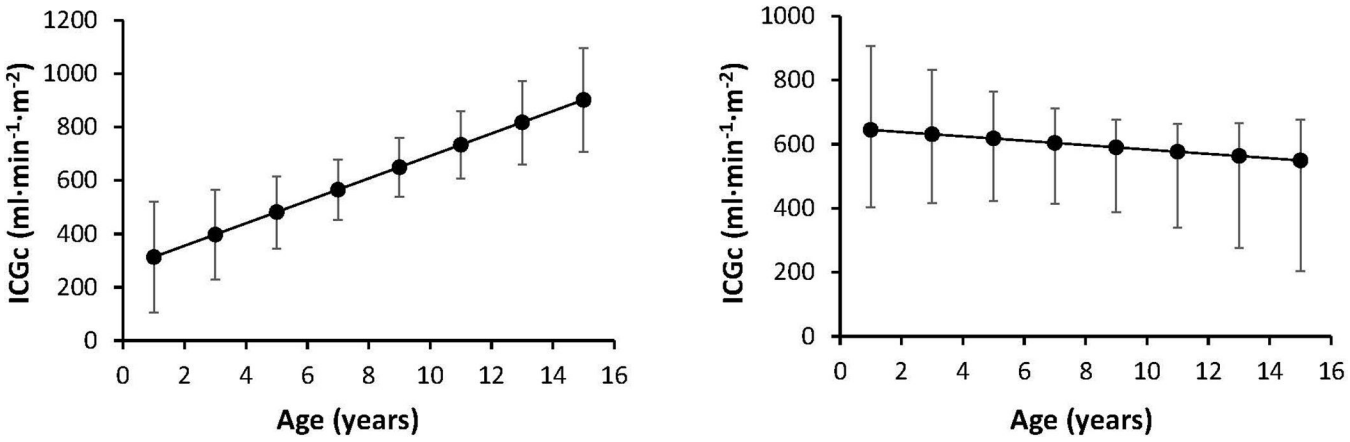


**Figure 1.**

Adjusted means and 95% confident intervals for ICGc by age during the acute phase of the burn injury (A) and at the time of discharge from the ICU (B). Means for (A) have been adjusted for hematocrit and time from burn injury.

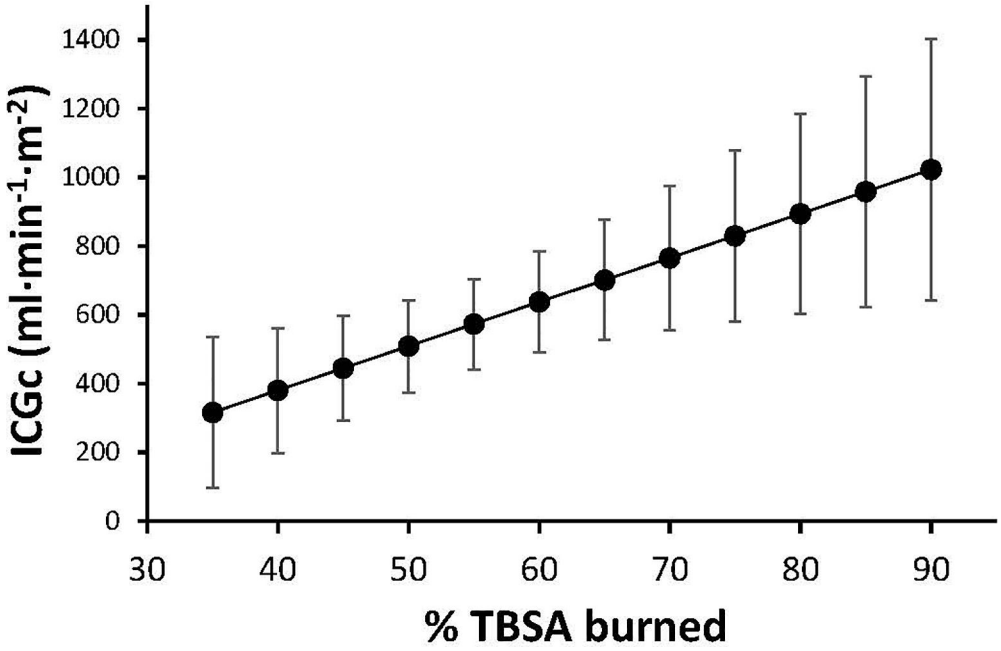


**Figure 2.**

Adjusted means and 95% confident intervals for ICGc by %TBSA burned. Means have been adjusted for hematocrit, inhalation injury and pre-existing chronic malnutrition.

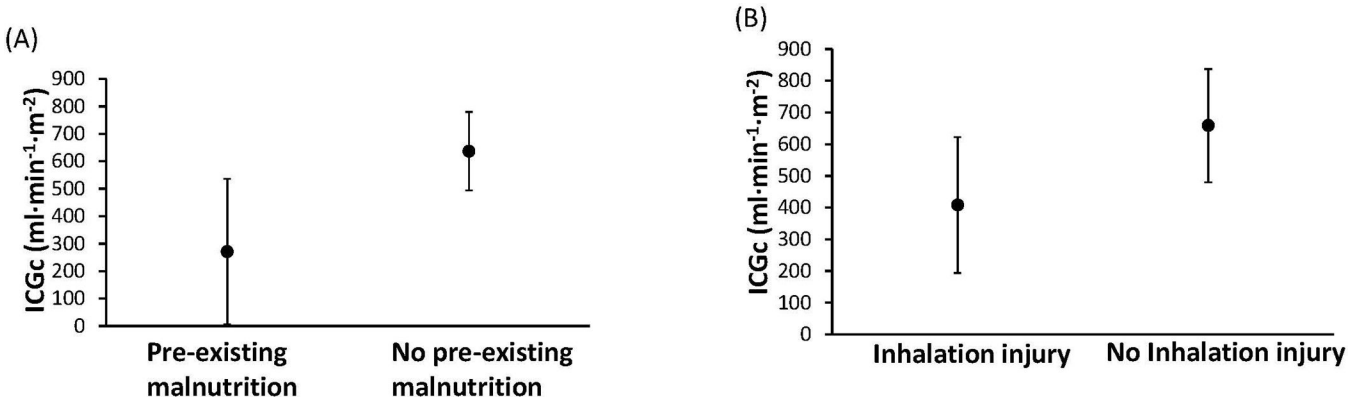


**Figure 3.**

Adjusted means and 95% confident intervals for ICGc in patients with pre-existing chronic malnutrition (A) or inhalation injury (B). Means have been adjusted between each other and hematocrit.

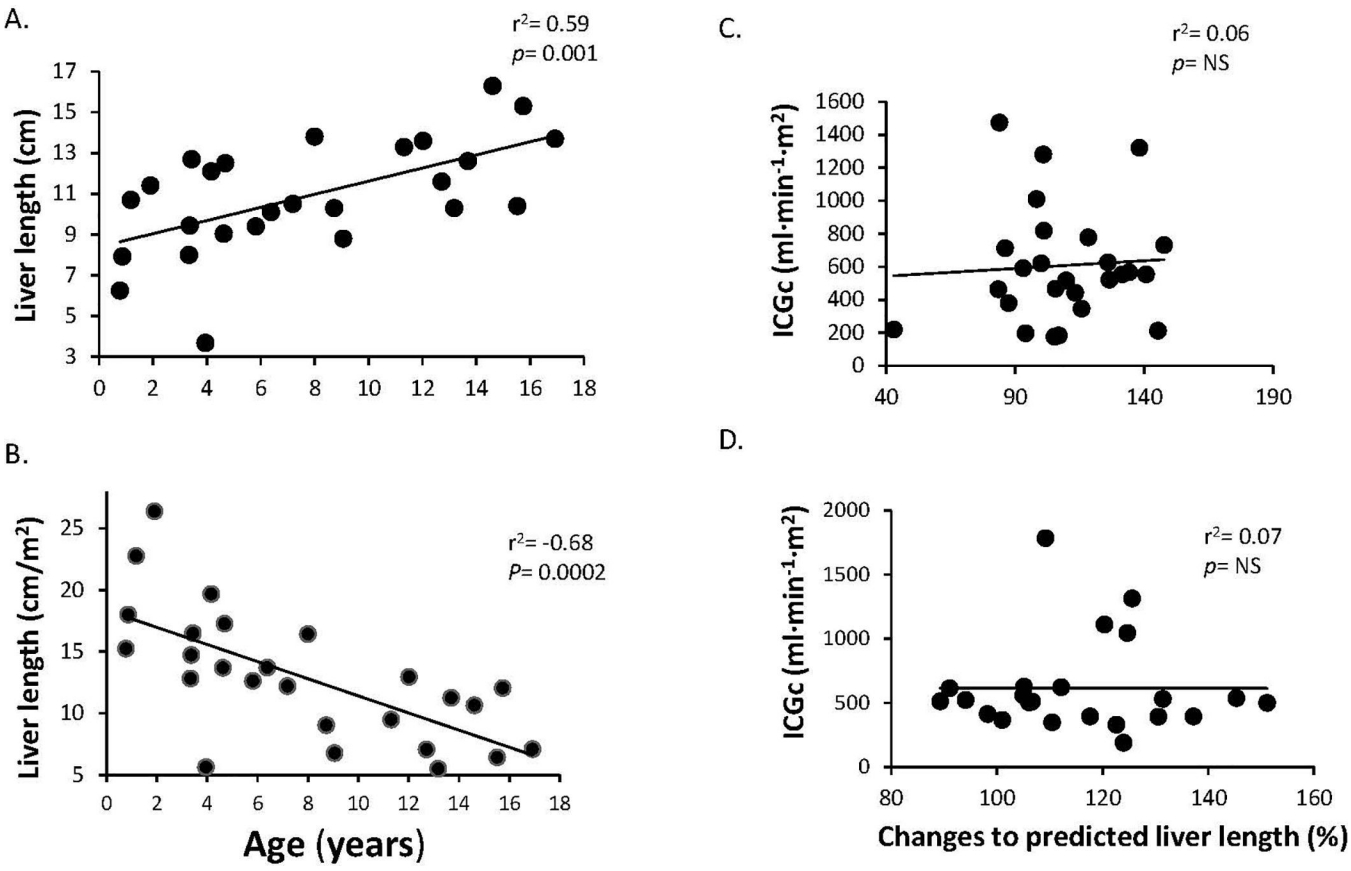


**Figure 4.**

Correlation between age and absolute liver length (A), liver length normalized to body surface area (B) during the acute admission. Relationship between change to predicted liver length and ICGc during the acute phase of the injury (C) and at the time of discharge from the ICU (D).

**Table 1.**

Patient characteristics.

| Variable | N=26 |
|---|---|
| Age, years, median (range) | 7 (0.8–17) |
| Male: Female | 19: 7 |
| Ethnicity, No. ( %) | |
| Hispanic | 25 (96) |
| Burn to admit, days, Median (Q1-Q3) | 5 (2–14) |
| Burn to 1st study, days, Median (Q1-Q3) | 14 (8–28) |
| Burn to 2nd study, days, Median (Q1-Q3) | 27 (21–40) |
| Admit to study, days, Median (Q1-Q3) | 6 (5–10) |
| Admit to 2nd study, day, Median (Q1-Q3) | 19 (14–25) |
| Etiology, No. (%) | |
| Flame | 20 (77) |
| Scald | 4 (15) |
| Electrical | 2 (8) |
| % TBSA burned, Median (Q1-Q3) | 50 (41–67) |
| % Third degree, Median (Q1-Q3) | 38 (24–55) |
| Inhalation injury, No. (%) | 11 (42) |
| Chronic malnutrition, No. (%) | 6 (23) |

Data expressed as medians (Q1-Q3), counts and percentages.

**Table 2.**

Multiple regression analyses to identify the most parsimonious model for ICGc.

| ICGc | Model | β | SE | $Pr^2$ | *p*-value | $R^2$ |
|---|---|---|---|---|---|---|
| **First acute** | Time from injury | -8.6 | 2.6 | 0.34 | 0.003 | 0.43 |
| | Hematocrit | -37.2 | 16.4 | 0.19 | 0.033 | |
| | Age | 29.3 | 11.6 | 0.23 | 0.019 | |
| **Discharge ICU** | %TBSA burned | 13.7 | 4.0 | 0.38 | 0.003 | 0.52 |
| | Malnutrition | -417 | 138.1 | 0.32 | 0.007 | |
| | Hematocrit | -62.1 | 22.3 | 0.29 | 0.012 | |
| | Inhalation | -306 | 138.1 | 0.21 | 0.039 | |

SE= standard error; $Pr^2$= squared partial correlation; TBSA= total body surface area