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Research Article

Prognosis Prediction in Liver Transplant Patients: A Comparison among Indocyanine Green Pulse-Spectrophotometry Clearance, Wagener, Donor Risk Index and Olthoff Scores

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Abstract

Background: Over the past few years, a multitude of liver function biomarkers have been validated with the intent of predicting outcomes after liver transplant, although it is still unclear which biomarkers might be better suited for which outcomes.

Aims: To measure the association between outcomes after liver transplant and the Wagener and Olthoff criterion, Donor Risk Index and the Indocyanine green pulse-spectrophotometry clearance.

Methods: This is a prospective registry conducted within a single academic hospital. Inclusion criteria involved all patients undergoing deceased donor liver transplant from any etiology. Outcomes of interest were the following complication types: Infectious, bleeding, re-operation, and acute renal failure requiring hemodialysis. All outcomes were collected during the in-hospital stay and throughout the first three months after transplant. We conducted analyses through a series of generalized linear models with binomial and Gaussian distribution families.

Results: The most frequent etiologies were hepatocellular carcinoma (50%) and C virus hepatitis (42.5%). The most common Child-Pugh classification was C (45%). We found that both Indocyanine green and the Wagener criterion could predict acute renal failure requiring hemodialysis in our sample. When we compared the predictive performance of each biomarker using the area under the curve, the Wagener criterion, Olthoff criterion, Donor Risk Index, and multiple versions of the Green Indocyanine biomarker did not display any statistically-significant differences among them.

Conclusions: Although indocyanine green is able to predict posttransplant infections and acute renal failure requiring hemodialysis, its predictive performance is similar to other biomarkers. Future studies should further investigate its diagnostic properties with larger samples.

Keywords: *Liver Transplantation; Indocyanine Green; Prognosis*

Introduction

Early graft dysfunction after liver transplantation is consistently associated with poor clinical outcomes [1,2]. For example, patients who develop early allograft rejection after a liver transplant tend to have longer hospital and intensive care unit stays and a greater mortality than those without rejection [3,4]. In spite of the proposal of multiple criteria as prognostic indices for early liver graft failure and complications after transplantation [3,5,6], the search for new biomarkers is still ongoing, especially concerning markers that might predict a range of clinical complications. Although Indocyanine Green has been described as a marker for both hepatic function and perfusion

[7,8], we are not aware of any previous studies simultaneously evaluating its prediction performance in comparison with the Wagener, Olthoff and Donor Risk Index scores with early complications after liver transplant procedures.

High levels of serum transaminase or bilirubin in recipients are known indicators of allograft dysfunction within the first week after liver transplantation. This criterion has previously been validated in the context of the Model for End-Stage Liver Disease (MELD), MELD greater than 19 on the fifth postoperative day being the criterion for a positive Wagener index. Specifically, these studies have demonstrated a strong clinical association with graft and patient survival at the six-month follow-up [5,6]. Assessing previous studies for initial graft function revealed that liver-specific parameters such as transaminase levels, prothrombin time and bilirubin levels had been used for graft classification during the first postoperative week [1,9]. For example, Deschenes., *et al*. developed the definition of early allograft dysfunction using a combination of bilirubin, prothrombin and individual hepatic-encephalopathy parameters based on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Transplant Database. Their model was able to predict groups of patients with the worst graft function and survival [3].

Indocyanine green is a non-toxic synthetic dye, whose elimination rate has been used to evaluate liver function and hepatic blood flow [7]. Previous studies employing invasive methods found that Indocyanine green clearance rates of up to 200 ml/minute 24 hrs after the liver transplant procedure have an association with donor-graft function [8]. This demonstrates that invasive and non-invasive methods are strongly associated [10], also acting as an accurate biomarker for reperfusion injury [8]. Similar results were reported with noninvasive methods [11], pulse-densitometric and the LiMON system (Impulse Medical System, Munich, Germany) [12,13]. In spite of many previously conducted evaluations, to our knowledge, no simultaneous comparisons have been performed comparing the Indocyanine green, Olthoff, Wagener and Donor Risk Index criteria.

In the face of this gap in the literature, our primary objective was to compare the Wagener [5] and Olthoff [6] criteria against Indocyanine green as prognostic markers for early postoperative complications in liver transplant patients. We hypothesized that Indocyanine green pulse-spectrophotometry clearance would present a better diagnostic performance in predicting the beginning of the complications after liver transplantation.

Methods

Study design

This is a prospective study to evaluate Indocyanine green pulse-spectrophotometry clearance, Donor Risk Index, Wagener and Olthoff scores as prognostic predictors of post-liver transplant complications. The description was made per the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines [14], and a total of 40 participants participated in this analysis.

Ethics

The Institutional Review Board of the School of Medicine at the University of Salo Paulo, Brazil approved our study. Informed consent was offered to all potential participants and subsequently signed before the implementation of any study protocol.

Setting

We collected all data from patients coming to a single tertiary outpatient clinic at the Hospital das Clinicas at the School of Medicine, University of Salo Paulo. Participant recruitment and follow-up occurred between July of 2014 and June of 2015, and all patients were followed-up throughout the care pathway.

Participants

We included all patients undergoing deceased donor liver transplant from any etiology, and excluded patients who refused to participate in the study, underwent living donor transplantation, as well as those allergic to the Indocyanine green dye.

Outcomes

Outcomes of interest included the following complications: bleeding; hemodialysis secondary to acute renal failure; re-operation; infections defined as conditions including septicemia, cytomegalovirus infection, operative wound infection, septic shock, and urinary tract infection; and death secondary to factors associated with the transplant procedure. We defined patients with acute renal failure as those whose conditions required hemodialysis for less than eight weeks. All outcome measures were collected from the date of transplant all the way to three months after surgery.

Predictors

Predictors included measures of the Indocyanine plasma clearance rate as well as the Olthoff, Wagener and Donor Risk Index criteria. Indocyanine green plasma clearance and retention rates at 15 minutes were measured using the LiMON method on the first, third and seventh postoperative days. The Olthoff criterion was defined as a total bilirubin level > 10 mg/dL, an INR > 1.6 on the seventh postoperative day or an AST or ALT level > 2000 IU/L within the first seven days [6]. The Wagener's criterion was defined as a MELD score greater than 19 on day five after the transplant [5]. The Donor Risk Index assesses the quality of donor liver allografts, its calculation including seven identified donor factors: Donor age, race, height, the cause of death, donation after cardiac death, partial or split liver graft (organ location) and cold ischemia time [15]. Clinical assessment and laboratory tests were conducted on a daily basis in the post-transplant period to verify the criteria for early graft dysfunction [3,5,6].

Data analysis

We started the analysis by performing a graphical exploratory analysis evaluating the frequency, percentage and near-zero variance (low frequency of a given category) for categorical variables, distribution for numeric variables, and missing value patterns of all variables [16]. The MELD cut-point of 14 was selected to make clinical sense as well as to reach an approximately equal number of study participants between the comparison groups [17]. Since the total sample size was small and the DRI was not normal, we dichotomized this variable at its mean value for modeling. We also compared different metrics of Indocyanine green in an attempt to identify the parameter with the best prediction performance, measuring predictive performance through the area under the curve (AUC). Also, we generated various Indocyanine green measures by weighted average, where different weights were attached to the measurements on days one, three and seven.

We modeled all previously described outcomes and their association with the four indices using generalized linear models with a binomial distribution family, i.e. logistic regression, to evaluate the predictive risk of a complication. We calculated odds ratios with 95% Confidence Intervals, with higher areas under the curve, i.e. closer to 1, indicating better performance prediction. Comparison of indices was performed using metrics for the area under the curve. An area under the curve can go from 0 to 1, with values close to 1 having a better predictive performance. Also, we calculated 95% confidence intervals to test whether different measures were better than others. All analyses were performed using the statistical language R [18].

Results

Most of our patients were in their early 50s (53.3 +/- 14.0), and male (70%). The most common etiologies were hepatocellular carcinoma and C virus hepatitis (50% and 42.5% respectively). The most famous Child-Pugh classification was C (45%), and the most common comorbidities were hypertension (27.5%), acute renal failure (12.5%) and smoking (12.5%).

Table 1 reports information on patients' outcomes as well as a stratification by a median MELD score of 14. Comparisons were performed using Chi-square and t-tests. We found that most patients presented a two-day stay in the intensive care unit, with an overall stay approaching three days total. The most common complication was an infection in nearly half of all patients. A total estimate of 22.5% of all patients had to undergo a reoperation.

Variable [Missing]	Total (40)	MELD < 14 (19)	MELD >= 14 (21)	p
ICU length of stay [0]	9.6 (+- 7.81)	8.26 (+- 5.53)	10.81 (+- 9.4)	0.299
Hospital length of stay [0]	22.62 (+- 16.32)	22.42 (+- 14.14)	22.81 (+- 18.41)	0.94
Bleeding complications [0]	11 (27.5 %)	5 (26.3 %)	6 (28.6 %)	1
Infectious complications [0]	19 (47.5 %)	7 (36.8 %)	12 (57.1 %)	0.334
Acute Renal Failure Hemodialysis [4]	14 (35 %)	6 (31.6 %)	8 (38.1 %)	0.732
Re-operation [29]	9 (22.5 %)	4 (21.1 %)	5 (23.8 %)	1

Table 1: *Sample description of post-graft complications, stratified by a median MELD score of 14*

None of our patients presented a floor or ceiling score effect with any of the four indices. The Indocyanine scores, however, demonstrated levels indicative of an increased plasma disappearance rate between days one and three, with little increment between days three and seven. Of importance, none of these variables presented a significant difference in relation to pre-transplant median MELD scores (Table 2).

Variable [Missing]	Total (40)	MELD < 14 (19)	MELD >= 14 (21)	p
Donor Risk Index [0]	1.28 (+- 0.23)	1.32 (+- 0.26)	1.25 (+- 0.2)	0.375
Wagener criterion [0]	17 (42.5 %)	8 (42.1 %)	9 (42.9 %)	1
Olthoff criterion [0]	15 (37.5 %)	5 (26.3 %)	10 (47.6 %)	0.288
Plasma Disappearance Rate Day 1 [0]	17.58 (+- 8.04)	18.54 (+- 5.95)	16.71 (+- 9.62)	0.47
Plasma Disappearance Rate Day 3 [3]	20.28 (+- 9.7)	20.84 (+- 8.28)	19.68 (+- 11.22)	0.724
Plasma Disappearance Rate Day 7 [4]	20.42 (+- 8.55)	20.29 (+- 7.84)	20.55 (+- 9.53)	0.93
Retention Rate 15 min Day 1 [0]	13.38 (+- 15.35)	9.06 (+- 8.92)	17.29 (+- 18.82)	0.083
Retention Rate 15 min Day 3 [3]	12.09 (+- 16.65)	12.35 (+- 19.59)	11.81 (+- 13.44)	0.921
Retention Rate 15 min Day 7 [4]	9.51 (+- 10.49)	10.42 (+- 12.68)	8.49 (+- 7.6)	0.58

Table 2: *Sample description of Olthoff, Wagener, Donor Risk Index criteria and Indocyanine plasma clearance and retention rate, stratified by a median MELD score of 14.*

When evaluating the association between scores and postoperative complications, we found that a renal complication preceded the time when the Wagener criterion could be calculated in 14 patients (35%), thus reducing the feasibility of this score as a prognostic predictor for this condition. In the remaining results for this article, results are only reported for outcomes with a sufficiently large number of events to allow for adjusted models and are not reported when models either did not converge or where predictions were unstable, i.e. minor changes in sensitivity analysis led to modifications in statistical significance.

Table 3 reports information on postoperative complications and its association with each of the scores (DRI and Green Indocyanine with cut points at the median value), using odds ratios and 95% confidence intervals. Odds ratios are interpreted as being statistically significant in relation to the reference when they do not cross a value of 1.0 (see values in bold under table 3. The presence of a positive Wagener criterion was associated with an increased risk of bleeding complications (OR 6.03, 95% CI 1.29, 36.9) and acute renal failure requiring hemodialysis (6.63 OR, 95% CI 1.49, 36.3). On the other hand, the Olthoff criterion and Donor Risk Index showed no significant association with any of our measured outcomes. Finally, the Indocyanine green test was significantly associated with an increased risk of both acute renal failure (OR 0.17, 95% CI 0.0302, 0.81; OR 0.19, 95% CI 0.0314, 0.92; OR 5.17 95% CI 1.09, 31.9) and post-transplant infection (OR 5.62 95% CI 1.22, 33.7).

	Infectious complications	Bleeding complications	Acute Renal Failure Hemodialysis
Wagener criterion False	1 [Reference]	1 [Reference]	1 [Reference]
Wagener criterion True	2.09 (0.56, 8.07)	**6.03 (1.29, 36.9)**	**6.63 (1.49, 36.3)**
Olthoff criterion False	1 [Reference]	1 [Reference]	1 [Reference]
Olthoff criterion True	0.47 (0.1, 1.83)	1.26 (0.26, 5.67)	1.31 (0.29, 5.71)
Donor Risk Index <= 1.17	1 [Reference]	1 [Reference]	1 [Reference]
Donor Risk Index > 1.17	1.96 (0.54, 7.59)	1.96 (0.44, 9.61)	0.24 (0.0387, 1.12)
Green Indocyanine Plasma Disappearance Rate Day 1 <= 17.6	1 [Reference]	1 [Reference]	1 [Reference]
Green Indocyanine Plasma Disappearance Rate Day 1 > 17.6	0.46 (0.11, 1.77)	0.73 (0.14, 3.75)	0.55 (0.12, 2.47)
Green Indocyanine Plasma Disappearance Rate Day 3 <= 20.2	1 [Reference]	1 [Reference]	1 [Reference]
Green Indocyanine Plasma Disappearance Rate Day 3 > 20.2	0.26 (0.0546, 1.09)	0.53 (0.0918, 2.69)	**0.17 (0.0302, 0.81)**
Green Indocyanine Plasma Disappearance Rate Day 7 <= 19.7	1 [Reference]	1 [Reference]	1 [Reference]
Green Indocyanine Plasma Disappearance Rate Day 7 > 19.7	**0.18 (0.0297, 0.82)**	1.51 (0.31, 8.12)	**0.19 (0.0314, 0.92)**
Green Indocyanine Retention Rate 15 min Day 1 <= 7.1	1 [Reference]	1 [Reference]	1 [Reference]
Green Indocyanine Retention Rate 15 min Day 1 > 7.1	2.17 (0.56, 8.72)	1.36 (0.27, 6.92)	1.82 (0.4, 8.41)
Green Indocyanine Retention Rate 15 min Day 3 <= 4.8	1 [Reference]	1 [Reference]	1 [Reference]
Green Indocyanine Retention Rate 15 min Day 3 > 4.8	2.82 (0.68, 12.8)	2.18 (0.42, 12.6)	3.71 (0.83, 18.7)
Green Indocyanine Retention Rate 15 min Day 7 <= 5.4	1 [Reference]	1 [Reference]	1 [Reference]
Green Indocyanine Retention Rate 15 min Day 7 > 5.4	**5.62 (1.22, 33.7)**	0.66 (0.12, 3.2)	**5.17 (1.09, 31.9)**

Table 3: *Adjusted odds of complication comparing the Olthoff, Wagener and Donor Risk Index.*

Footnotes: Bold numbers represents significant association.

We then compared the predictive performance of each biomarker using the area under the curve. An area under the curve can range from 0 to 1, with values close to 1 having a better predictive performance. Also, we calculated 95% confidence intervals to test whether some measures were better than others. As demonstrated in table 4, the Wagener criterion, Olthoff criterion, Donor Risk Index, and multiple versions of the Green Indocyanine biomarker did not display any statistically significant differences among them.

	Infectious complications	Bleeding complications	Acute Renal Failure Hemodialysis
Wagener criterion	0.65 (0.47, 0.83)	0.76 (0.6, 0.92)	0.76 (0.6, 0.93)
Olthoff criterion	0.64 (0.47, 0.82)	0.65 (0.43, 0.86)	0.65 (0.45, 0.85)
Donor Risk Index	0.68 (0.5, 0.85)	0.66 (0.45, 0.87)	0.74 (0.57, 0.91)
Green Indocyanine Plasma Disappearance Rate Day 1	0.69 (0.52, 0.85)	0.37 (0.16, 0.59)	0.64 (0.44, 0.84)
Green Indocyanine Plasma Disappearance Rate Day 3	0.78 (0.63, 0.93)	0.62 (0.38, 0.87)	0.78 (0.62, 0.94)
Green Indocyanine Plasma Disappearance Rate Day 7	0.78 (0.62, 0.94)	0.65 (0.44, 0.85)	0.72 (0.53, 0.92)
Green Indocyanine Retention Rate 15 min Day 1	0.69 (0.52, 0.85)	0.37 (0.16, 0.59)	0.64 (0.44, 0.84)
Green Indocyanine Retention Rate 15 min Day 3	0.76 (0.6, 0.91)	0.65 (0.4, 0.89)	0.74 (0.56, 0.91)
Green Indocyanine Retention Rate 15 min Day 7	0.78 (0.62, 0.94)	0.65 (0.44, 0.85)	0.72 (0.53, 0.92)

Table 4: *Area under the curve (predictive performance) for the Wagener criterion, Olthoff criterion, DRI index and measures of green indocyanine clearance.*

Discussion

To the best of our knowledge, this is the first article validating the Indocyanine green pulse-spectrophotometry clearance test as a predictor of complications after liver transplant in comparison with the Wagener, Donor Risk Index, and Olthoff criteria. We found that both Indocyanine green and the Wagener criterion could predict acute renal failure requiring hemodialysis in our sample. No statistical difference was found when comparing the Wagener criterion, Olthoff criterion, DRI index and measures of indocyanine green clearance scores.

Indocyanine Green Plasma disappearance rate (IG-PDR) increased in the first three days after transplantation, but remained only moderately changed from days three through seven. Conversely, the 15-minute retention rate decreased more prominently in the second evaluated period. It has been demonstrated that one day after transplantation the IG-PDR decreased as compared to baseline values, owing to cellular damage after revascularization [19]. The absence of baseline measurements prevents us from making this comparison. However, in patients with higher MELD scores, IG-PDR increased from day one to seven, resembling the revascularization damage pattern. Although no cut-off points have been established, an IG-PDR lower than 12.85%/minute was predictive of complications after liver transplantation [13], a level lower than what we found as the average for our sample.

Indocyanine green measurements were able to predict some of the important complications sustained by liver transplantation recipients. For example, lower IG-PDR and higher retention rates were risk factors for developing infections after transplantation. Importantly, none of the other indices evaluated were capable of predicting infections, although they predicted some complications that evaded the indocyanine indices. For instance, participants with increased Wagener criterion were at a higher risk of bleeding. On the other side, both the Wagener criterion and indocyanine green retention rates predicted acute kidney injury requiring hemodialysis. Higher levels of ICG-PDR were previously correlated with complications after surgery [13,20]. A MELD score greater than 19 on day five after the transplant (i.e. the Wagener criterion) was associated with early allograft dysfunction [5], but only a MELD score higher than 30 predicted the risk of infections [21]. Echoing our results, increases in MELD scores elevated the relative risk of bleeding [22]. Moreover, reports of MELD scores being able to predict the risk of renal failure are controversial, some indicating increased risks with higher scores [23], while others point to a lack of association [24]. Although not evaluated through the Olthoff criterion, early allograft dysfunction has been associated with

increased rates of acute kidney injury and end-stage renal disease [25]. Given that different indices were able to predict a wide spectrum of complications, our results support the use of ICG as a complement of other criteria incorporating demographic and clinical data.

Current models are unable to accurately predict which patients will have the best post-transplantation outcomes or complications [26]. Biomarkers and scales have been developed to anticipate early complications following liver transplantation. Many scores have been tested to predict the occurrence of early allograft dysfunction and other serious complications after liver transplantation, Wagener, and Olthoff criterion, being two recent examples. Unfortunately, these criteria have the inconvenience of relying on metrics that are measured five and seven days after liver transplantation, respectively. As a result, some important complications develop even before the score can be computed. Likewise, when evaluating the association between scores and postoperative complications, we found that a renal complication preceded the time when the Wagener criterion could be calculated in 35% of the sample, hence reducing the feasibility of this score as a prognostic predictor for this condition [1,27], sodium concentration [9], and ammonia levels [1] have enabled the assessment of early allograft dysfunction within days or weeks after liver transplant. However, these tests only reflect the degree of hepatic injury as opposed to dynamic tests which can point toward the extent of liver graft recovery [28]. Recently, indocyanine green plasma disappearance rate (ICG-PDR) has been investigated as a predictor of early post-transplantation complications. Given its noninvasive nature and inexpensiveness, this marker could become a tool to improve the prognostic capacity of current models.

Despite adding an important and novel aspect to the literature, our study does have limitations. First, we have a relatively small sample, making it difficult to evaluate less common adverse postoperative outcomes. Second, we did not include self-reported measures of quality of life, which we might have associated with the hepatic functions. Both of these limitations resulted from logistical limitations in our data collection system, where additional fields and new protocols occur at the expense of other clinical activities. Another limitation is that we did not measure static biomarkers, including bilirubin. When evaluating the association between scores and postoperative complications, we found that a renal complication preceded the time when the Wagener criterion could be calculated in 14 patients (35%), thus reducing the feasibility of this score as a prognostic predictor for this condition. Since hyperbilirubinemia is related to falsely low ICG-PDR, the measurement of static markers will be relevant to improve predictive modeling in future studies. Other measurements related to ICG, including its elimination rate constant could also be incorporated in further investigations. Previous studies have used ICG in conjunction with MELD scores, demonstrating an improvement in the predictive ability of the corresponding models. However, significantly larger sample sizes will be required to achieve that goal.

Conclusion

In conclusion, although indocyanine green is able to predict post-transplant infection and acute renal failure requiring hemodialysis, its predictive performance is similar to other biomarkers. Future studies should further investigate its diagnostic properties with larger samples.

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