EGYPTIAN JOURNAL OF ANAESTHESIA
2020, VOL. 36, NO. 1, 273–281
https://doi.org/10.1080/11101849.2020.1848239

Evaluation of serum taurine as a prognostic marker for graft function in adult Egyptian patients undergoing living donor liver transplant

Hanaa El-Gendy[a], Ibrahim M. El Agouza[b], Hager A. Abd Elmoneem[c], Mohamed M. Bahaa[d] and Manar M. Salah[e]

[a]Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt; [b]Department of Zoology, Faculty of Science, Cairo University, Cairo, Egypt; [c]Department of Zoology, Faculty of Science, Benha University, Benha, Egypt; [d]Department of General Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt; [e]Department of Tropical Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Background: Taurine has been investigated as a potential screening marker for early diagnosis of hepatocellular carcinoma and other liver diseases. This study was conducted to evaluate serum taurine as a potential prognostic marker for graft function in Egyptian patients undergoing living donor liver transplant.

Methods: A prospective cohort study was conducted during August 2019 to May 2020. We measured serum taurine levels using high-performance liquid chromatography in patients with end-stage liver disease who were candidates for living donor liver transplant before transplant, then on the 7th, 14th, and 30th day post-transplant. Patients were followed up to detect graft dysfunction, Seventh Day Syndrome, and the 30-day mortality.

Results: Sixty patients were enrolled in this study. Preoperative serum taurine levels did not correlate significantly with liver function tests, and its predictive performance for primary graft dysfunction and 30-day mortality was poor (area under curve [AUC] = 0.662; $p = 0.038$ and AUC = 0.642; $p = 0.202$, respectively). Serum taurine level at the 7th post-transplant day had good diagnostic performance for primary graft dysfunction (AUC = 0.827; $p < 0.001$) and good predictive performance for 30-day mortality (AUC = 0.888; $p < 0.001$). Only two patients with taurine level <30 μmL^{-1} developed Seventh Day Syndrome.

Conclusion: Preoperative serum taurine level had poor prognostic value for primary graft dysfunction or 30-day mortality. However, its serum level at the 7th day post-transplant had good diagnostic value for primary graft dysfunction and good prognostic value for 30-day mortality. Future research should investigate the potential predictive value of taurine levels regarding primary graft dysfunction and Seventh Day Syndrome.

ARTICLE HISTORY
Received 19 August 2020
Revised 6 September 2020
Accepted 5 November 2020

KEYWORDS
Biomarkers; end-stage liver disease; graft rejection; prognosis; taurine; transplant

1. Introduction

Liver transplantation is the only definitive management for end-stage liver disease. One of the major complications of liver transplantation is primary graft dysfunction (PGD), which is associated with higher morbidity in the early post-transplant period and may compromise long-term graft survival [1]. The occurrence of PGD is attributed mainly to ischemia/reperfusion (I/R) injury [2]. Although Seventh Day Syndrome (7DS) is a distinct clinical entity characterized by extensive apoptosis of hepatocytes with sudden failure of the liver graft about 1 week after transplantation; sufficient evidence is lacking considering its etiology and pathogenesis [3,4].

Taurine is an essential amino acid that is present at high concentrations in the liver [5]. The role of taurine in liver diseases has been investigated as a potential screening marker for early diagnosis of hepatitis C virus (HCV)-induced liver fibrosis [6] and early hepatocellular carcinoma (HCC) [7] as well as a potential prophylactic agent against HCC [8]. Taurine was reported to minimize reperfusion injury after liver transplantation in rats [9]. It was suggested that assessment of serum taurine level in the sera of HCC patients may have a role in identifying end-stage liver disease patients who are candidates for liver transplantation [7], a suggestion that needs further research.

Although the hepatoprotective properties of taurine are well established and its beneficial role to inhibit starvation-triggered endoplasmic reticulum apoptosis in ARPE-19 cells (spontaneously immortalized cell line of human retinal pigment epithelium) by modulating the expression of calpain-1 and calpain-2 is confirmed [10,11], the evaluation of its perioperative serum levels in the recipients of living donor liver transplantation (LDLT) for assessment of graft function and 7DS has not been investigated so far. The present study aimed to evaluate serum taurine as a potential prognostic marker for graft function and 7DS in Egyptian patients undergoing LDLT.

CONTACT Hanaa El-Gendy hanaa.elgendy0@gmail.com hanaa.elgendy@med.asu.edu.eg; Faculty of Medicine, Ain-Shams University, Cairo, Egypt

2. Methods

2.1. Ethical considerations and settings

This study adheres to the uniform requirements for manuscripts submitted to biomedical journals and has been conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. After approval by the Institutional Review Board (IRB 0006379), this prospective cohort study was conducted on patients scheduled to undergo right-lobe living donor liver transplant for the first time at Ain Shams University Specialised Hospital during August 2019 to May 2020. The study was registered at ClinicalTrials.gov (NCT04047043). An informed consent was obtained from each patient, and the confidentiality of patients' data was ensured.

2.2. Eligibility criteria

The study included adult Egyptian patients (≥18 years of age), with end-stage liver disease who were candidates for LDLT. The selection of patients to undergo LDLT was based on indications recommended by previous studies [12–14]. Donor selection criteria included age between 18 and 45 years, ABO group compatibility with the recipient, and normal psychological workup.

Recipients with pre-existing renal failure requiring hemodialysis or continuous hemofiltration, glomerular filtration rate ≤30 ml min^{-1} by renal scan, re-transplant, HbA1c >7%, and pregnancy were excluded. Living donors who had fatty liver, estimated remnant liver volume for donor <30% of total liver volume, body mass index >28 kg $m^{-}2$, abnormal biliary anatomy, and steatosis >10% were excluded.

2.3. Preoperative assessment and preparation

Preoperative assessment and preparation were conducted according to the standard protocol of our institution. Thorough clinical examination was performed. The model for end-stage liver disease score was corrected for serum sodium level [15]. Imaging techniques were done for all recipients, including abdominal ultrasonography, abdominal triphasic CT Scan, CT volumetry, CT chest, bone scan in HCC patients, renal scan in patients with urinary creatinine clearance <60 ml min^{-1}, carotid duplex, and dobutamine echocardiography. Serum levels of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, gamma-glutamyl transferase, bilirubin, albumin, prothrombin, INR, partial thrombin time, factor V, fasting blood glucose, complete blood picture, C-reactive protein (CRP), procalcitonin, urea, creatinine, urinary creatinine clearance, serum electrolytes as well as urine and stool analyses were requested. In addition, serum levels of specific markers such as alpha-fetoprotein, hepatitis C virus (HCV), hepatitis B virus (HBV), cytomegalovirus Ig M, Epstein-Barr virus IgM, herpes simplex virus IgM, human immunodeficiency virus, and serum taurine were assessed for all patients. Liver biopsy, upper and lower gastrointestinal endoscopy, and pulmonary function tests were done.

2.4. Intraoperative procedures

Intraoperatively, both standard anesthetic and piggy-back techniques for hepatic transplantation were performed by the same anesthesia and surgical team. Graft weight to recipient weight ratio was recorded.

2.5. Postoperative follow-up

At the end of the surgery, patients were transferred to the intensive care unit (ICU), were monitored, and received the standard protocol for postoperative management after liver transplantation. All patients were assessed for graft function on a daily basis during the first week post-transplant. The criteria for diagnosis of PGD included presence of one or more of the following variables within the first week postoperative: (a) total bilirubin ≥ 10 mg dl^{-1}; (b) INR ≥ 1.6; and (c) ALT or AST > 2000 IU L^{-1} [16].

The criteria for diagnosis of 7DS included: (a) severe liver failure with sudden extremely high liver enzymes at the 7th postoperative day; (b) reduced blood flow in both the portal and hepatic vein; (c) high fever; (d) no evidence of vascular thrombosis or stenosis; and (e) massive necrosis in liver biopsy [17].

Patients with an uncomplicated postoperative course and good liver function were transferred from the ICU to an inpatient transplantation unit, where they were closely followed up by the surgical and medical teams, as well as by pharmacists, nutritionists, and physical therapists.

2.6. Outcomes

The primary outcome of the present study was the relationship between recipients' serum taurine level and PGD. Secondary outcomes included 7DS, 30-day mortality, and the duration of ICU and hospital stays.

2.7. Specimen collection and measurement of serum taurine

After 12 hours fasting, 10 ml of venous blood was collected in a plain tube and allowed to clot for half an hour. The collected specimens were then centrifuged at 3,000 rpm for 10 minutes. The serum was separated and stored at -20 C° to avoid loss of biological activity until the batch analysis for serum taurine was done. Measurements of serum taurine were performed at four-time points for the recipients (preoperatively before induction of anesthesia, then on the

7th, 14th, and 30th days post-transplant) according to the pre-column extraction and derivatization methodology of McMahon et al. [18] using high-performance liquid chromatography (Japan HPLC-Jasco/Japan series 2000; UV-VIS 2070; column c18 RP; and Chrom Nav data system).

2.8. Sample size and sampling method

After reviewing the literature, we found no previous similar human research assessing the relationship between the recipients' serum taurine levels and graft survival. We aimed to assess whether serum taurine can predict the occurrence of PGD after liver transplant. We assumed a value for area under the curve (AUC) of 0.8 for taurine (if it is a good predictor), a null hypothesis value for the AUC of 0.5, an alpha level of 0.05, a power of 0.80, and an incidence of PGD of 15% [19]. Using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015), the required sample size was 56 patients. A 10% was added to compensate for drop-out of cases, and the total sample size was 60 patients. The sampling technique was a non-probability, convenience sample.

2.9. Statistical analysis

Collected data were analyzed using the IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Categorical variables were summarized as numbers and percentages, and associations were tested using Pearson's Chi square test, Fisher's exact test, or Fisher-Freeman-Halton exact test as appropriate. Numerical variables were tested for distribution using Shapiro-Wilk test. Normally distributed variables were summarized using mean and standard deviation, and the differences between groups were assessed using one-way ANOVA test (followed by post hoc Tukey test if ANOVA test was significant). Repeated measures ANOVA was used to examine differences between multiple taurine measurements. Variables that did not follow normal distribution were summarized using median and interquartile range (IQR; expressed as 25th – 75th percentiles), and the differences between groups were tested using Kruskal-Wallis test (followed by post hoc Dunn-Boneferroni test if significant). Univariate binomial logistic regression analysis was performed to identify factors that affect PGD, then a multivariate logistic regression analysis was performed in which all variables with p value <0.2 in the univariate analysis were entered. Receiver operating characteristic curve was performed to analyze the relation between true-positive and false-positive results for each measurement. The area under curve (AUC) was graded as follows: 0.90–1 = excellent; 0.80–0.90 = good; 0.70–0.80 = fair; and 0.60–0.70 = poor. Multiple regression was used to identify potential factors affecting preoperative serum taurine level. P value was set at <0.05 for significant results.

3. Results

In the present study, 72 patients were assessed for eligibility, out of whom 12 patients were excluded (three declined participation and nine did not meet the inclusion criteria). Sixty patients were categorized according to preoperative serum taurine level into three groups: group I (>30 μmol L^{-1}), group II (30–-20 μmol L^{-1}), and group III (<20 μmol L^{-1}). All patients' data were complete.

Table 1 summarizes the characteristics of the studied recipients. The age ranged from 19 to 65 years-old, with an average of 49.0 ± 11.5 years. The body mass index (BMI) ranged from 19.3 to 30 Kg m^{-2}, with an average of 25.8 ± 2.6 Kg m^{-2}. Most patients were men (73.3%). The model for end-stage liver disease score ranged from 6 to 27, with an average of 16.9 ± 4.6. Hepatitis C and B, as well as HCC were present in 70%, 1.7%, and 36.7% of patients, respectively. The length of ICU stay ranged from 2 to 67 days, with a median of 5 days. The hospital stay ranged from less than 1 day to 180 days, with a median of 24 days. Only six patients (10%) suffered from PGD. Nine patients (15%) died within the first 30-days post-transplant. Comparison between the three categories of patients showed that age was significantly higher in group III compared to group I (54.3 ± 7.3 vs 44.6 ± 13.5; p = 0.014). The mean BMI was also significantly higher in group III compared to group I (27.0 ± 2.2 vs 24.9 ± 2.7; p = 0.030). Group III was significantly associated with higher percentage of patients with HCV (95%; P = 0.007) and HCC (100%; P < 0.001). There was a significantly higher percentage of patients with cryptogenic hepatitis in group II compared with group I (35% vs 5%; p = 0.044). The median hospital stay was significantly longer in group II compared to group I (median = 28 days vs 19 days; p = 0.049). There were no significant differences between the three groups as regards gender (p = 0.551), model for end-stage liver disease score (p = 0.321), graft weight to recipient weight ratio (p = 0.217), HBV (p = 1.000), the length of ICU stay (p = 0.456), PGD (p = 0.150), or 30-day mortality (p = 0.150). Only two patients (3.3%) with taurine levels less than 30 μm L^{-1} developed 7DS, one in group II and the other in group III, with no statistically significant difference (p = 1.000).

Table 2 shows the results of preoperative laboratory investigations in the studied recipients. There were no significant differences among the three studied groups as regards liver function tests, CRP, or procalcitonin (p > 0.05).

Table 1. Baseline patients' characteristics (total n = 60).

		Groups according to serum taurine level				Tests of significance	
		Group I (> 30 µmol L^{-1}) (n = 20)	Group II (20–30 µmol L^{-1}) (n = 20)	Group III (< 20 µmol L^{-1}) (n = 20)	Total (n = 60)	Test statistic	p
Age (years)	Range	19.0–61.0	25.0–61.0	34.0–65.0	19.0–65.0	4.785	0.014*
	Mean ± SD	44.6 ± 13.5 [c]	48.2 ± 11.1	54.3 ± 7.3 [a]	49.0 ± 11.5		
BMI (kg m^{-2})	Range	20.0–29.0	19.3–29.1	21.0–30.0	19.3–30.0	3.749	0.030*
	Mean ± SD	24.9 ± 2.7 [c]	25.5 ± 2.6	27.0 ± 2.2 [a]	25.8 ± 2.6		
Gender	Female	7 (35.0%)	5 (25.0%)	4 (20.0%)	16 (26.7%)	1.193	0.551
	Male	13 (65.0%)	15 (75.0%)	16 (80.0%)	44 (73.3%)		
MELD score	Range	10.0–26.0	9.0–27.0	6.0–24.0	6.0–27.0	1.160	0.321
	Mean ± SD	16.9 ± 4.0	18.0 ± 4.6	15.7 ± 5.0	16.9 ± 4.6		
GRWR	Range	0.8–2.0	0.8–1.6	0.8–1.5	0.8–2.0	1.569	0.217
	Mean ± SD	1.2 ± 0.3	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.3		
HCV		13 (65.0%) [c]	10 (50.0%) [c]	19 (95.0%) [a,b]	42 (70.0%)	10.000	0.007*
HBV		0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (1.7%)	1.851	1.000
HCC		0 (0.0%) [b,c]	2 (10.0%) [a,c]	20 (100.0%) [a,b]	22 (36.7%)	52.249	< 0.001*
Other	AIH	4 (20.0%)	1 (5.0%)	0 (0.0%)	5 (8.3%)	FE	0.342
	AIH/SLE	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	FE	1.000
	BCS	0 (0.0%)	2 (10.0%)	0 (0.0%)	2 (3.3%)	FE	0.487
	Cryptogenic	1 (5.0%) [b]	7 (35.0%) [a]	0 (0.0%) [b]	8 (13.3%)	FE	0.044*
	PSC	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	FE	1.000
ICU stay (days)	Range	2.0–14.0	3.0–67.0	2.0–23.0	2.0–67.0	1.571	0.456
	Median	4.0	5.0	5.0	5.0		
	(IQR)	(3.5–5.5)	(4.0–7.5)	(3.5–7.5)	(4.0–7.0)		
Hospital stay (days)	Range	<1.0–48	<1.0–180	<1.0–77	<1.0–180.0	6.047	0.049*
	Median	19	28	25	24.0		
	(IQR)	(19–25) [b]	(23–32) [a]	(14–32)	(19.0–31.0)		
PGD	No	20 (100.0%)	16 (80.0%)	18 (90.0%)	54 (90.0%)	4.239	0.150
	Yes	0 (0.0%)	4 (20.0%)	2 (10.0%)	6 (10.0%)		
7^{th} day syndrome	No	20 (100.0%)	19 (95.0%)	19 (95.0%)	58 (96.7%)	1.276	1.000
	Yes	0 (0.0%)	1 (5.0%)	1 (5.0%)	2 (3.3%)		
30-day Mortality	Survival	18 (90.0%)	18 (90.0%)	15 (75.0%)	51 (85.0%)	2.098	0.474
	Death	2 (10.0%)	2 (10.0%)	5 (25.0%)	9 (15.0%)		

FE: Fisher's exact test; IQR: interquartile range; n: number; SD: standard deviation; a: significant difference with group I; b: significant difference with group II; c: significant difference with group III; BMI: body mass index; MELD: model for end-stage liver disease; GRWR: graft weight to recipient weight ratio; HCV: hepatitis C virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; ICU: intensive care unit; PGD: primary graft dysfunction; AIH/SLE: autoimmune hepatitis/systemic lupus erythematosus; BCS: Budd Chiari syndrome; PSC: primary sclerosing cholangitis

*significant at $p < 0.05$.

Serum taurine level had a steady increase on the 7th, 14th, and 30th days post-transplant, with significant difference between each time point.

Table 3 demonstrates the presence of negative, moderate, significant correlation between serum taurine on the 7th day and each of AST (r_s = -0.396; p = 0.002), ALT (r_s = -0.385; p = 0.003), total bilirubin (r_s = -0.379; p = 0.003), direct bilirubin (r_s = -0.324; p = 0.012), and INR (r_s = -0.349; p = 0.007). Similar correlation was detected between serum taurine on the 14th day and AST (r_s = -0.365; p = 0.007), ALT (r_s = -0.301; p = 0.027), total bilirubin (r_s = -0.416; p = 0.002), direct bilirubin (r_s = -0.354; p = 0.009), and INR (r_s = -0.495; p < 0.001).

Table 4 shows the results of univariate and multivariate binomial logistic regression analyses, which were conducted to assess factors contributing to PGD. Variables in the univariate regression that had a p value <0.2 were entered multivariate regression model. The multivariate analysis showed that preoperative serum taurine level did not affect significantly the probability of PGD. On the other hand, increased serum taurine level at the 7th postoperative day by one unit was significantly associated with decreased likelihood of PGD (OR = 0.815, 95% CI = 0.687–0.966, p = 0.018) when the model was adjusted for the effects of gender, cryptogenic hepatitis, and preoperative taurine level.

Table 5 displays the diagnostic and predictive performance of taurine preoperatively and on the 7th day post-transplant as regards PGD and 30-day mortality. Preoperative serum taurine level showed poor prediction of PGD (AUC = 0.662; p = 0.038) and 30-day mortality (AUC = 0.642; p = 0.202). Serum taurine on 7th day after transplant had good diagnostic performance for PGD (AUC = 0.827; p < 0.001) and good predictive value of 30-day mortality (AUC = 0.888; p < 0.001). At a cut-off value of 24 µmol L^{-1} or less, serum taurine had a sensitivity, specificity, positive predictive value, and negative predictive value of 83.3%, 81.5%, 33.3%, and 97.8% as a predictor of PGD, respectively. At a cut-off value of 22 µmol L^{-1} or less, serum taurine had a sensitivity, specificity, positive predictive value, and negative predictive value of 88.9%, 98%, 88.9%, and 98% as a predictor of 30-day mortality, respectively.

Table 6 compares between patients with MELD score <20 and those with MELD score ≥20. There were no significant differences in serum taurine between the two groups at any of the measurement

Table 2. Comparison of the results of preoperative laboratory investigations between the studied groups.

		Groups according to serum taurine level				Tests of significance	
		Group I (> 30 µmol L^{-1}) (n = 20)	Group II (20–30 µmol L^{-1}) (n = 20)	Group III (< 20 µmol L^{-1}) (n = 20)	Total (n = 60)	Test statistic	p
WBCs*10^3 (U L^{-1})	Range	1.9–11.4	1.5–8.0	1.6–6.1	1.5–11.4	2.816	0.245
	Median (IQR)	4.3 (3.1–6.4)	3.7 (2.6–4.7)	3.7 (2.9–4.4)	3.8 (3.0–4.9)		
Platelets*10^3 (U L^{-1})	Range	38.0–189.0	18.0–227.0	43.0–190.0	18.0–227.0	0.560	0.756
	Median (IQR)	62.0 (54.0–104.5)	76.0 (53.0–112.5)	78.5 (65.5–103.5)	77.0 (55.0–104.5)		
Urea (mg dl^{-1})	Range	6.0–83.0	9.0–45.0	7.0–31.0	6.0–83.0	4.975	0.083
	Median(IQR)	14.0 (11.0–19.5)	22.0 (16.5–32.5)	17.0 (11.5–23.0)	18.0 (11.0–24.0)		
Creatinine (mg dl^{-1})	Range	0.4–1.4	0.6–1.9	0.5–1.7	0.4–1.9	4.252	0.019*
	Mean ± SD	0.9 ± 0.3 [b]	1.2 ± 0.4 [a]	0.9 ± 0.3	1.0 ± 0.4		
Creatinine clearance (ml min^{-1})	Range	64.0–235.0	36.0–293.0	49.0–240.0	36.0–293.0	1.468	0.244
	Mean ± SD	105.4 ± 38.9	94.3 ± 60.4	126.3 ± 59.2	108.9 ± 54.3		
AST (U L^{-1})	Range	10.0–120.0	10.0–74.0	6.0–98.0	6.0–120.0	1.985	0.371
	Median (IQR)	45.0 (25.5–84.0)	47.0 (25.5–52.5)	33.0 (25.0–52.0)	41.5 (25.0–55.5)		
ALT (U L^{-1})	Range	13.0–165.0	12.0–135.0	8.0–129.0	8.0–165.0	4.663	0.097
	Median (IQR)	54.5 (36.5–67.0)	37.0 (20.0–51.5)	36.0 (21.5–51.0)	41.5 (21.5–57.0)		
Total bilirubin (mg dl^{-1})	Range	0.7–18.0	0.8–14.4	0.4–8.5	0.4–18.0	1.786	0.409
	Median (IQR)	3.2 (1.4–6.1)	2.7 (1.9–5.4)	2.2 (1.1–5.0)	2.0 (1.4–6.0)		
Direct bilirubin (mg dl^{-1})	Range	0.3–8.7	0.3–7.6	0.1–7.1	0.1–8.7	3.503	0.173
	Median (IQR)	1.6 (0.6–3.3)	1.5 (0.8–3.2)	0.8 (0.3–2.5)	1.2 (0.5–3.3)		
Albumin (g dl^{-1})	Range	1.5–4.0	1.8–3.6	1.8–4.1	1.5–4.1	0.720	0.491
	Mean ± SD	2.8 ± 0.5	2.6 ± 0.5	2.7 ± 0.8	2.7 ± 0.6		
INR	Range	1.3–2.1	1.2–2.4	1.0–2.3	1.0–2.4	1.030	0.364
	Mean ± SD	1.6 ± 0.2	1.7 ± 0.4	1.6 ± 0.4	1.6 ± 0.3		
Factor V (%)	Range	17.6–82.0	12.1–76.0	17.8–97.0	12.1–97.0	0.965	0.617
	Median (IQR)	39.0 (33.5–42.5)	41.5 (25.8–52.5)	39.0 (29.0–70.0)	39.0 (29.8–52.0)		
AFP (ng ml^{-1})	Range	1.2–14.7	0.6–24.0	1.7–298.0	0.6–298.0	12.192	0.002*
	Median (IQR)	3.5 (2.0–8.6) [c]	2.8 (1.8–4.2) [c]	13.0 (3.5–33.5) [a,b]	3.7 (2.1–10.0)		
CRP (mg dl^{-1})	Range	0.3–5.1	0.3–3.4	0.1–3.7	0.1–5.1	5.699	0.058
	Median (IQR)	1.9 (0.6–3.0)	1.0 (0.6–2.0)	0.8 (0.3–1.6)	1.4 (0.5–2.0)		
Procalcitonin (pg dl^{-1})	Range	0.10–0.50	0.10–0.40	0.04–0.40	0.04–0.50	1.009	0.604
	Median (IQR)	0.20 (0.10–0.25)	0.20 (0.10–0.25)	0.10 (0.10–0.30)	0.20(0.10–0.30)		

IQR: interquartile range; n: number; SD: standard deviation; a: significant difference with group I; b: significant difference with group II; c: significant difference with group III; WBCs: white blood cells; AST: aspartate aminotransferase; ALT: alanine transaminase; AFP: alpha-fetoprotein; CRP: C-reactive protein; INR: international normalized ratio

*significant at $p < 0.05$.

Table 3. Correlation between serum taurine and results of laboratory investigations at different time points.

		Serum taurine level		
		7^{th} day	14^{th} day	30^{th} day
WBCs*10^3 (U L^{-1})	r_s	-0.029	0.008	0.007
	p	0.825	0.954	0.962
	n	59	54	51
Platelets*10^3 (U L^{-1})	r_s	0.318	0.094	0.154
	p	0.014*	0.499	0.286
	n	59	54	50
Urea (mg dl^{-1})	r_s	-0.160	-0.183	-0.170
	p	0.226	0.186	0.234
	n	59	54	51
Creatinine (mg dl^{-1})	r	-0.386	-0.175	-0.173
	p	0.003*	0.206	0.225
	n	59	54	51
AST (U L^{-1})	r_s	-0.396	-0.365	-0.167
	p	0.002*	0.007*	0.243
	n	59	54	51
ALT (U L^{-1})	r_s	-0.385	-0.301	-0.162
	p	0.003*	0.027*	0.257
	n	59	54	51
Albumin (g dl^{-1})	r	0.036	0.093	0.319
	p	0.786	0.503	0.022*
	n	59	54	51
Total bilirubin (mg dl^{-1})	r_s	-0.379	-0.416	-0.171
	P	0.003*	0.002*	0.231
	N	59	54	51
Direct bilirubin (mg dl^{-1})	r_s	-0.324	-0.354	-0.213
	P	0.012*	0.009*	0.133
	N	59	54	51
INR	r	-0.349	-0.495	-0.223
	P	0.007*	<0.001*	0.119
	N	58	53	50

r: coefficient of Pearson's correlation; rs: coefficient of Spearman's rank-order correlation; WBCs: white blood cells; AST: aspartate transaminase; ALT: alanine transaminase; INR: international normalized ratio

*significant at $p < 0.05$.

Table 4. Univariate and multivariate binomial logistic regression analyses to identify factors affecting significantly PGD.

	Univariate analysis				Multivariate analysis			
	Wald	p	OR	95% CI for OR	Wald	p	OR	95% CI for OR
Age (years)	0.023	0.880	0.994	0.925–1.069	-	-	-	-
BMI (Kg m^{-2})	0.610	0.435	1.151	0.809–1.637	-	-	-	-
Gender (male)	1.718	0.190	0.317	0.057–1.766	4.170	0.041*	0.077	0.007–0.902
MELD score	0.104	0.747	0.970	0.805–1.169	-	-	-	-
HCV	1.203	0.273	0.385	0.070–2.121	-	-	-	-
HCC	0.499	0.480	1.842	0.338–10.033	-	-	-	-
Cryptogenic hepatitis	2.050	0.152	4.000	0.600–26.683	3.404	0.065	10.048	0.866–116.576
GRWR	0.132	0.716	0.514	0.014–18.602	-	-	-	-
Preoperative Taurine (μmol L^{-1})	2.280	0.131	0.890	0.765–1.035	0.073	0.787	1.032	0.823–1.293
Taurine at 7^{th} day (μmol L^{-1})	4.629	0.031*	0.847	0.729–0.985	5.576	0.018*	0.815	0.687–0.966

CI: confidence interval; OR: odds ratio; PGD: primary graft dysfunction
*significant at $p < 0.05$.

Table 5. Diagnostic and predictive performance of serum taurine at different time intervals.

Outcome	Variable	AUC	95% CI	p	Cut-off (μmol L^{-1})	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PGD	Serum Taurine preoperative	0.662	0.528–0.779	0.038*	≤ 28	100.0	44.4	16.7	100.0
	Serum Taurine at the 7^{th} day	0.827	0.708–0.913	< 0.001*	≤ 24	83.3	81.5	33.3	97.8
30-day Mortality	Serum Taurine preoperative	0.642	0.507–0.761	0.202	≤ 19.5	55.6	70.6	25.0	90.0
	Serum Taurine at the 7^{th} day	0.888	0.780–0.955	< 0.001*	≤ 22	88.9	98.0	88.9	98.0

AUC: area under the ROC curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; PGD: primary graft dysfunction
*significant at $p < 0.05$.

Table 6. Comparison between patients with low and high MELD scores.

		MELD score		Tests of significance	
		20 or less (n = 45)	> 20 (n = 15)	Test statistic	p
Preoperative serum Taurine (μmol/L)	Range	17.5–39.5	17.5–39.0	0.236	0.814
	Mean ± SD	26.6 ± 7.9	27.2 ± 7.7		
Serum Taurine at 7th day (μmol/L)	Range	18.0–49.0	21.0–49.5	0.203	0.840
	Mean ± SD	32.9 ± 9.7	33.5 ± 9.3		
Serum Taurine at 14th day (μmol/L)	Range	17.5–54.0	30.0–54.0	1.194	0.238
	Mean ± SD	40.8 ± 9.9	44.2 ± 7.1		
Serum Taurine at 30th day (μmol/L)	Range	21.0–61.0	47.0–60.5	1.341	0.186
	Mean ± SD	50.6 ± 8.7	53.9 ± 4.7		
PGD	No	38 (86.4%)	16 (100.0%)	FE	0.179
	Yes	6 (13.6%)	0 (0.0%)		
7th day syndrome	No	43 (97.7%)	15 (93.8%)	FE	0.466
	Yes	1 (2.3%)	1 (6.2%)		
30-day mortality	No	37 (84.1%)	14 (87.5%)	FE	1.000
	Yes	7 (15.9%)	2 (12.5%)		
ICU stay days	Range	2.0–67.0	3.0–8.0	0.220	0.826
	Median (IQR)	5.0 (4.0–7.5)	4.5 (4.0–6.5)		
Hospital stay days	Range	0.0–180.0	0.0–45.0	0.470	0.638
	Median (IQR)	25.0 (19.0–32.0)	23.5 (19.0–28.5)		

FE: Fisher's exact test; IQR: interquartile range; n: number; SD: standard deviation

time points ($p > 0.05$). In addition, no significant differences were found regarding patients' outcomes, including PGD ($p = 0.179$), 7th day syndrome ($p = 0.466$), 30-day mortality ($p = 1.000$), or length of ICU stay ($p = 0.826$) and hospital stay ($p = 0.638$).

Table 7 shows the results of multiple regression analysis that examined the effects of age, BMI, gender, HCV, HBV, HCC, and cryptogenic hepatitis on preoperative serum taurine level. Only HCC and cryptogenic hepatitis were found to affect serum taurine level significantly ($p < 0.001$ and $p = 0.003$, respectively).

4. Discussion

Previous studies have reported the association between low serum taurine levels and liver impairment [20,21]. The present study attempted to cover a gap in the knowledge about the relationship between serum taurine level and outcome in patients undergoing LDLT.

The studied patients were divided into three groups according to their preoperative serum taurine level (>30 μmol L^{-1}, 30–20 μmol L^{-1}, and <20 μmol L^{-1}). This categorization was based on previous studies that

Table 7. Multiple regression test to examine effect of relevant patients' parameters on preoperative serum taurine.

	Unstandardized Coefficients				95.0% Confidence Interval for B	
	B	Standard Error	t	p	Lower Bound	Upper Bound
Age (years)	0.000	0.067	0.004	0.997	-0.135	0.135
BMI (kg m^-2)	-0.179	0.216	-0.828	0.411	-0.613	0.255
Gender (female)	0.526	1.251	0.421	0.676	-1.984	3.036
HCV	-0.023	2.184	-0.011	0.992	-4.406	4.360
HBV	0.979	4.802	0.204	0.839	-8.658	10.615
HCC	-14.117	1.329	-10.620	<0.001*	-16.784	-11.450
Cryptogenic hepatitis	-7.547	2.438	-3.095	0.003*	-12.441	-2.654

BMI: body mass index; HCV: hepatitis C virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma.
*significant at $p < 0.05$.

considered hepatic patients are in the safe zone when their serum taurine levels were above 50 μmol L^{-1}, while those with taurine levels between 40 and 50 μmol L^{-1} were highly susceptible to hepatic complications, whereas advanced liver cirrhosis and susceptibility for HCC increased when taurine levels decreased below 30 μmol L^{-1}. A lot of researches considered taurine levels less than 20 μmol L^{-1} as a cut off value for HCC [6,7].

We found that the mean preoperative serum taurine was 26.8 ± 7.8 μmol L^{-1} in our series of patients, which is nearly similar to the taurine levels reported in cirrhotic patients [6] (28.865 ± 3.07661 μmol L^{-1}), but lower than the level reported in hepatitis patients (46.7 ± 3.3 μmol L^{-1}) [7]. These differences among the studies may be attributed to variations in the severity of liver injury in the studied patients that mandated liver transplantation, as the level of serum taurine was reported to correlate with the severity of liver insult. A serum taurine level ranging from 40 to 50 μmol L^{-1} may indicate liver impairment in the early stages of disease, whereas a level below 40 μmol L^{-1} is associated with a higher likelihood of developing cirrhosis within 5 or 10 years [7].

Preoperative serum taurine level did not correlate significantly with liver function tests in the present series of patients, most probably due to low levels of taurine and deteriorated liver functions in all patients, with little variations among the patients. However, serum taurine showed significant, negative, moderate correlation with AST, ALT, bilirubin, and INR on 7th and 14th day post-transplant. This indicated that improvement in liver function over the first two post-operative weeks was associated with increased levels of serum taurine. The relationship between taurine levels and liver function could be explained by the fact that taurine synthesis takes place mainly in the liver. Therefore, impairment of liver function results in reduced taurine synthesis, with low plasma taurine levels being seen in severe liver damage or cirrhosis [22,23].

Earlier research suggests that the relationship between serum taurine and liver function is bidirectional; liver impairment results in low taurine levels and elevated taurine levels can prevent/improve liver injury. Its hepatoprotective role was reported by experimental studies in animals [24–26]. Liver protection was attributed to taurine-mediated modulation of pro-inflammatory cells [27].

A major challenge of liver transplantation is the need to clamp portal vein during hepatectomy in the donor, which could lead later to I/R injury in the recipient. The precise mechanism of I/R injury in these cases is not yet known [28]. However, several intermingling factors are suggested, including disturbed hepatic microcirculation [29], interaction between platelets [30], leukocytes [31], activation of Kupffer cells [32], and the expression of adhesion molecules [33].

The activation of Kupffer cells plays a principal role in the pathogenesis of I/R injury. The activated Kupffer cells release pro-inflammatory mediators (e.g., tumor necrosis factor α, interleukin-1) that result in induction of graft reperfusion injury. These cells represent a main source of free radicals that contribute to the inflammatory reaction [34,35]. In addition, the expression of adhesion molecules is induced by Kupffer cells in the liver vasculature, resulting in recruitment of leukocytes and augmentation of the inflammatory reaction [36].

Taurine was reported to prevent I/R injury in in vitro animal models [37–39]. Similarly, preoperative treatment with taurine in in vivo experimental animal models improved graft survival and reduced liver injury [9,40].

The mechanisms underlying this effect involve the binding of taurine to cellular chloride ion channel, leading to hyperpolarization of the Kupffer cell membrane, thereby reducing the lipopolysaccharide-induced increase in intracellular calcium ions and the production of tumor necrosis factor α [9,40,41].

Seventh-day Syndrome is one of the most serious and fatal complications of liver transplant and is characterized by sudden failure of a graft that had been working normally about 1 week after transplantation. In the current study, two patients (3.3%) developed 7DS with serum taurine levels less than 30 μmol L^{-1}. Likewise, a retrospective analysis of 111 consecutive LDLT over a 17-year period revealed that three patients (2.7%) developed clinical sequences typical of 7DS [17].

Up to the best of the authors' knowledge, the relationship of preoperative serum taurine levels in the recipients and the occurrence of PGD and 7DS has

not yet been investigated. Although patients who developed PGD had lower mean preoperative serum taurine levels than those with intact graft, this difference did not reach statistical significance.

Logistic regression analysis was conducted to determine factors that contributed significantly to the occurrence of PGD. We found that increased serum taurine level at the 7th postoperative day, and not preoperative taurine level, was significantly associated with decreased probability of developing PGD, after adjusting for potential confounders. Statistical analysis with receiver operating characteristic curve showed that preoperative taurine had poor prognostic value for PGD (AUC = 0.662; p = 0.038) or 30-day mortality (AUC = 0.642; p = 0.202).

However, we found that taurine level on the 7th day after transplant had good diagnostic value for PGD (AUC = 0.827; p < 0.001) and good predictive value of 30-day mortality (AUC = 0.888; p < 0.001). The value of taurine level on the 7th day as a predictor of 30-day mortality have potential important implications in the care of those patients. Early identification of patients at high risk of mortality can help providing optimal care which may improve their outcomes. On the 7th day, serum taurine level of 22 μmol L^{-1} or less had a sensitivity of 88.9%, a specificity of 98%, a positive predictive value of 88.9%, and a negative predictive value of 98% as a predictor of 30-day mortality. In light of these results, it appears that taurine level before the 7th day post-transplant could potentially predict PGD and 30-day mortality. Further research is warranted to explore this point.

The present study also investigated the relationship between serum taurine and other parameters. Significant differences in mean age, BMI, HCV, HCC, and cryptogenic hepatitis were found in univariate analysis among the three studied groups. However, multiple regression analysis revealed that age, BMI, gender, HCV, and HBV did not contribute significantly to changes in preoperative taurine levels (p = 0.997, 0.411, 0.676, 0.992, and 0.839, respectively). Only HCC and cryptogenic hepatitis were found to affect significantly preoperative taurine level (p < 0.001 and p = 0.003, respectively), which is in partial agreement with previous studies that reported significantly low taurine levels in HCV [4] and HCC [5] patients.

5. Conclusions

Preoperative serum taurine level had no prognostic value for PGD or 30-day mortality. However, taurine level at the 7th day post-transplant had good diagnostic value for PGD and good prognostic value for 30-day mortality. Future research should investigate the potential value of taurine levels within the first week post-transplant as a predictor or diagnostic marker for PGD and seventh day syndrome post liver transplant. In addition, randomized clinical trials are required to evaluate the safety and efficacy of perioperative taurine supplementation in patients who are candidates for LDLT.

6. Limitations of the study

The sample size was relatively small as it was an exploratory study, and follow-up after 30 days was not recorded in the current study. Included patients were all Egyptians who suffered from liver diseases common in Egypt, thus generalizability of the results to other populations with different liver diseases is questionable. Daily assessment of serum taurine levels starting from first day post-transplant is warranted to assess early graft dysfunction and possibility of 7DS.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Hanaa El-Gendy http://orcid.org/0000-0003-4493-1635
Manar M. Salah http://orcid.org/0000-0001-9909-4016

References

[1] Hoyer DP, Paul A, Gallinat A, et al. Donor information based prediction of early allograft dysfunction and outcome in liver transplantation. Liver Int. 2015;35 (1):156–163. .
[2] Zhai Y, Petrowsky H, Hong JC, et al. Ischaemia-reperfusion injury in liver transplantation–from bench to bedside. Nat Rev Gastroenterol Hepatol. 2013;10:79–89.
[3] Memon MA, Karademir S, Shen J, et al. Seventh Day Syndrome–acute hepatocyte apoptosis associated with a unique syndrome of graft loss following liver transplantation. Liver. 2001;21:13–17.
[4] Lan X, Li B, Wang XF, et al. Potential etiopathogenesis of seventh day syndrome following living donor liver transplantation: ischemia of the graft? Hepatobiliary Pancreat Dis Int. 2010;9:22–26.
[5] Batista TM, Ribeiro RA, da Silva PM, et al. Taurine supplementation improves liver glucose control in normal protein and malnourished mice fed a high-fat diet. Mol Nutr Food Res. 2013;57:423–444.
[6] El-Agouza I, Fouad R, Ahmed R, et al. Comparison between Fibroscan and Serum Taurine for Early diagnosis of liver fibrosis in egyptian patients infected with HCV. Clin Med Biochem. 2017;3:1–6.
[7] El-Agouza IM, Ghaffar MMA, Abd-Allah AA, et al. Comparison between serum taurine and specific tumor markers for early detection and diagnosis of HCC in egyptian patients. World J Adv Health Res. 2019;3:99–101.
[8] El-Houseini ME, El-Agoza IA, Sakr MM, et al. Novel protective role of curcumin and taurine combination against experimental hepatocarcinogenesis. Exp Ther Med. 2017;13:29–36.

[9] Schemmer P, Liang R, Kincius M, et al. Taurine improves graft survival after experimental liver transplantation. Liver Transpl. 2005;11:950–959.
[10] Uzunhisarcikli M, Aslanturk A. Hepatoprotective effects of curcumin and taurine against bisphenol A-induced liver injury in rats. Environ Sci Pollut Res Int. 2019;26:37242–37253.
[11] Zhang Y, Ren S, Liu Y, et al. Inhibition of starvation-triggered endoplasmic reticulum stress, autophagy, and apoptosis in ARPE-19 cells by taurine through modulating the expression of calpain-1 and calpain-2. Int J Mol Sci. 2017;18:E2146.
[12] Ishigami M, Katano Y, Hayashi K, et al. Risk factors of recipient receiving living donor liver transplantation in the comprehensive era of indication and perioperative managements. Nagoya J Med Sci. 2010;72:119–127.
[13] Kiuchi T, Kasahara M, Uryuhara K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation. 1999;67:321–327.
[14] Shah SA, Levy GA, Adcock LD, et al. Adult-to-adult living donor liver transplantation. Can J Gastroenterol. 2006;20:339–343.
[15] Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007;45:797–805.
[16] Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl. 2010;16:943–949.
[17] Kawachi S, Tanabe M, Shinoda M, et al. Pathogenesis and clinical features of seventh-day syndrome after adult living donor liver transplantation. Transplantation. 2014;98:691.
[18] McMahon GP, O'Kennedy R, Kelly MT. High-performance liquid chromatographic determination of taurine in human plasma using pre-column extraction and derivatization. J Pharm Biomed Anal. 1996;14:1287–1294.
[19] Salviano MEM, Lima AS, Tonelli IS, et al. Primary liver graft dysfunction and non-function: integrative literature review. Rev Col Bras Cir. 2019;46:e2039.
[20] Weisdorf SA, Freese DK, Fath JJ, et al. Amino acid abnormalities in infants with extrahepatic biliary atresia and cirrhosis. J Pediatr Gastroenterol Nutr. 1987;6:860–864.
[21] Yamamoto S. Plasma Taurine in liver cirrhosis with painful muscle cramps. In: Huxtable RJ, Azuma J, Kuriyama K, et al., editors. Taurine 2: basic and clinical aspects. Boston, MA: Springer US; 1996. p. 597–600.
[22] Chawla RK, Berry CJ, Kutner MH, et al. Plasma concentrations of transsulfuration pathway products during nasoenteral and intravenous hyperalimentation of malnourished patients. Am J Clin Nutr. 1985;42:577–584.
[23] Cooper A, Betts JM, Pereira GR, et al. Taurine deficiency in the severe hepatic dysfunction complicating total parenteral nutrition. J Pediatr Surg. 1984;19:462–466.
[24] Chen X, Sebastian BM, Tang H, et al. Taurine supplementation prevents ethanol-induced decrease in serum adiponectin and reduces hepatic steatosis in rats. Hepatology. (Baltimore, Md). 2009;49:1554–1562.
[25] Waters E, Wang JH, Redmond HP, et al. Role of taurine in preventing acetaminophen-induced hepatic injury in the rat. Am J Physiol Gastrointest Liver Physiol. 2001;280:G1274–1279.
[26] Yalcinkaya S, Unlucerci Y, Giris M, et al. Oxidative and nitrosative stress and apoptosis in the liver of rats fed on high methionine diet: protective effect of taurine. Nutrition. 2009;25:436–444.
[27] Kim H, Jeon H, Kong H, et al. A molecular mechanism for the anti-inflammatory effect of taurine-conjugated 5-aminosalicylic acid in inflamed colon. Mol Pharmacol. 2006;69:1405–1412.
[28] Lemasters JJ, Thurman RG. Reperfusion injury after liver preservation for transplantation. Annu Rev Pharmacol Toxicol. 1997;37:327–338.
[29] Thurman RG, Marzi I, Seitz G, et al. Hepatic reperfusion injury following orthotopic liver transplantation in the rat. Transplantation. 1988;46:502–506.
[30] Gao WS, Takei Y, Marzi I, et al. Carolina rinse solution–a new strategy to increase survival time after orthotopic liver transplantation in the rat. Transplantation. 1991;52:417–424.
[31] Takei Y, Marzi I, Gao WS, et al. Leukocyte adhesion and cell death following orthotopic liver transplantation in the rat. Transplantation. 1991;51:959–965.
[32] Jung J-Y LS. The roles of Kupffer cells in hepatic dysfunction induced by ischemia/reperfusion in rats. Arch Pharm Res. 2005;28:1386–1391.
[33] Ala A, Dhillon AP, Hodgson HJ. Role of cell adhesion molecules in leukocyte recruitment in the liver and gut. Int J Exp Pathol. 2003;84:1–16.
[34] Bouwens L. Structural and functional aspects of Kupffer cells. Revis Biol Celular. 1988;16:69–94.
[35] Dixon LJ, Barnes M, Tang H, et al. Kupffer cells in the liver. Compr Physiol. 2013;3:785–797.
[36] Saliba F, Lakehal M, Pageaux GP, et al. Risk factors for new-onset diabetes mellitus following liver transplantation and impact of hepatitis C infection: an observational multicenter study. Liver Transpl. 2007;13:136–144.
[37] Kincius M, Liang R, Nickkholgh A, et al. Taurine protects from liver injury after warm ischemia in rats: the role of Kupffer cells. Eur Surg Res. 2007;39:275–283.
[38] Minor T, Yamaguchi T, Isselhard W. Effects of taurine on liver preservation in UW solution with consecutive ischemic rewarming in the isolated perfused rat liver. Transpl Int. 1995;8:174–179.
[39] Wettstein M, Haussinger D. Taurine attenuates cold ischemia-reoxygenation injury in rat liver. Transplantation. 2000;69:2290–2296.
[40] Sun K, Chen Y, Liang SY, et al. Effect of taurine on IRAK4 and NF-kappa B in Kupffer cells from rat liver grafts after ischemia-reperfusion injury. Am J Surg. 2012;204:389–395.
[41] Seabra V, Stachlewitz RF, Thurman RG. Taurine blunts LPS-induced increases in intracellular calcium and TNF-alpha production by Kupffer cells. J Leukoc Biol. 1998;64:615–621.