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Noninvasive Biochemical and Hematological Markers in the Development of Early Dysfunction for Transplanted Liver in Egyptian Patients

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Abstract

Background: Early allograft dysfunction (EAD) is associated with graft failure and mortality after liver transplantation (LT). The present prospective study aimed to determine the role of some biochemical markers to predict EAD development after living donor liver transplantation (LDLT). Patients and Methods: One hundred twenty patients under went living donor liver transplantation in Gastrointestinal Surgery Center Mansoura University were subjected to the present study. Patients were divided into two groups: Eighty-two non-early allograft dysfunction group (NEAD) and thirty-eight early allograft dysfunction group (EAD). Blood levels of different biochemical markers were estimated at preoperative day and postoperative from day one to day seven using bio and immunochemical assays. Results: Some of biochemical marker levels on preoperative day and on different postoperative days from day one to day seven were significantly different in EAD than NEAD group (p values ranged from < 0.05 to < 0.0001). According to multiple logistic regression analysis of most significant independent variables for prediction of EAD, there were four prediction models were constructed. Model-1 represented the combination among five variables; aspartate aminotransferase (AST) on postoperative day one, direct bilirubin (DB) on postoperative day seven, gamma-glutamyl transferase (GGT) on postoperative day four, hemoglobin (HG) and platelets (PLT) on preoperative day. Model-2 was a combination between DB, GGT, PLT on postoperative day seven and uric acid (UA) on postoperative day five. Model-3 represented the combination among five variables; AST on postoperative day one, DB on postoperative day three, GGT on postoperative day four, HG and PLT on preoperative day. Model-4 was a combination between AST on postoperative day one, GGT on postoperative day four, HG and PLT on preoperative day. All four models revealed a prediction potential for EAD in LDLT that showed an extremely significant ($p<0.0001$). Moreover, they have high AUCs with high sensitivity and specificity for four models (for model-1; AUC=0.877, sensitivity=84.2%, specificity=78%, for model-2; AUC=0.842, sensitivity=84.2, specificity=76.8%, model-3 and model-4 had AUC 0.875, 0.853 respectively; both sensitivity=84.2 and specificity=75.6%) Conclusion: Estimation of some biochemical and hematological markers on preoperative and postoperative days from day one to day seven correlated with EAD development and the four current models had a significant prediction potential for EAD

in LDLT.

Keywords: Early allograft dysfunction, Living donor liver transplantation, Platelets. Biomarkers, noninvasive, and Egypt

Introduction

For patients suffering from end-stage liver disease, acute liver failure, and a small proportion of patients with primary and secondary hepatic malignancies, liver transplantation represents a potentially life-saving therapeutic option **(Quaresima et al.,2023)**. Nowadays, LT is thought to be a long-lasting procedure and the recommended treatment for a variety of illnesses that seriously compromise liver function **(Mahmud, 2020)**. Patient results greatly depend on the restoration of graft function both during and immediately following surgery **(Rajakumar et al., 2023)**.

In Egypt, living donor liver transplantation (LDLT) showed to be the only reasonable option to save many patients who are in impetuous requirement for liver graft, LDLT the first performed in Egypt in 1991 by the surgical team at the National Liver Institute (NLI). Since this time, there were (13 centers) doing LDLT and increase number of cases of LDLT with great efforts to improvement of the results, by the end of June 2014, the total number of cases reached 2,406, this number comprised 2,246 adult cases (93%) and 160 pediatric cases (7%), the vast majority of indications of LDLT were HCV hepatitis **(Amer and Marwan, 2016)**. The slow progress of HCV-related HCC, even after HCV treatment, shows that the occurrence of HCC in Egypt may not have peaked yet. The yearly incidence of HCC was reported to be 29/1000/year in Egyptian cirrhotic patients who accomplished sustained virologic response (SVR) following DAA treatment, however, such slow improvement indicates that the incidence of HCV-induced HCC in Egypt is still high **(Shiha et al.,2020).** An increased infiltration pattern rate among HCC patients after DAA treatment is also recognized, viral hepatitis is one of the main public health issues in Egypt that requires great attention and funding from health policymakers **(Elbahrawy et al.,2021).** The annual percentage of metabolic-associated fatty liver disease (MAFLD) associated hepatocellular carcinoma (HCC) increased significantly from 4.3% in 2010 to 20.6% in 2020, whereas HCV-related HCC decrease from 94.8% to 76.7%, **(Fouad et al.,2022).** The emersion of direct acting antivirals (DAAs) in 2013 evident a turning point in the administration of HCV, providing short treatment duration, low side effects, and high cure rate, to the extent that the short- and long-term results of liver transplantation for HCV are nearly identical to those of liver transplantation for other reasons **(Moein et al., 2025)**. Between July 2018 and January 2020, the registry database of the Egyptian Ministry of Health has reported 380 LDLT operations were performed in Egypt **(Abd Elbaset et al., 2021).** With the movement in health care and science, more uncommon liver disorders than previously thought are being discovered **(Abdelhamed and El-Kassas. 2024)**. Current statistics on the exact number of LDLT surgeries required to be done in Egypt is still unclear.

n patients underwent liver transplant (LT), Specific identification of early allograft dysfunction (EAD) is essential to reduce mortality and morbidity (Liu et al., 2024). Early and perfect diagnosis is critical for timely intervention and improved patient outcomes, but their diagnosis depend currently on invasive biopsy sampling. However, raising the search for non-invasive biomarkers for detection these complications in LT recipients timely with suitable biomarkers is essential **(Pia et al., 2024)**.

Recent advances in biochemical technology and bioinformatic analysis have improved our understanding of perioperative graft injury and have led to the discovery of possible strategies for graft function restoration **(Verhoeven et al.,2017)**. As a result, protocol (blood) measurements are applied to LT recipients based on their clinical status during follow-up; this might range from daily monitoring in the intensive care unit right after surgery. Liver function parameters are also important for assessing the quality of the graft,

particularly in the initial post-LT days **(Lin et al., 2023).** The present study aimed to determine the role of some biological markers for prediction development of early allograft dysfunction in living donor liver transplantation.

Patients and Methods:

The Research and Ethical Committees of Al-Azhar Faculty of Medicine, Damietta, Egypt, approved this prospective study. One hundred twenty patients were enrolled in the study over eight months from December 2023 to July 2024. The study population was residents in the Gastrointestinal Surgery Center Mansoura University Egypt, undergoing LDLT.

Patients were classified according to the early allograft dysfunction within the first week of transplantation into the following groups: non early allograft dysfunction group (NEAD, 82 patients) and early allograft dysfunction group (EAD, 38 patients). EAD was defined according to the following criteria: total serum levels of bilirubin ≥ 10mg/dL or INR ≥ 1.6 on POD-7; and ALT or AST level > 2000 U/L within the first 7 postoperative days. Five milliliters of peripheral blood were collected from each patient on preoperative day and postoperative days from day one to day 7. Each sample was divided into two parts, the first part was collected into a tube containing anticoagulant for hematological study using haematology analyser device Cell Tac MEK – 6510 -6500. Japan. The second part was collected into clean dry tube to prepare serum for routine laboratory tests using bio and immunochemical assays from manufactured for MG science and technology center (STC). Enzyme-linked Immunosorbent Assay (ELIZA) confirmed patients with HCV and/or HBV positive antibodies. All spectrophotometric measurements used Hitachi 902 analyzer. Pathological features of patients were performed in pathology laboratories of Gastrointestinal Surgery Center Mansoura University.

Statistical analysis:

Continuous data are expressed as the mean ± standard deviation or median and interquartile range (IQR) and were compared by the student *t* test, or the Mann–Whitney *U* test when appropriate. Categorical data were presented as the number and proportion and evaluated using the χ^2 test or Fisher's exact test, as appropriate. Changes in biochemical, and hematological levels between the preoperative samples and those taken on postoperative from day one to day seven were analyzed using the Wilcoxon signed rank test. The accuracy of the predictive markers and models for the development of EAD was analyzed using the area under the receiver operating characteristics curve (AUC). The association between independent variables and EAD development were investigated using simple logistic regression analyses as appropriate. Factors with potential significance were entered into the multiple logistic regression analyses. All of the tests were two sided, and a *P*-value<0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 26.0 for Windows (SPSS Inc., Chicago, IL).

Results:

Demographic and Clinicopathological data of study participant

Table (1) showed that males represent the higher percentage than females of cases in two the groups. The median age for (NEAD) group and (EAD) group were 52 and 46 years respectively. There were no significant differences between the two groups in terms of age, gender, hepatitis C virus (HCV), hepatitis B virus (HBV), cirrhosis, hepatocellular carcinoma (HCC), cholecystitis, autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC), ($p>0.05$). However, there were non-significant trends towards a higher prevalence of cholestasis and steatosis in the NEAD group ($p=0.522$, 0.067 respectively). In addition, there were no cases of primary sclerosing cholangitis (PSC) in the (EAD) group compared to 4 cases in the (NEAD) group ($p=0.166$). However, there was significant differences of portal vein thrombus (PVT) in the (EAD) group ($p=0.036$) (table 1).

Table 1. Demographic, clinical and pathological characteristics of patients with and without early allograft dysfunction in living donor liver transplantation.

Variable	NEAD group N = 82	EAD group N = 38	P value
Age Median (IQR)	52(41 – 57.25)	46(36.75 – 56)	0.246
Gender (male) n (%)	62(75.6%)	33(86.8%)	0.159
HCV n (%)	43(52.4%)	13(34.2%)	0.063
HBV n (%)	3(3.7%)	4(10.5%)	0.135
Cirrhosis n (%)	76(92.7%)	38(100.0%)	0.087
HCC n (%)	19(23.2%)	7(18.4%)	0.557
Cholecystitis n (%)	76(92.7%)	35(92.1%)	0.911
Cholestasis n (%)	17(20.7%)	6(15.8%)	0.522
Steatosis n (%)	11(13.4%)	1(2.6%)	0.067
AIH n (%)	12(14.6%)	7(18.4%)	0.597
PSC n (%)	4(4.9%)	0(0.00%)	0.166
BCS n (%)	2(2.4%)	1(2.6%)	0.095
PVT n (%)	0(0.00%)	2(5.3%)	0.036*

EAD: Early allograft dysfunction, NEAD: Non-EAD, HCV: Hepatitis C virus, HBV: Hepatitis B virus, HCC: Hepatocellular carcinoma, AIH: Autoimmune Hepatitis, PSC: Primary sclerosing cholangitis, BCS: Budd-Chiari syndrome, PVT: Portal vein thrombus. IQR: Interquartile range, * significant.

Assessment of investigated biomarkers

Data on tables 2 revealed that serum levels of different biochemical parameters on preoperative day (0) and postoperative days from day one to day seven (1-7) after LDLT, patients with EAD had significant difference ($p< 0.05$) in serum levels of AST on post days (1,2), total and direct bilirubin on post days (2,3,4,5,6,7), GGT on post days (4,5,6,7), ALB on post days (5,6,7), LDH on post days (1, 2,4), UA on post days (3,4,5,6,7). However, patients with EAD didn't show significant difference in serum levels of ALT and CRP ($p>0.05$). Regarding to INR there are significant difference between two groups on preoperative day ($p= 0.047$) and highly significant difference on postoperative days from day one to day seven ($p=0.000$).

Table 2. Serum levels of different biochemical parameters on preoperative day (0) and postoperative days from day one to day seven (1-7) in patients with and without early allograft dysfunction in living donor liver transplantation.

Variables	NEAD group Median (IQR) N=82	EAD group Median (IQR) N=38	P value	Variables	NEAD group Median (IQR) N=82	EAD group Median (IQR) N=38	P value
TB0	2(1.3 – 3.3)	2.5(1.5 – 4.5)	0.224	AST0	41(26 – 80)	32(225 – 47)	0.065
TB1	3.2(2.2 – 3.5)	4.15(2 -5.7)	0.162	AST1	182(111 – 318)	290(108 – 913)	0.043*
TB2	2.3(1.6 – 3.6)	3.7(2.15 – 6.1)	0.012*	AST2	110(68 – 183)	146(68 – 642)	0.023*
TB3	2.6(1.7 – 4.6)	4.6(2.3 – 8.4)	0.007**	AST3	65(44 – 101)	77(45 – 277)	0.099
TB4	3(1.6 – 5)	4.5(3 – 8.7)	0.002**	AST4	45(29 – 66)	44(31 – 128)	0.175
TB5	3(2.1 – 5.1)	5.2(3.3 – 9.2)	0.001**	AST5	38(25 – 58)	37(26 – 79)	0.472
TB6	2.6(1.9 – 4.6)	5.6(2.1 - 8.8)	0.001**	AST6	34(21 – 49)	34(23 – 59)	0.633
TB7	2.6(1.7 – 2.4)	6(2.2 – 8.6)	0.000***	AST7	32(22 – 43)	29(21 – 49)	0.797
GGT0	28(14 – 51)	22(13 – 48)	0.863	DB0	1.3(0.6 – 1.8)	1.1(0.7 – 2.6)	0.259
GGT1	27(16 – 45)	23(15 – 32)	0.460	DB1	1.6(0.9 – 2.6)	2.3(1.1 – 4.3)	0.082
GGT2	23(16 – 41)	24(18 – 30)	0.824	DB2	1.4(0.8 – 2.6)	2.3(1.1 – 4.3)	0.012*
GGT3	37(20 – 65)	28(19 – 45)	0.132	DB3	1.6(1 – 3.3)	3.5(1.2 – 7)	0.004**
GGT4	60(36 – 103)	41(22 – 62)	0.002**	DB4	2.1(1.2 – 4)	3.4(2 – 7)	0.004**
GGT5	91(45 – 148)	45(23 – 76)	0.000***	DB5	2.1(1.2 – 4)	4.2(2.4 – 7.5)	0.001**
GGT6	104(52– 195)	48(29 – 103)	0.001**	DB6	2(1.3 –3.7)	4.4(1.6 – 7.3)	0.001**
GGT7	112(65 – 208)	52(32 – 123)	0.000***	DB7	1.8(1.1 – 3.3)	4.5(1.4 – 6.5)	0.000***
LDH0	239(144 – 332)	217(144 – 340)	0.917	ALB0	2.9(2.5 – 3.4)	2.8(2.4 – 3.3)	0.711
LDH1	270(196 – 419)	439(222 – 782)	0.007**	ALB1	3(2.6 – 3.3)	2.9(2.6 – 3.2)	0.417
LDH2	219(165 – 330)	314(183 – 654)	0.019*	ALB2	2.9(2.6 - 3.1)	2.8(2.5 – 3.1)	0.465
LDH3	219(176 – 281)	258(173 – 454)	0.087	ALB3	3(2.7 – 3.3)	2.9(2.7 – 3.2)	0.326
LDH4	220(171 – 309)	274(183 – 420)	0.048*	ALB4	3.1(2.7 – 3.3)	3(2.7 – 3.2)	0.203
LDH5	233(184 – 307)	260(185 – 425)	0.131	ALB5	3.2(2.9 – 3.4)	3(2.8 – 3.2)	0.028*
LDH6	233(189 – 285)	256(188 – 402)	0.158	ALB6	3.2(3 – 3.5)	3(2.7 – 3.2)	0.006**
LDH7	233(188 – 285)	260(193 – 417)	0.112	ALB7	3.1(3 – 3.6)	2.9(2.7 – 3.3)	0.002**

UA0	4.2(3.2 – 5.9)	4.4(3.2 – 5.7)	0.735	INR0	1.5(1.3 – 1.9)	1.7(1.4 – 2)	0.047*
UA1	3.8(2.5 – 5.6)	4.7(3.1 – 6)	0.113	INR1	1.8(1.6 – 2.3)	2.6(2.1 – 3.4)	0.000***
UA2	3.7(2.7 – 5.4)	4.5(3.4 – 6.2)	0.054	INR2	1.6(1.4 – 1.8)	2.1(1.8 – 2.5)	0.000***
UA3	3.7(2.7 – 5.5)	4.8(3.3 – 6.3)	0.038*	INR3	1.4(1.2 – 1.6)	1.8(1.6 – 2.1)	0.000***
UA4	3.6(2.5 – 5.2)	4.6(3.2 – 6.4)	0.027*	INR4	1.3(1.2 – 1.6)	1.7(1.5 – 2)	0.000***
UA5	3.5(2.5 – 5.3)	5.4(3.8 – 6.7)	0.001**	INR5	1.3(1.2 – 1.5)	1.8(1.5 – 2)	0.000***
UA6	3.9(2.7 – 5.5)	5.3(3.9 – 7)	0.002**	INR6	1.3(1.2 – 1.4)	1.7(1.6 – 2.1)	0.000***
UA7	4(2.8 – 5.6)	5.3(4 – 6.7)	0.003**	INR7	1.2(1.1 – 1.4)	1.7(1.6 – 2)	0.000***

EAD: Early allograft dysfunction, **NEAD:** non-EAD, **T-Bili.:** Total bilirubin, **D-Bili:** Direct bilirubin, **Alb.:** Albumin, **ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase, **ALP:** Alkaline phosphatase, **GGT:** Gamma-glutamyl transferase, **UA:** Uric acid, **INR:** International Normalized Ratio, **CRP:** C-reactive protein, **IQR:** Interquartile range, *significant** highly significant, ***extremely significant

Assessment of investigated Hematological markers

Patients with EAD had a significant difference in WBC, RBC on post day seven (p= 0.019 and 0.027 respectively) and hemoglobin on day (0) p=0.025 and on post days (1,7) (p=0.013 and 0.002 respectively). As for neutrophil and lymphocyte had significant difference on post days (4 - 7 & 2,3,6,7 respectively) ($p<0.05$). However, PLT count in EAD group had significant difference on preoperative day and highly significance on postoperative days from (1 – 7) compared to NEAD group. table 3.

Table (3). Hematological parameters on preoperative day (0) and postoperative days from day one to day seven (1-7) in patients with and without early allograft dysfunction in living donor liver transplantation.

Variables	NEAD group Median (IQR) N=82	EAD group Median (IQR) N=38	P value	Variables	NEAD group Median (IQR) N=82	EAD group Median (IQR) N=38	P value
WBC0	3.8(2.7 – 5.7)	2.9(2 -5.1)	0.051	RBC0	3.6(3 – 4)	3.4(2.8 – 3.9)	0.224
WBC1	11.8(9.1 – 15)	9.7(7.1 – 15.1)	0.087	RBC1	2.9(2.7 – 3.3)	2.7(2.5 -3.2)	0.204
WBC2	7(4.9 – 10.7)	5.9(4.1 – 9.2)	0.162	RBC2	2.7(2.4 – 3.1)	2.7(3.5 – 3.1)	0.955
WBC3	5.1(4 – 8.1)	5.1(3.1 – 8.9)	0.567	RBC3	2.7(2.5 – 3.1)	2.8 (2.4 – 3.1)	0.843
WBC4	5.6(4 – 8.1)	4.6(3.2 – 10.6)	0.425	RBC4	2.7(2.4 – 3.2)	2.8(2.5 – 3.3)	0.769
WBC5	6(4.1 – 8)	4.5(3.1 – 8.8)	0.259	RBC5	2.8(2.4 – 3.2)	2.7(2.5 – 3)	0.705
WBC6	6.6(4.1 – 8.7)	5.1(3.6 – 7.9)	0.170	RBC6	2.9(2.5 – 3.3)	2.7(2.4 – 3.1)	0.705
WBC7	7.1(4.9 – 9.1)	5.6(3.5 – 8)	0.019*	RBC7	3(2.6 – 3.3)	2.6(2.5 – 3)	0.027*
PLT0	63(48 – 103)	56.7(32 – 75.95)	0.011*	NEU0	55(45 – 65.22)	58.9(47 – 69.7)	0.420
PLT1	61.7(39 – 85)	47.95(30 – 63.2)	0.005**	NEU1	86.9(81.7 – 90)	87(85.3 – 89.7)	0.333
PLT2	37.5(27 – 57)	30(20 – 51.37)	0.038*	NEU2	83(78.7 – 87.7)	85(79 – 89)	0.233
PLT3	39.7(27 – 61)	30.5(20 – 38.4)	0.003**	NEU3	79(74.6 – 86.6)	84(78.2 – 88.2)	0.058
PLT4	43(30.6 – 72)	34.4(19 – 52.8)	0.009**	NEU4	78.60(70 – 86)	81(76 – 86.9)	0.048*
PLT5	52.5(37 – 85)	32(22.7 – 58.2)	0.002**	NEU5	77.7(69.7 – 84)	79.6(71 – 86.7)	0.045*
PLT6	61.8(37 – 87)	36(21.9 – 64.3)	0.001**	NEU6	73(65.2 – 84.2)	79.4(70 – 87.5)	0.046*
PLT7	75(50 – 102)	44(26 – 68.37)	0.000***	NEU7	72.9(62.7 – 84)	82.7(69 – 34.5)	0.008**
LYM0	26.7(16 – 37)	22.3(16.4 – 34.5)	0.311	HG0	10(8.1 – 11.3)	8.3(7.4 – 10)	0.025*
LYM1	6.4(4.6 – 8.8)	5.75(3.8 – 7.8)	0.175	HG1	7.7(6.9 – 8.6)	7(6.2 – 7.9)	0.013*
LYM2	7.9(5.4 – 10)	5.85(4.2 -9.5)	0.036*	HG2	7(6.3 – 7.8)	6.9(6.3 – 7.4)	0.330
LYM3	9.7(6.6 – 8.8)	6.4(5.1 – 10.3)	0.004**	HG3	7.3(6.8 – 8.1)	7.1(6.3 – 7.8)	0.147
LYM4	10.9(7 – 15.4)	8.6(5.2 – 13.57)	0.044*	HG4	7.4(6.8 – 8.3)	7.1(6.5 – 7.9)	0.177
LYM5	11.2(7.9 – 15)	8.4(5.4 – 14.95)	0.033*	HG5	7.5(6.9 – 8.3)	7.3(6.7 – 7.8)	0.083
LYM6	13.3(7.9 – 17)	9.35(7 – 15)	0.028*	HG6	7.6(6.9 – 8.2)	7.3(6.4 – 8.1)	0.104
LYM7	13.9(9 – 13.4)	9.3(6.4 – 12.6)	0.003**	HG7	7.8(7.3 – 8.7)	7.1(6.4 – 7.9)	0.002**

EAD: Early allograft dysfunction, **NEAD:** non-EAD, **HG:** Hemoglobin, **RBCs**: Red blood cells, **WBCs**: White blood cells, PLT: platelets, LYM: Lymphocyte, NEU: Neutrophil, **IQR:** Interquartile range, *significant** highly significant, ***extremely significant

Diagnostic performance of biochemical and hematological markers in EAD prediction

Serum levels of GGT on postoperative days (4, 5, 6, 7) exhibited area under curves (AUC) ranged from 0.680 to 0.711with (sensitivity from 63% - 71%, specificity from 64% - 70%, p=0.002 – 0.000). Serum levels of ALB on postoperative days (5,6,7) exhibited area under curves (AUC) ranged from 0.657 to 0.677 711with (sensitivity from 68% - 73%, specificity from 50% - 53%, p=0.029 – 0.002).

Serum levels of LDH on postoperative days (1,2,4) exhibited area under curves (AUC) ranged from 0.613 to 0.656 with (sensitivity from 62% - 67%, specificity from 53% - 55%, p=0.048 – 0.007). Serum activity of AST on postoperative days (1,2) exhibited area under curves (AUC) ranged from 0.615 to 0.629with (sensitivity from 60% - 63%, specificity from 53% - 65%, p=0.043 – 0.023). Serum levels of TB on postoperative days (2,3,4,5,6,7) exhibited area under curves (AUC) ranged from 0.642 to 0.707with (sensitivity from 68% - 76%, specificity from 52% - 69%, p=0.012 – 0.000). Serum levels of DB on postoperative days (2,3,4,5,6) exhibited area under curves (AUC) ranged from 0.644 to 0.699 with (sensitivity from 68% - 73%, specificity from 52% - 70%, p=0.004 – 0.000). Serum levels of UA on postoperative days (3,4,5,6,7) exhibited area under curves (AUC) ranged from 0.618 to 0.682 with (sensitivity from 65% - 81%, specificity from 52% - 59%, p=0.038 – 0.001). On the other hand, count of WBC on postoperative day (7) exhibited area under curve (AUC) 0.633 with (sensitivity 71%, specificity57%, p=0.019) and the count of RBC on postoperative day (7) exhibited area under curve (AUC) 0.625 with (sensitivity 71%, specificity53%, p=0.027). while percentage of HG on preoperative day and postoperative days (1,7) exhibited area under curves (AUC) ranged from 0.627 to 0.676 with (sensitivity from 63% - 73%, specificity from 52% - 58%, p=0.025 – 0.002). However, count of PLT on preoperative day and postoperative days (1- 7) exhibited area under curves (AUC) ranged from 0.618 to 0.682 with (sensitivity from 65% - 81%, specificity from 52% - 59%, p=0.038 – 0.001). The count of NEU on postoperative days (4,6,7) exhibited area under curves (AUC) ranged from 0.612 to 0.652 with (sensitivity from 65% - 71%, specificity from 52% - 59%, p=0.048 – 0.008) and count of LYM on postoperative days (2,3,6,7) exhibited area under curves (AUC) ranged from 0.619 to 0.667 with (sensitivity from 71% - 78%, specificity from 52% - 58%, p=0.036 – 0.003).

Table 4. Area under curve (AUC), sensitivity, and specificity of statistically significant variables for prediction of EAD in patients underwent living donor liver transplantation.

Variable	AUC (95% CI)	Cut off	Sen %	Spe %	P value	Variable	AUC ((95% CI)	Cut off	Sen %	Spe %	P value
AST1	0.615 (0.499-0.732)	185.50	63	53	0.043*	UA3	0.618 (0.510 – 0.725)	3.8	65	65	0.038*
AST2	0.629 (0.514-0.744)	127	60	65	0.023*	UA4	0.626 (0.519 – 0.732)	3.6	68	68	0.027*
TB2	0.642 (0.529 – 0.756)	2.3	73	52	0.012*	UA5	0.682 (0.583 – 0.781)	3.5	81	81	0.001**
TB3	0.653 (0.540 – 0.765)	2.7	68	54	0.007**	UA6	0.678 (0.578-0.778)	3.9	76	76	0.002**
TB4	0.673 (0.564 – 0.782)	3.4	73	58	0.002**	UA7	0.668 (0.567 – 0.768)	4.3	71	71	0.003**
TB5	0.686 (0.576 – 0.797)	3.4	76	59	0.001**	WBC7	0.633 (0.520-0.746)	6.7	71	57	0.019*
TB6	0.686 (0.572 – 0.800)	3.2	71	58	0.001**	RBC7	0.625 (0.517 – 0.734)	2.9	71	53	0.027*
TB7	0.707 (0.595 – 0.819)	3.3	68	69	0.000***	PLT0	0.645 (0.538 – 0.752)	61.25	63	53	0.011*
DB2	0.644 (0.531– 0 .756)	1.4	68	53	0.012*	PLT1	0.658 (0.557 – 0.760)	55.80	68	61	0.005**
DB3	0.663 (0.553 – 0.772)	1.7	68	53	0.004**	PLT2	0.618 (0.506 – 0.730)	36.25	60	55	0.038*
DB4	0.662 (0.552 – 0.773)	2.1	73	52	0.004**	PLT3	0.666 (0.566-0.767)	37.60	76	55	0.003**
DB5	0.685 (0.576 – 0.795)	2.5	76	59	0.001**	PLT4	0.650 (0.544 – 0.755)	39.85	63	55	0.009**
DB6	0.687 (0.574 – 0.801)	2.4	73	59	0.001**	PLT5	0.680 (0.577-0.784)	48.55	71	57	0.002**
DB7	0.699 (0.587 – 0.810)	2.5	68	70	0.000***	PLT6	0.693 (0.589-0.797)	53.10	71	63	0.001**
GGT4	0.680 (0.583 - 0.778)	47.50	68	64	0.002**	PLT7	0.735 (0.640 – 0.830)	67.25	76	59	0.000***
GGT5	0.708 (0.609-0.806)	62	71	68	0.000***	HG0	0.627 (0.522 – 0.732)	9.9	73	52	0.025*
GGT6	0.694 (0.591 – 0.798)	58	63	70	0.001**	HG1	0.641 (0.513 – 0.750)	7.5	63	58	0.013*
GGT7	0.711	80.50	71	65	0.000***	HG7	0.676	7.7	71	53	0.002**

	(0.610 – 0.812)						(0.571 – 0.781)				
ALB5	0.657 (0.519 – 0.730)	3.1	68	53	0.029*	LYM2	0.619 (0.513 – 0.752)	7.65	71	54	0.036*
ALB6	0.677 (0.550 – 0.764)	3.1	73	58	0.006**	LYM3	0.662 (0.560 – 0.764)	9.65	73	52	0.004**
ALB7	0.677 (0.572-0.783)	3.1	68	50	0.002**	LYM6	0.652 (0.517 – 0.733)	12.70	73	54	0.028*
LDH1	0.656 (0.545 – 0.767)	284	67	54	0.007**	LYM7	0.667 (0.564 – 0.770)	12.05	78	58	0.003**
LDH2	0.634 (0.486 – 0.721)	233	67	53	0.019*	NEU4	0.612 (0.509-0.721)	80.40	65	59	0.048*
LDH4	0.613 (0.486 – 0.721)	288	62	55	0.048*	NEU6	0.613 (0.566-0.772)	73.50	71	52	0.046*
NEU4	0.612 (0.509-0.716)	80.40	65	59	0.048*	NEU7	0.652 (0.548-0.56)	73.15	68	52	0.046*

EAD: Early allograft dysfunction, **CI:** Confidence interval, **Sen** %: Sensitivity, **Spe%:** Specificity, *significant** highly significant, ***extremely significant

Multiple logistic regression analysis

Most of significant independent variables in prediction of EAD according to multiple logistic regression analysis, there were four models; model-1 represented the combination among five variables; AST1 on postoperative day one, DB7on postoperative day seven, GGT4 on postoperative day four, HG0 and PLT0 on preoperative day. Model-2 was a combination betweenDB7, GGT7, PLT7 on postoperative day seven and UA5 on postoperative day five. Model-3 represented the combination among five variables; AST0 on postoperative day one, DB3 on postoperative day three, GGT4 on postoperative day four, HG0 and PLT0 on preoperative day. While, model-4 was a combination between AST1 on postoperative day one, GGT4 on postoperative day four, HG0 and PLT0 on preoperative day (table 5).

The accuracy of predictive potential of these four models for EAD development were analyzed using ROC analysis that revealed an extremely significant ($p<0.0001$) high AUCs with high sensitivity and specificity for four models (for model-1; AUC=0.877, sensitivity=84.2%, specificity=78%, for model-2; AUC=0.842, sensitivity=84.2, specificity=76.8%, model-3 and model-4 had AUC 0.875, 0.853 respectively; both sensitivity=84.2 and specificity=75.6%) as shown in (table 6 and figure 1).

The accuracy of predictive potential of these four models for EAD development were analyzed using ROC analysis that revealed an extremely significant ($p<0.0001$) high AUCs with high sensitivity and specificity for four models (for model-1; AUC=0.877, sensitivity=84.2%, specificity=78%, for model-2; AUC=0.842, sensitivity=84.2, specificity=76.8%, model-3 and model-4 had AUC 0.875, 0.853 respectively; both sensitivity=84.2 and specificity=75.6%) as shown in table 5.

Table 5. Area under curve (AUC), sensitivity, and specificity of different forms of prediction equation for prediction of EAD in patients underwent living donor liver transplantation.

Model No.	AUC	Cutoff	Sen%	Spe%	95% CI	P value
1	0.877	0.3073	84.2	78	0.815 – 0.940	0.000***
2	0.842	0.3061	84.2	76.8	0.761 – 0.923	0.000***
3	0.875	58	84.2	75.6	0.809 – 0.941	0.000***
4	0.853	80.50	84.2	75.6	0.78 – 0.926	0.000***

EAD: Early allograft dysfunction, **AUC:** Area under curve**, Sen** %: Sensitivity, **Spe%:** Specificity, **CI:** Confidence interval, ***extremely significant

Table 6. Different forms of prediction equations according to different models of multiple logistic regression for prediction of EAD.

Model No.	Prediction Equation
1	0.002(AST1) + 0.268(DB7) – 0.025(GGT4) – 0.277(HG0) – 0.025(PLT0) + 3.272
2	0.353(DB7) – 0.009(GGT4) + 0.276(UA5) – 0.015(PLT7) – 1.107
3	0.002(AST1) + 0.273(DB3) – 0.028(GGT4) – 0.288(HG0) – 0.024(PLT0) + 3.277
4	0.003(AST1) – 0.029(GGT4) – 0.344(HG0) – 0.023(PLT0) + 4.576

Discussion:

Liver transplantation (LT) attitudes as a life-saving curative pathway for individuals

suffered from end-stage liver disease, acute liver failure, and a part of patients afflicted with primary and secondary hepatic malignancies **(Quaresima et al., 2023)**. Many previous studies have demonstrated that early allograft dysfunction (EAD) is a prospector step in the pathway to eventual graft loss **(Vos et al., 2014)**.

In the present study, the accuracy of predictive power of different biochemical and hematological markers to diagnose EAD on preoperative day (0) and postoperative days from day one to day seven (1-7) after LDLT were analyzed using receiver operating characteristics curve (ROC). Aspartate-aminotransferase (AST) were significantly associated with EAD development in LDLT on post two days after surgery, (AUC= 0.615, 0.629 sensitivity=63%, 60% and specificity=53%, 65% respectively). These results agree with previous studies found that AST on postoperative day one presented significant correlation with early graft failure **(Diaz-Nieto et al., 2019)**. High level of AST in serum is ordinarily reached through the first 24–48 h after operation, at times being 100- fold increased or higher **(Verhoeven et al., 2017)**. Patients with EAD had highly significant differences in serum levels of total and direct bilirubin starting from the second day to the seventh day after surgery, exhibited (AUCs) reached to 0.707 with sensitivity reached to 76%, specificity reached to70%. These results demonstrated that serum levels of total and direct bilirubin revealed a good prediction marker for EAD development in LDLT. Previous studies revealed that in LDLT, serum bilirubin was the pre-eminent predictor in prediction EAD evolution **(Fodor et al., 2020)**. Other study revealed that serum total bilirubin through the neo-hepatic phase may reflect the severity of ischemia and could prognosticate the primary graft outcome instantly after LT **(Ko et al., 2020)**. Due to ischemia-reperfusion injury, EAD or PNF, hepatocyte injury is associated with elevation in direct bilirubin and liver transaminases, these alternations can occur early after liver transplantation (**(Verhoeven et al., 2017)**). Direct bilirubin (DB) level may have more profitable role than total bilirubin (TB) level in prediction of patients with cirrhotic liver, because indirect bilirubinemia results from other reasons rather than impaired hepatic function itself **(Lee et al., 2021)**. Albumin is the most superabundant plasma human protein, and it controls various body functions **(Abe et al., 2023).** Hypoalbuminemia considered as a marker of disease severity and may be a part of the pathophysiology of it. Finding in present study, revealed that levels of serum albumin considered as a good predictor for EAD development on post days five, six and seven after LDLT. A prospective cohort study showed that a postoperative decrease in serum albumin (especially by ≥ 1.0 g/dL on postoperative day 1) is a predictor of early complications following major abdominal surgery **(Labgaa et al., 2017)**. Other study also showed that a reduction in postoperative albumin levels is a marker of operation stress and a predictor of clinical outcome **(Hübner et al., 2016)**. Previous study showed that if albumin was given in adequate amount and for a sufficient duration, could significantly decrease the incidence of life-threatening complications of cirrhosis and patient mortality. For these reasons, albumin management favorite to patients with decompensated cirrhosis wait-listed for liver transplantation **(Mauro et al., 2019)**. Many tissue types contain large amounts of the enzyme lactate dehydrogenase (LDH), which is released into the bloodstream when these cells necrotize. Thus, an increase in serum LDH serves as a non-specific marker for the body's cell deterioration **(Green et al., 2017)**. On present study, determined of serum LDH showed relatively low predictive values reached to AUC (0.656), sensitivity (67%) and specificity 54%, on post days one, two and four, suggesting poor predictive performance for EAD. Agree with previous study found that, in a sequence of forty-eight transplanted patients, LDH was not a reliable predictive marker for allograft dysfunction. **(Koyama et al., 2020)**. Other study showed that serum LDH is a beneficial prognostic marker, which can allow to differentiate graft ischemic damage and early acute rejection **(Green et al., 2017)**. Regarding GGT the data obtained show that a significant difference in serum levels GGT between EAD and NEAD groups on post days (4,5,6,7) after surgery. The accuracy of predictive power of GGT to diagnose EAD on post days four and seven show good area under curve (AUC) 0.680 and 0.711 (sensitivity 64% and 71%, specificity 64% and 65% respectively) GGT had a good sensitivity and specificity for predicting EAD. These results suggested that GGT with combination with other markers may be a

perfect predictor for EAD. Prior research has demonstrated that elevated GGT is thought to be a sign of a poor prognosis following liver resection and transplantation **(Shi et al.,2017, Ma et al., 2014, Fu et al.,2016)**. However, an analysis of a study that looked at the relationship between GGT and disease-specific and all-cause mortality indicated that there was a positive correlation between GGT and death for every cause of mortality that was looked at. Additionally, the analysis showed that GGT was positively connected with total cancer mortality. GGT may be a useful marker for mortality linked to the liver, it has a high correlation with both alcoholic and nonalcoholic fatty liver disease and is incredibly sensitive in detecting liver damage **(Cho et al., 2023)**. The accuracy of predictive power of uric acid to diagnose EAD had good prediction on postoperative days three to seven specially on post day five exhibited area under curve (AUC) 0.682 with sensitivity and specificity 81%. This result demonstrated that uric acid associated with developed EAD specially on post day five after LDLT. Within one week following transplantation, early allograft dysfunction (EAD) was linked to postoperative acute kidney damage (AKI) and a greater death rate **(Wadei et al., 2016, Agopian et al., 2018)**. A lower preoperative blood uric acid was linked to a higher incidence and risk for EAD, according to a prospective study looking at uric acid as a predictor for early allograft dysfunction following living donor liver transplantation **(Hu et al., 2021).**Prior research revealed that uric acid (UA), which is thought to be the sixth cardiometabolic criteria for liver disease linked to steatosis and metabolic dysfunction (MASLD), Because of its close pathogenic relationship to fatty liver disease, UA has attracted a great deal of scientific attention in recent years **(Rinella et al., 2023, Russo et al., 2020)**.

Poor "functional" recovery of the new liver after liver transplantation and pre-existing anomalies of multiple disorders often lead to in blood loss **(Feltracco et al., 2013)**. Regarding to our finding for red blood cells (RBCs) and hemoglobin (HG). The accuracy of predictive power of RBCs and HG to diagnose EAD had good prediction on post day seven. However, HG also have predictive values on preoperative day and post day one These results reveled that low count of RBCs and low levels of HG may be a risk factor for early allograft dysfunction in LDLT. According to studies on hemoglobin and red blood cells for EAD in LT Patients they have a significant risk of intraoperative blood loss and red blood cell (RBC) transfusion, especially in pediatric patients **(Ma et al., 2024).** Clinical studies show that receiving blood transfusions when hemoglobin levels are low is beneficial **(Hébert et al., 1999; Lacroix et al., 2007)**. Red blood cell (RBC) transfusion and blood loss are distinct risk variables that have been shown in LT studies to influence patient outcomes in both adult and pediatric patients **(Rana et al., 2013; Nacoti et al., 2012)**. According to pertinent publications, there is an 8% rise in the incidence of postoperative EAD in receivers for every unit increase in red blood cells utilized during surgery **(Hudcova et al., 2021)**. The accuracy of predictive power of PLT to diagnose EAD have predictive values on preoperative and postoperative days from (pos-1 to pos-7). These results demonstrated that low level of PLT had good prediction and associated with development of EAD in LDLT. A prior study found a correlation between platelet counts and both the early and late results of liver transplantation, patient complications were predicted by platelet counts on day five **(Lesurtel et al., 2014)**. Thrombocytopenic patients had three times the incidence of early allograft dysfunction and twice the frequency of serious complications **(Li et al., 2015)**. Prior research has demonstrated that platelets are involved in physiological hemostasis as well as liver damage, ischemia-reperfusion injury, tissue repair, and liver regeneration. A reduction in platelet count can result in spontaneous bleeding, infection, and other complications that can have a major negative influence on the prognosis of the patient. Patients examined in a study by Qiang et al. (2024) showed that following LT, about half of the patients experienced persistent thrombocytopenia, on POD7 there was the most prominent reduction in platelet counts **(Qiang et al., 2024)**. Count of WBCs and alternation of differential WBC counts is crucial to understand the body’s defense against pathogens and injury. WBCs are considered a reliable biomarker of inflammation, elevation in WBCs counts in present study are associated with poor out comes for EAD specially on pos-7 day. The correlation between WBCs and impairment following liver transplantation may have a beginning in the increased levels of

inflammation that high WBCs reflect, which could adversely affect other organs including the liver **(Weiss et al., 2021; Casulleras et al., 2020)**. Conversely, a prospective study discovered a correlation between preoperative WBC counts and weakness following liver transplantation **(Liu et al., 2024).** Total white blood cell (WBC) levels were found to be a significant predictor of waitlist mortality in other earlier studies **(Jalan et al., 2014)**. Our finding regarding neutrophils and lymphocytes counts showed predictive values in progression of EAD through seven post days after operation. These findings are consistent with a study by Liu et al. (2022) that demonstrated the role of neutrophil infiltration in the liver's inflammatory environment and immune cell activation. A growing body of research suggests that neutrophils play a role in the development of several liver transplant complications **(Liu et al., 2022)**. A prior study found a correlation between mortality and changes in the absolute lymphocyte count (ALC) prior to transplant. In the period preceding liver disease (LT), rapid reductions in lymphocyte numbers may indicate immunological compromise, malnutrition, or the advancement of liver disease (**Kitajima et al., 2023**).

Given the results on present study, the predictive power of each marker separately was relatively low; to improvement, predictive performance for EAD the combination between some markers must be reliable. Thus, according to multiple logistic regression analysis of most significant independent variables for prediction of EAD and improvement the predictive power of some biochemical markers, there were resulted in more than model the best of them were four models; model-1 represented the combination among five variables; (AST1, DB7,GGT4, HG0 and PLT0) Model-2 was a combination between (DB7,GGT7, PLT7 and UA5).Model-3 represented the combination among five variables (AST1, DB3 , GGT4, HG0 and PLT0). While, model-4 was a combination between (AST, GGT4, HG0 and PLT0). The accuracy of predictive potential of these four models for EAD development were analyzed using ROC analysis that revealed an extremely significant ($p<0.0001$) high AUCs with high sensitivity and specificity for four models (for model-1; AUC=0.877, sensitivity=84.2%, specificity=78%, for model-2; AUC=0.842, sensitivity=84.2, specificity=76.8%, model-3 and model-4 had AUC 0.875, 0.853 respectively; both sensitivity=84.2 and specificity=75.6%). These four models have strong predictive values for prediction development of EAD from day one to day seven after LDLT.

Combining the four models scores with other previously validated liver function markers such as fibrosis-4 index **(Montasser et al.,2019)** and glypican 3 **(Tahon et al., 2019)** may improve predictive performance for EAD.

Conclusion:

Determination of some biochemical markers were correlated with EAD development on preoperative day and postoperative days from day one to day seven and the most significant correlations were (aspartate transaminase, direct bilirubin, gamma-glutamyl transferase, uric acid hemoglobin and platelets) and combination among those represented four current models had a significant prediction potential for EAD in LDLT.

Limitations and future research recommendations

This study has some limitations, first, the relatively small sample size reduces the communal-application of our results. Second, because of the nature of the patients' end-stage liver diseases, we could not exclude confounding factors that may alter the risk of adverse biochemical and hematological adverse events. Bigger sample size and combining the four models scores with other previously validated liver function markers such as fibrosis-4 index **(Montasser et al.,2019)** and glypican 3 **(Tahon et al., 2019)** may improve predictive performance for EAD. Additional prospective studies are needed to define and the predictors parameters of early allograft dysfunction following liver transplantation with uniform inclusion and exclusion criteria. In addition, to understand the impact of the specific donor or recipient risk factors, a predictive models and newer biomarkers should be derived using newer cutoffs through statistical analysis to allow standardized and continuous grading of early complication and predict the risk of graft failure.

Declarations

Competing interest statement

The authors declare no competing interests

Ethics approval

All procedures, involving human participants in this study, were performed in accordance with the Declaration of Helsinki 1964 and its later amendments. This observational prospective study was reviewed and approved by The Research and Ethical Committees of Al-Azhar Faculty of Medicine, Damietta, Egypt.

Informed consents

Informed written consent was obtained from all participants and/or their legal guardian (s) before enrollment. Informed consent was obtained from the attending physician who collected clinical specimens.

Author contributions

All authors contributed to conception, design, data acquisition, administration, statistical analysis, literature review, analysis, manuscript writing and revision. M.M.A and D.J. contributed equally to writing the manuscript, D.J. provided Endnote X9 software required for the production of this manuscript.

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Data availability statement

All data generated during this study are included in the published article. Source files can be provided after permission of the corresponding author.

Declaration of Generative AI and AI-assisted technologies in the writing process:

During the preparation of this work the authors did not use any AI-assisted technology

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الملخص العربي

عنوان البحث: بعض المؤشرات الحيوية غير التداخلية في التنبؤ بتطور الخلل الوظيفي المبكر للكبد المزروع في المرضي المصريين

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خلفية الدراسة: تعتبر عملية زراعة الكبد العلاج الوحيد الفعال لفشل الكبد في المرحلة النهائية وعلى الرغم من التقدم الكبير في البحث العلمي والتحسين المستمر لنتائج زراعة الكبد، فإن خلل وظيفة العضو المزروع يرتبط بفشل الطعم والوفاة بعد زراعة الكبد. الهدف من الدراسة: تهدف الدراسة الحالية إلى تحديد دور بعض العلامات الكيميائية الحيوية للتنبؤ بتطور خلل الطعم المبكر بعد زراعة الكبد من متبرع حي. طريقة البحث: تم عمل هذه الدراسة على مائة وعشرين مريضًا خضعوا لعملية زرع كبد من متبرع حي في مركز جراحة الجهاز الهضمي بجامعة المنصورة. تم تقسيم الأشخاص الذين شملتهم الدراسة إلى المجموعات الآتية: المجموعة الأولى: مجموعة الخلل الوظيفي غير المبكر تشمل اثنان وثمانون مريضا. المجموعة الثانية: مجموعة الخلل الوظيفي المبكر تشمل ثمانية وثلاثون مريضا. تم تقدير مستويات الدم من العلامات البيوكيميائية المختلفة في اليوم السابق للزراعة ومن اليوم الأول إلى اليوم السابع بعد الزراعة باستخدام الاختبارات الحيوية الكيميائية والمناعية. النتائج: كان هناك ارتباط ما بين مستويات كل من المتغيرات الاتية وتطور الخلل الوظيفي المبكر في اليوم السابق لزراعة الكبد والأيام السبعة الأولى بعد الزراعة، انزيم اسبارتات امينو ترانسفيراز في اليوم الأول، والصفراء المباشر في اليوم الثاني والثالث، انزيم جاما جلوتاميل ترانسفيريز في اليوم الرابع والسابع، حمض البوليك في اليوم الثالث والخامس، عد كرات الدم الحمراء في اليوم السابع بعد زراعة الكبد، ونسبة الهيموجلوبين في اليوم السابق قبل الزراعة واليوم الأول بعدها. نتج عن الجمع بين معظم المتغيرات المستقلة المهمة للتنبؤ بالخلل الوظيفي المبكر أربعة نماذج تم تحليل دقة الإمكانات التنبؤية لهذه النماذج الأربعة وقد أظهرت قيم تنبؤية قوية مع حساسية وخصوصية مرتفعة. الاستنتاج: تم تحديد بعض العلامات الكيميائية الحيوية المرتبطة بتطور الخلل الوظيفي المبكر في اليوم السابق للجراحة وأيام ما بعد الجراحة من اليوم الأول إلى اليوم السابع وكانت الارتباطات الأكثر أهمية هي (أسبارتات ترانسفيراز، الصفراء المباشر، جاما جلوتاميل ترانسفيراز، حمض البوليك، الهيموجلوبين والصفائح الدموية) والجمع بين تلك الدلائل الحيوية في أربعة نماذج مبتكرة.