

## Early Clinical Complications after Living Donor Liver Transplantation

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### Abstract

Liver transplantation (LT) is a proven treatment for both acute and chronic end-stage liver disease. Living donor liver transplantation (LDLT) is the only practical choice for liver-transplanted patients. Early allograft dysfunction (EAD) is a well-known early clinical complication that occurs within the first week following transplantation and is thought to have a key impact on the graft and patient outcomes. Graft incapability leads to many numerals of postoperative complications, rising mortality, and hazard of organ damage. The functional estimation of transplanted liver in an early postoperative stage feature as a preference for transplant clinicians, as it mirrors the technological success of liver transplant and heavily affects recipient results. Diagnosis of early allograft dysfunction with possibility to recover with painstaking postoperative attention is urgent need. The present review aimed to highlight liver transplantation and some of biochemical markers associated with early complication after liver transplantation.

**Keywords:** Liver transplantation (LT) - Early allograft dysfunction (EAD) – Living donor liver transplantation (LDLT)

### Introduction

Liver transplantation (LT) considered as live-saving treatment for patients with liver complications of cirrhosis and hepatocellular carcinoma. The need for liver transplantation (LT) increase with increasing cirrhosis burden heightens. The etiologies of cirrhosis are strolling supplementary, with more need for

transplantation through patients with nonalcoholic/metabolic fatty liver disease, alcohol-associated liver disease and less for viral hepatitis, though hepatitis B remnant substantial significance for transplant in regions with high endemicity (Terrault et al., 2023). Liver transplantation (LT) has developed from a semi-experimental proceeding since the 1960s to be a routine involvement with perfect outcomes in patients with acute or chronic liver diseases (Gupta and O'Beirne, 2022). Recently LT accepted as standard of therapy for

patients with end-stage liver diseases, acute liver failure (ALF), hepatocellular carcinoma (HCC), and some metabolic diseases (**Rajakumaret al., 2023**). Regardless of persistent development in the field of liver transplantation, considerable ratio of patients still experiences from the post-transplant dysfunction. Early allograft dysfunction (EAD) is a prevalent post liver transplant dysfunction that has been correlated with graft failure and risk for poor prediction (**Fodor et al., 2020**). Particular correspondence of early allograft dysfunction is critical to decrease mortality and morbidity in liver transplantation (**Nosoudiet al., 2022**). Post-transplant, the function of the new graft liver is pursued by intensivists and operators over the monitoring of symptoms and clinical markers by laboratory blood examinations, in spite of they are well-known to have poor sensitivity and specificity regarding EAD (**Gupta et al., 2018**).

#### *Common etiologies of liver diseases leading to liver transplantation*

##### *Cirrhosis*

Liver diseases fundamentally caused by complications of cirrhosis, hepatocellular carcinoma and viral hepatitis and considered approximately two million deaths yearly. Cirrhosis is the extreme common cause of death globally however liver cancer is the major cause of death. The most prevalent causes of cirrhosis worldwide are related to viral hepatitis, alcohol, and non-alcoholic fatty liver disease. Nearly two billion people who consume alcohol worldwide are diagnosed with alcohol-use disorders and are at risk of alcohol-associated liver disease. About two billion adults are overweight or obese and meanwhile four hundred million have diabetes; obesity and diabetes are risk factors for hepatocellular carcinoma and non-alcoholic fatty liver disease. Etiological factor in most cases of acute liver diseases due to hepatitis viruses, most of cases due to drug-induced liver injury. This excitement of liver disease worldwide is an update of the 2019 modified version and converge fundamentally on areas where important new information is obtainable like hepatocellular carcinoma, viral hepatitis, alcohol-associated liver disease, non-alcoholic fatty liver disease (Asrani et al., 2019; **Devarbhavi et al., 2023**).

##### *Alcohol-associated liver disease*

Alcohol is the leading cause of cirrhosis globally and increases the risk of liver disease (**Hagström et al., 2021**). Also, alcohol consumption increases the risk of liver cancer in patients who are overweight, obese and/or have NAFLD-related cirrhosis (**Hart et al., 2010**). Alcohol is the most major cause for liver transplantation among males in the United State, and the second after non-alcoholic fatty liver diseases for females (**Younossi et al., 2021**).

##### *Non-alcoholic fatty liver disease (NAFLD)*

The prevalence of NAFLD is 32.4% worldwide. The total deaths percentage from all causes regarded to NAFLD increased from 0.1% to 0.17%. (**Devarbhavi et al., 2023**). NAFLD is tightly related to metabolic comorbidities. The growing number of metabolic comorbidities increases the prevalence of NAFLD and increases places patients at higher risk for advanced liver disease. NAFLD is recently among the top etiologies for hepatocellular carcinoma and signal for liver transplantation (LT) in the United States (**Younossi et al., 2019**).

##### *Viral hepatitis*

Viral infections affecting the liver have significant effectiveness; they have led to respectable mortality and morbidity in patients with chronic and acute infections (**Castaneda et al., 2021**). Liver transplantation frequently reserves destination treatment for HCC or HCV decompensated cirrhosis in candidates who are not considered suitable for surgical resection. In fact, HCV infection remains the major leading etiology for liver transplantation in the world (**Ruiz de Morales et al., 2020**). HBV patients that developed HCC, acute liver failure or decompensated liver cirrhosis can potentially submit liver transplantation as eventual therapy (Jothimani et al., 2020).

The progression rates of HCV, HAV and HEV viruses infection have continued stable since 1990-2019, but the incidence of acute hepatitis B has descend, partially because of increasing vaccination rates of HBV (**Zeng et al., 2021**). Age-standardized (A) incidence and (B) DALY rates of acute viral hepatitis per 100,000 population from 1990 through 2019

categorized according to country and territory, stratified by sex or SDI. Age-standardized (C) incidence of AVH per 100,000 person-years by country and territory in 2019. DALY, disability-adjusted life year; SDI, socio-demographic index, (Figure 1) reproduced from (Zeng et al., 2021).

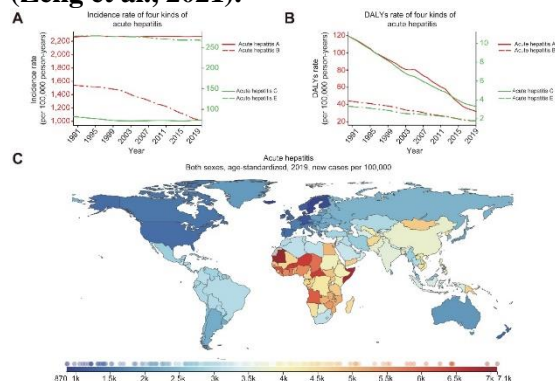


Figure 1: Burden of acute viral hepatitis for 204 countries and territories (Zeng et al., 2021). The most regions that infected with viral hepatitis were found in most African countries. But the lowest burden was found in North America and north Europe. However, moderate ratio was found in Egypt and son African countries,

### Hepatocellular carcinoma (HCC)

Liver cancer considers the fourth-leading cause of cancer-related mortality globally and the second-leading cause of cancer-related mortality in men. Because chronic hepatitis B virus (HBV) carriers are similarly common in sub-Saharan Africa and Eastern Asia, over 80% of instances of hepatocellular carcinoma (HCC) occur there. Globally, the epidemiology and etiology of HCC have lately evolved. Even though HBV infection is the primary cause of HCC development, in 1990, HBV was responsible for over half of HCCs worldwide. In 2019 this number has dropped to 42%. The incidence of hepatitis C virus-related HCC has significantly declined in Japan and Europe because of the extensive usage of direct acting as antiviral. However, the percentage of patients with nonalcoholic steatohepatitis (NASH) and alcoholic steatohepatitis (NASH) increased from 5% to 6% and from 13% to 18%, respectively (Kim, 2024). Chronic viral HBV, HCV infections can lead to the progress of cirrhosis, which is found in many patients with HCC and is a significant risk factor for HCC regardless of the etiology (El-Serag, 2012). NAFLD and obesity performance act as co-factors to change the prevalence of HCC

worldwide, in addition, elevated BMI and diabetes mellitus and may lead to elevate risk of HCC (Pearson-Stuttard et al., 2018). Hepatocellular carcinoma is the most common cancer of the liver demonstrate a significant impendence to public health, liver transplantation is considerable as effective treatment for HCC (Xiang et al., 2023).

### Assessment and Monitoring of end-stage liver diseases for liver transplantation

From laboratory investigations, there are multiplied scoring procedures that employ particular serum markers to estimate disease advancement and identify cirrhotic patients (Tapper and Lok, 2017). There are two predictive models are utilized to define the prediction of patients with liver cirrhosis. The Child-Pugh is correlating with the grade of liver dysfunction and the probability of evolving liver cirrhosis complications and model for end-stage liver disease (MELD) mainly used to prognosticate thirty days mortality rates in cirrhosis patients and candidate patients for liver transplantation (Perez et al., 2021).

Compensated cirrhotic patients are commonly asymptomatic and have a major probability of preserving function of liver if risk factors eliminated and the implicit situation is treated. Advancement of fibrosis in cirrhotic liver may lead to worsening of portal hypertension and complications, which lead to high morbidity and mortality, it is very important to recognize and indicate these patients early to transplant centers for evaluation of liver transplantation (Perez et al., 2021).

In the world, etiologies of cirrhosis leading to LT different by region and are variable over time. In spite of progress made in the treatment of hepatitis C and B, viral infection continuous the precept cause of cirrhosis and hepatocellular carcinoma in Africa, Southeast Asia and the East Mediterranean zones. However, in the Europe and United State, from 2014 spectacular reduction in hepatitis C virus (HCV) as significance for LT (Terrault and Pageaux, 2018).

### Liver transplantation (LT)

Liver transplantation must be considered

refractory to medical therapy in patients suffered complications from liver disease in end-stage (**Martin et al., 2014**). Liver transplantation is substantial therapeutic preference for patients with liver diseases such as end-stage liver disease, acute liver failure or primary hepatic cancers. It is therefore crucial for healthcare provisioner look after patients with liver disease to be aware of the common significance for transplantation (**Mahmud, 2020**).

Liver transplantation present life-saving therapy for patients with complications of liver cirrhosis and hepatocellular carcinoma. Because high and increasing cirrhosis encumbrance elevates the need for liver transplantation. The etiologies of cirrhosis are changing over time, need for transplantation increase among patients with alcohol-associated liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) and less for viral hepatitis, however HBV virus rests an remarkable significance for transplant in regions with high endemicity. During the last twenty years, important changes in the projection of LT have taken place, with the reduction of HCV virus, the increasing burden of NAFLD, older age at transplantation, and more comorbidities (**Terrault et al., 2023**).

The advanced alternation in indications for LT such as the elevated in hepatocellular carcinoma and non-alcoholic fatty liver disease caused an increased focus on long-term outcomes and the concept of transplant interest when selecting candidates. To maximize these outcomes new matching and distribution systems have been expansion to maximize these outcomes by selecting patients to appropriate grafts. Management of post-transplantation in the pre status is involved fundamentally with surgical and immunological complications however long-term management condense on decreasing the risk to the patient from the complications of immunosuppression such as cancers and cardiovascular disease (**Gupta et al., 2022**).

Patients undergoing liver transplantation should advantage from an improved quality of life or should have the expansion of life expectation beyond the natural course of survival. Liver transplantation is the medication of option for patients with decompensated cirrhotic liver, liver cancer, metabolic conditions led to systemic disease. Liver transplantation considered the first attempted,

continued improvement in surgical mechanisms and understanding of the immunological role in the rejection and detection novel efficient immunosuppressants have varied the conception of liver transplantation to relatively safe and standard methods for patients with end-stage liver diseases (**Mehta and Bojanapu, 2023**).

#### *Living donor liver transplantation (LDLT)*

It has evolved into a great acceptable treatment chosen to dissolve the problem of the incapability of cadaveric livers for deceased donor liver transplantation (**El-Gazzaz and El-Elemi, 2010**). LDLT preparation is very essential defined of successful outcomes for both donors and recipients. Preoperative work-ups of LDLT are exemplary to provide correct information about the function, anatomy and volume of the allograft and remnant donor liver. These are united with recipient clinical data to define the best surgical strategy to gain the best outcomes and decline deaths (**Quintini et al., 2014**).

#### *Liver transplantation in Egypt*

Chronic liver diseases are a frontier health attention in Egypt. The high prevalence of chronic liver diseases has led to increasing numbers of Egyptian patients suffering from end stage liver disease (ESLD), require liver transplantation (LT). Living donor liver transplantation (LDLT) demonstrate to be the only sensible option to save many patients who are candidate for LT. LDLT are now routinely and successfully performed in Egypt with reasonable donor and recipient outcomes. There are thirteen LDLT centers in Egypt (Figure 2), including six university centers, two military centers, three private centers and two centers in the ministry of health hospital (**Amer and Marwan, 2016**).

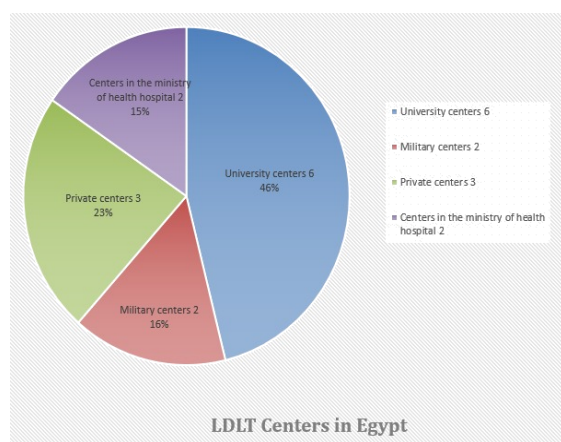


Figure 2: LDLT centers in Egypt (Amer and Marwan, 2016)

Chronic liver disease is more common in Egypt due to the high incidence of hepatitis C virus (HCV) (El-Zanaty and Way, 2009). The prevalence of HCV in the 15–59 age range was 14.7% in 2016. Egypt accounted for over half of all transplant cases in Arab nations. The Egyptian medical syndicate created the LDLT regulations (Amer and Marwan, 2016). End-stage liver disease (ESLD), which requires liver transplantation (LT), has become more common in Egypt due to the country's endemic high frequency of chronic liver disorders.

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., 2024). 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%, (table 1) (Fouad et al., 2021).

Table 1: Liver diseases associated hepatocellular carcinoma

HCC reported 2.9% /year (Shiha et al., 2020)
-MAFLD related HCC (Increase 4.3% from 2010 to 20.6 in 2020)
-HCV related HCC (Decrease from 94.8 % to 76.7% in 2021)
(Fouad et al.,2021)

Abbreviations: Hepatitis C virus (HCV), Hepatocellular carcinoma (HCC), Metabolic-associated fatty liver disease (MAFLD)

The slow progress of HCV-related HCC, even after HCV treatment, shows that the occurrence

of HCC in Egypt may not have peaked yet. Recently, 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).

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. Living donor liver transplant (LDLT) was firstly done in Egypt in 1991 by the surgical team at the National Liver Institute (NLI) (Amer and Marwan, 2016). Since the time, different centers conduct LDLT. By the end of June 2014, the total number of cases reached 2,406 (figure 3), this number comprised 2,246 adult cases (93%) and 160 pediatric cases (7%), the vast majority of indications of LDLT were HCV hepatitis (figure 4) (Amer and Marwan, 2016).

The number of LDLT done in Egypt by the end of jun 2014



Figure 3: The number of living donor liver transplantation (LDLT) in Egypt 2014 (Amer and Marwan, 2016)

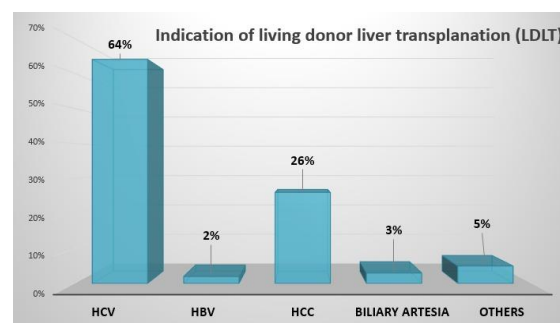


Figure 4: The major indication of living donor liver transplantation (LDLT) (Amer and Marwan, 2016)

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.

### *Early allograft dysfunction (EAD)*

In spite of continued advanced in the area of liver transplantation, great ratio of patients remains afforded from the postoperative graft dysfunction, identification as early allograft dysfunction (EAD) (**Masiar and Grate, 2022**).

Liver transplantation has been confirmed as a life-saving therapy for end-stage liver failure but the increased number of recipients instancy for improved post-transplantation care inclusive infection control, tolerance induction, and solving immunosuppressant drugs adverse effects (**Assadiasl et al., 2021**).

The early identification and management of allograft dysfunction in early times after liver transplantation is crucial to decrease the length of stay (LOS), reduction morbidity and mortality for patients. Enhanced recovery after surgery (ERAS) led to the clinical care protocols, aiming to reduce surgical stress response and improve clinical outcomes and post-surgery recovery (**Gustafsson et al., 2019**).

### *Definition of EAD*

Amongst a number of definitions, presently, the ultimate public one is that suggested by **Olthoff et al. (2010)** from Pittsburgh. Allowing to this definition, EAD can be diagnosed by meeting at least one of the following criteria: On postoperative day 7, serum total bilirubin  $\geq 10$  mg/dL, INR  $\geq 1.6$ . However, within the first 7 postoperative days ALT or AST  $> 2,000$  IU/ml.

Early allograft dysfunction (EAD) is a well-known clinical syndrome that mirrors graft dysfunction within the first week after transplantation (**Cho et al., 2023**). EAD probably take place in 20-40% of recipients and is a significant risk factor for poor allograft and patient survival after LT (**Jackson et al., 2022**). It is a critical complexity after liver transplantation and related with risk for graft failure, poor prognosis, and mortality after living donor liver transplantation (LDLT). The

correlation risk factors and complications for the progression of EAD have recovered novel attention (**Tsai et al., 2021**).

After liver transplantation EAD is an important clinical complication that negatively effects on graft and outcomes of patient. The increase progression of EAD and association with LDLT is a highly advantageous field which is a convention literature item that has not yet been thoroughly examined. Ultimate of the researches on EAD is established on experiments in deceased donor liver transplantation (DDLTL), and fixed information is obtainable in the status of LDLT (**Dhirajand Sanjiv, 2023**).

EAD was spreading from 5.2% to 36.3% (**Chen and Xu, 2014**). However, EAD-correlated mortality runs to 18.8% (**Lee et al., 2016**). EAD is referred by many factors included hepatic steatosis in donors (**Alvarez-Mercado et al., 2019**), diagnosis of hepatic cancer and dialysis in recipients at transplantation, requiring blood transfusion because intraoperative blood loss and prolonged ischemia time (**Tomescuand et al., 2018**). Furthermore, age is known as an important risk factor for the evolution of EAD (**Haugen et al., 2019**).

Liver allograft dysfunction information out of vision in post-transplantation and clinical presentation. This can be extended from moderate transitory dysfunction of liver tests to acute liver disease potentially leading to graft failure. The occasion of graft dysfunction can be classified to early and late graft dysfunction. Up normal levels of biochemistry liver tests are still the major investigation used in surveillance for dysfunction (**Kok et al., 2019**).

Liver transplantation recipients may be living longer than ever today and abundant will experiment some composing of allograft abnormalities. The prevalent sources of allograft dysfunction differ by the time of liver transplant. Generality allograft dysfunctions are manageable with minimally invasive proceedings, treatments, and lifestyle modulation. The great popular differential diagnoses by post-operative time after surgery and administration regards, are highlighted. Management and cooperation of liver-transplanted recipients among primary concern and the transplant hepatologist is critical for improvement recipient and allograft outcomes (**Hirschhaeuser et al., 2011**).



Allograft dysfunction is still an important clinical problem in despite of fundamental advancement in scientific research and the persistent refinement of the outcomes of transplanted liver. After reperfusion, some patients may defiance liver failure instantly, which is manifested as primary nonfunction (PNF) or impaired in liver function in the initial period after transplantation what is defined as an early allograft dysfunction (EAD). Graft incapability leads to many numerals of postoperative complications, rising mortality, and hazards of organ damage (**Younossi et al., 2019**).

The functional estimation of transplanted liver in an early postoperative stage feature as a preference for transplant clinicians, as it mirrors the technological success of liver transplant and heavily impacts recipient results. Early allograft dysfunction (EAD) defined as an initially peripheral function state of the liver transplanted, and it really imperils the morbidity and mortality of patients (**Deschenes, 2013**).

Advancement in the perioperative administration of recipients underwent liver transplants participated significantly to progress patient results mirrored in reduction length of hospital stay mortality and morbidity. A function of graft help in patient recovery in addition it can prospective outcome of the whole methods. Graft dysfunction after liver transplantation (LT) is not un-collective and residue a critical status challenging clinicians and patients. The scientific designation is not regularly related to the characterization and introduction of graft dysfunction and implicates changing terms for a series of conditions established on the timing and degree of severity of graft dysfunction. Initial poor function considerably referred to as early allograft dysfunction (EAD). However, initial non-function explains the border at every end of the primary graft pathology continuum (**Chen and Xu, 2014**).

When recovery of graft function turn-into unattainable, multi-organ dysfunction starts in at the delayed periods of graft failure in EAD. Therefore, distinguishing grafts with possibility to recover with painstaking postoperative attention is urgent need. Furthermore, it is imperious to characterize markers of early graft failure to determine if imperative re-transplantation. Estimation of graft function should begin at once after reperfusion and

persistence onto the postoperative period. EAD usually demonstrates in the postoperative period (**Rajakumar et al., 2023**).

#### *Risk Factors of EAD*

##### *Small-for-size graft*

Graft dysfunction, also known as small-for-size syndrome (SFSS), can occur when a graft is too tiny to fit the recipient's needs (Dahm et al., 2005). Since EAD was present in patients of all graft sizes and does not involve signs of portal hypertension, it may be different from SFSS. Originally, LDLT used smaller left lobes in grafts, but studies have revealed a higher percentage of EAD in left lobe recipients compared to right lobe graft recipients (34% vs. 16%) (Pomposelli et al., 2016).

##### *The quality of the graft*

The incidence of EAD is significantly influenced by the quality of the graft. Using a proton density fat fraction MRI or CT scan, living donors are thoroughly screened for steatosis in LDLT. In certain situations, biopsies are used to evaluate the quality of the graft. According to Jackson et al. (2023), the majority of centers exclude donors who have steatohepatitis or steatosis higher than 10% (ranging up to 20%). Conversely, micro-vesicular steatosis is typically overlooked as a risk factor for EAD because it is a minor, curable illness (Croome et al., 2019).

##### *Surgical techniques*

Despite the vascular and biliary systems' frequent anatomical variances many centers now accept these donors as their experience grows (**Watson and Harper, 2015**). However, to maximize graft performance, a fine surgical approach is essential. The receiver may be at undue danger from several ductal anastomoses and arterial reconstructions. Inadequate graft function has been linked to biliary problems and posttransplant hepatic artery thrombosis. Establishing adequate venous drainage of the anterior sector of the right hemi-liver graft is essential when transplanting a right lobe graft without middle hepatic vein (MHV) drainage. Interposition vascular grafts should be used to properly repair the MHV venous tributaries from the right anterior sector on the back table

(Rammohan et al., 2022).

### *Ischemia-Reperfusion Injury (IRI)*

Graft dysfunction, implicating EAD and its ultimate progress form Primary Nonfunction (PNF), are a clinical demonstration of ischemia-reperfusion injury (IRI). Estimation the effect of IRI on the outcomes of liver transplantation, IRI was appreciate from the biopsies taken midst transplantation. The entity of severe IRI was statistically significantly associated with the incidence of EAD, PNF and the requirement for 90-day re-transplantation. Graft dysfunction and PNF have incidence to occur in the patients with severe IRI in 54.5% and 9.1% of patients, respectively. In the patients without IRI, graft dysfunction influenced 13% of recipients, while there was no PNF. The relevance between IRI and the existence of EAD was definite. In the association with moderate/severe IRI, incidence of EAD manifest in 42.9% of patients compared to 24.8% of those without IRI (Ito et al., 2021).

### *Donor and Recipient-Related Factors*

Determined risk factors have significant to many sources as the age and sex of the donor, cold ischemic time (CIT), the time which donor's institution in the intensive care unit, the period of the transplant, and the proceeding dissonant with the main blood groups (Uemura et al., 2007). In addition, there are other factors that increment the risk of EAD represented in the donor's body mass index (BMI), graft steatosis, the activity of gamma-glutamyl transferase for the last pretransplant donor, and cold ischemic time CIT (Hoyer et al., 2015). According to Cieślak et al. (2009), graft steatosis is regarded as a risk factor for EAD, and micro steatosis is also linked to a decline in early graft function following transplantation. The risk of EAD following liver transplantation has increased proportionately due to the need to use grafts with a graft-to-recipient weight ratio (GRWR) of less than 0.8, grafts with macro-steatosis greater than 10%, grafts from donors older than 50, grafts with complex anatomy, and liver transplantation in high-acuity recipients due to a growing global organ shortage (Agrawal and Saigal, 2023). Some of risk factors for EAD in LDLT related donor and recipient showed in table 2.

Table 2: Some of risk factors of early allograft

dysfunction related donor and recipient

Early allograft dysfunction		
Doner-related	Recipient-related	
Age>45years	Recipient severity-High score	disease MELD
Macro vesicular steatosis	Sarcopenia	
Graft fibrosis	Porto-systemic shunts	
GRWR ≤ 0.8	Impaired regeneration	graft

Abbreviations: Model for end-stage liver disease (MELD), A graft-to-recipient weight ratio (GRWR) (Agrawal and Saigal, 2023).

### *-Other Factors*

The function of the proportion of apoptosis in the graft as a factor negatively correlated with the incidence of EAD (Zhu et al., 2018). Rise risk of EAD evolution in patients with lower levels of interleukin 6 (IL-6) and a reverse association with interleukin 2R levels. Cold ischemic time (CIT) is one of the important risk factors which negatively impact outcome of transplanted liver. Not only the period of cold preservation is driver but also the utilize of specific forms of preservation solutions is correlated with several risks (Friedman et al., 2012). The increase risk is related with the utilize of histidine-tryptophan-ketoglutarate (Van et al., 2021). Technical information of the method showing to play a function likewise. The revascularization time is a significant risk factor for EAD. The time of revascularization was known as the time from the extraction of the liver from the ice to reperfusion through the portal vein (Buchholz et al., 2015). The risk factors for donor and recipient related with EAD: Percent of macro-steatosis, donor position, donor BMI, type of organ transplanted, recipient with hepatocellular carcinoma (HCC), intensity postreperfusion syndrome (PRS), and the amount of fresh frozen plasma (FFP) transfused (Nicolau-Raducu et al., 2017).

Risk factors may impact early mortality after liver donor liver transplantation (LDLT) implicate preoperative factors as poor-quality grafts and higher MELD scores and small grafts. Operative factors include great amounts of intraoperative blood loss and technical insufficiency. Postoperative factors implicated postoperative abnormal laboratory results. Recognizing predictors of early mortality after LDLT is a substantial problem that can help to progress the outcome of LDLT (Gad et al.,



2016).

In LDLT patients, many factors have been involved in the evolution of EAD included small size grafts, high concentration of preoperative serum bilirubin for recipient, increase recipient portal reperfusion pressure, older age of donor, and a donor with higher BMI (**Pomposelli et al., 2016**). The inflammatory state of patients likewise plays a significant function in outcomes after transplantation. In patients with end-stage liver disease (ESLD), systemic inflammatory response syndrome was closely related with complications from decompensation cirrhotic liver and mortality (**Cazzaniga et al., 2009**).

#### *Prediction of EAD*

The early assessment and administration of EAD in liver transplantation is crucial to reduce the length of stay (LOS) and decrease patient morbidity and mortality. The prognosis of EAD is highly pertinent in LT, as it confers transplant physicians to confirm the patients with regard to their risk of graft failure and correlated requirement for pressing relisting for transplant. Various studies have research biomarkers, molecular pathways of disadvantage, and genomic expression models to prognosis of EAD (**Tsai et al., 2019 and Kim et al., 2017**). Nevertheless, there is no international unanimity concerning the early predict of EAD in clinical pursuit yet.

From all the operations of solid organ transplants, biomarkers are facilely ready to estimate effective graft function in LT. These have to be utilized with clinical parameters to evaluate graft function and early graft dysfunction. Graft function is generally estimated by incorporation of appreciation of operative field and produce of bile, clinical markers, need for multiorgan instrument, laboratory biomarkers, and the requirement for blood outputs, specifically for clotting support. However, the clinical and laboratory disturbance are not quite particular for graft function and can be defective due to pre-existing medical condition of the patient and other new starting perioperative factors (**Rajakumar et al., 2023**).

The common EAD is determined by higher level concentration of ALT, AST, INR, or bilirubin within 7 days after LT (**Olthoff et al., 2010**). The elevation of those liver functions markers is generally in equivalent with

evidence allograft failure, detection of accurate allograft damage at a very early stage after LT is difficult to detect, however retardant efficient interference. There are other biomarkers such as inflammatory cytokines, chemokines, metabolites, lipid profile, and factor V were also demonstrated to be associated with EAD. Inflammatory response that excited by ischemia and reperfusion injury. They are significant markers for graft injury, which will lead to EAD, and metabolic dysfunction. Therefore, the inflammatory mediators such as cytokines, chemokines, and factors from coagulation system as well as the metabolomics signature also possess the potential to predict EAD (**Yang et al., 2017; Faitot et al., 2018; Gorgen et al., 2019; Hu et al., 2021**).

#### *Some predictive biomarkers for prediction of EAD*

The development of biochemical technologies and bioinformatic analysis in recent years helps us better understand graft injury during the perioperative period and find potential ways to restore graft function (**Verhoeven et al., 2017**). Therefore, LT recipients are subjected to protocol (blood) measurements depending on their clinical status during follow-up; varying from daily monitoring at the intensive care unit directly after surgery. Markers of liver function are also of importance for the evaluation of graft quality, especially in the first days following LT (**Lin et al., 2023**).

#### *Alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST)*

Alanine-aminotransferase (ALT) is considered to be more liver specific compared to AST. However, because of their differences in intralobular distribution, elevation of AST levels is usually faster than ALT. Nevertheless, serum or plasma ALT has proven to be of value in the diagnostic process of various liver diseases. For instance, in acute viral hepatitis, serum ALT can quickly rise up to 20-fold its normal range, while levels of AST remain lower or show only mild increase (**Verhoeven et al., 2017**). Chronic viral hepatitis results in milder elevations of AST and ALT. When levels of AST become higher than ALT, one should be aware of cellular necrosis. Despite being markers of hepatocellular injury, biliary

obstruction can also result in liver injury and therefore increased levels of AST and ALT. Furthermore, peak serum ALT levels in the first week following LT have been associated with the development of severe biliary complications (De Ritis et al., 2006).

#### *Total bilirubin (TB) and direct bilirubin (DB)*

Based on total and direct bilirubin, one can distinguish different causes for hyperbilirubinemia. Strong elevation of unconjugated bilirubin indicates prehepatic pathophysiology like hemolysis or dysfunction of hepatocytes and conjugation at the hepatic level. However, most complications that can occur following liver transplantation will cause conjugated hyperbilirubinemia (den Dulk et al., 2015). Total bilirubin (TB) level changes slowly and gradually increase along the clinical course in failing grafts. The initial TB level is dependent on pre-LT TB level and transfusions, which are performed intensely during the initial post-LT period (Rhu et al., 2021). Changes in bile composition after liver transplantation can serve as a diagnostic and prognostic tool to predict posttransplant complications, such as primary nonfunction, acute cellular rejection, or non-anastomotic biliary strictures (Brüggenwirth et al., 2020).

#### *Albumin (ALB)*

Human serum albumin is the most abundant plasma protein, and it regulates diverse body functions (Abe et al., 2023). Albumin has important roles in human physiology: maintaining normal colloid osmotic pressure, binding and transport of minerals, hormones, proteins and medications. Also act as an acid-base buffer and antioxidant, as well as enhancing immunologic status (Schalk et al., 2006 and Chien et al., 2017), therefore hypoalbuminemia may be not only a marker of disease severity, but also a part of the pathophysiology as well.

#### *-Lactate dehydrogenase(LDH)*

LDH is an abundant enzyme in the cells of several tissue types, necrosis of these cells releases LDH into the bloodstream. A rise in serum LDH is, thus, a non-specific marker for the destruction of cells in the body (Green et al., 2017). Serum LDH levels are correlated

with poor survival rate in patients with solid tumors and hematological malignancies. Given this relationship of serum LDH with patient outcomes, the levels of serum LDH may act as a valuable biomarker to predict the prognosis and survival of patients with various malignancies (Wulaningsih et al., 2015; Petrelli et al., 2015).

#### *Gamma Glutamyl Transferase (GGT)*

Gamma Glutamyl Transferase (GGT) is a key transferase involved in the transpeptidation of functional gamma glutamyl groups to various receptor moieties, very sensitive for the diagnosis of liver injury, given its cellular role in antioxidant functions. It act as a surrogate biomarker of oxidative stress (Brennan et al., 2022). GGT had positively associated with overall cancer mortality and can be a relevant indicator for liver-related mortality. It is very sensitive for the detection of liver injury and strongly associated with alcoholic and nonalcoholic fatty liver disease (Cho et al., 2023).

#### *Uric acid (UA)*

Uric acid (UA) has been recently studied for its antioxidant activity in various diseases. UA is a final breakdown product of purine nucleotides, and its metabolism involves factors that regulate both hepatic production and renal excretion (Hu et al., 2022). Renal function deterioration significantly impacts the survival rates of liver recipients, and serum uric acid (SUA) is associated with both acute and chronic renal function disorder (Hu et al., 2024). Early allograft dysfunction (EAD) within one week after transplantation has also been identified as associated with postoperative acute kidney injury (AKI) and a higher mortality rate (Agopian et al., 2018).

#### *Hemoglobin (Hb)*

Blood loss during liver transplantation is a common consequence of pre-existing abnormalities of many complications and poor “functional” recovery of the new liver (Feltracco et al., 2013). Anemia is common in these patients as a result of chronic disease, malnutrition, or occult bleeding. Bleeding complications may not be primarily related to impaired coagulation (Liu et al., 2024).

Patients who underwent LT have a significant risk of intraoperative blood loss and need red blood cell (RBC) transfusion (Ma et al., 2024).

#### *Platelets (PLT)*

Platelets are believed to have a significant role in the regeneration of hepatocytes and persistent thrombocytopenia can affect the graft function adversely. This thrombocytopenia is associated with multiple factors. Platelet dysfunction and thrombocytopenia of chronic liver disease are usually carried forwards in the peri-operative period and have implications early post-transplant. Thrombocytopenia is usually encountered in advanced liver disease. It is sometimes thrombocytopenia, investigations of which culminate in the diagnosis of liver disease in the first place (**Parikh, 2024**). Platelets not only participate in physiological hemostasis but also play a major role in liver ischemia-reperfusion injury, liver damage, tissue repair, and liver regeneration. A decrease in platelet count can lead to spontaneous bleeding, infection, and other complications that can seriously impact patient prognosis (**Qiang et al., 2024**).

#### *Neutrophils and lymphocytes*

Alternation of differential WBC counts is crucial to understand the body's defense against pathogens and inflammation; it is widely believed that neutrophilia may be a more definite immune response to specific infections, tissue damage, or inflammation (**George-Gay and Parker, 2003**). Neutrophils, the most abundant type of WBCs, play a vital role in the immune response and have been implicated in various inflammatory and pathological processes (**Kim et al., 2023**). Lymphocytes are essential in cell-mediated immunity, especially in combating cancer cells through cytotoxic activities (**Chen et al., 2023; Roxburgh and McMillan, 2010**).

#### *Neutrophil-to-lymphocyte ratio (NLR)*

The inflammation scores as neutrophil-to-lymphocyte ratio (NLR) have emerged as a proxy of systemic inflammatory status, reflecting the balance between innate and adaptive immune function (**Templeton et al., 2014**). An accumulating body of research has

suggested that NLR is a reliable indicator of systemic inflammation. In patients with end-stage liver disease, with prevalent systemic inflammation associated with poor prognosis (**Oweira et al., 2016**). Increasing NLR was proportionally associated with higher risk of EAD (**Kwon et al., 2019**).

#### *Cytokines for prediction of EAD*

Cytokines are soluble immune mediators involved in inflammation and immune responses, play a critical role in the pathogenesis of autoimmune, allergic and infectious diseases. Furthermore, they implicated in the initiation and evolution of allograft rejection. Cytokines with a predominance of proinflammatory and regulatory properties might be reflected prospect curative targets for eclectic suppression or growing of the immune responses in recipients (**Assadiasl et al., 2021**).

Cytokines are crucial mediators that supervise and organize immune and inflammatory responses through complex communication and avail as biomarkers for considerable diseases. Measurement values of cytokines are important in both clinical medication and biology as the levels supply premeditation into pathological and physiological methods and used as assist diagnosis and medication. Cytokines and their clinical importance are inserted from the spectacle of their pro- and anti-inflammatory response. Operators assuming cytokines measurements in biological body fluids, innate levels in various body fluids and soluble cytokine receptors are researched. Sample treatment and storage conditions are sensibility to freeze-thaw (**Liu et al., 2012**).

Cytokines are excreted by many of immune cells as macrophages, lymphocytes, stromal cells, mast cells and natural killer (NK) cells. Cytokines are dissolvable proteins with lower molecular weight which cooperated in the immune reaction and doing as significant moderators correlated with the connection of the immune system (**Kulbe et al., 2012**).

Cytokines are organizers of responses to contagion, immune responses, inflammation, and injury. Some cytokines are proinflammatory which mirror the worst of disease, however, others anti-inflammatory which decrease inflammation and elevate recovery (**Dinarelo, 2000**).

### Interleukin-6

Interleukin-6 (IL-6) is a proinflammatory cytokine that acts a crucial role in the physiology and pathogenesis of inflammatory and autoimmune diseases, recognized as pleiotropic cytokine excreted by monocytes and endothelial cells that cause harmful immune, inflammatory, and fibro-genic responses. Recently, IL-6 is considered to be a well predictive marker for the results following main abdominal operation (**Nada et al., 2023**).

During physiological inflammatory reactions, interleukin-6 triggers the synthesis of acute phase response and extend the development of particular immunity. It adjusts the proliferation, differentiation and activation of T- and B-cells and induces monocyte, endothelial, and stromal cells to improve a pro-inflammatory feature. Most immune and stromal cells in the human body can be produced interleukin-6. These include abundant of immune and non-immune cells, involve monocytes, T lymphocytes, B lymphocytes, endothelial cells, fibroblasts, and smooth muscle cells and adipocytes (**Kang et al., 2015**). Interleukin-6 considered the main purpose of clinical interference in many of diseases. Implicated immune-mediated allograft injury, produced IL-6, which is stimulate in cancer, infection and most inflammatory situations (**Garbers et al., 2018**). IL-6 arise as a major systematic of physiologic and immune processes including various cellular and organ systems, involving the acute phase reaction, apoptosis, hematopoiesis, cellular metabolism, innate and adaptive immunity (**Kwon et al., 2019; liu et al., 2021**).

Interleukin-6 is a main factor in raising liver cells regeneration and preserving liver homeostasis (**Verleden et al., 2018**). In liver transplantation, the function of IL-6 is less clear but results from many studies involve IL-6 in acute liver rejection (Yao et al., 2013). There are great results from experiential and human studies associated IL-6 to allograft injury (Scheller et al., 2011). Studies in human recipients of different organ allografts persistent show that elevated levels of IL-6 are connected with worse outcomes (Perez-Villa et al., 2006).

### Interleukin- 17

Interleukin 17 (IL-17) is a

proinflammatory cytokine that has been the focus of intensive research because of its crucial role in the pathogenesis of different diseases across many medical specialties (**José María et al., 2020**).

Interleukin-17 is fundamentally produced by neutrophils, mast cells and lymphoid-tissue inducer-like cells (Ebihara et al., 2015). IL-17 is essential for host preservation against fungal and bacterial pathogens, and induces the output of pro-inflammatory cytokines, attracting neutrophils and macrophages to inflammation positions (**Mei et al., 2011; Ji et al., 2014**). Interleukin 17A (IL-17A)-reproduction T helper 17 (Th17) cells were specified as a subset of T helper cells that play a significant role in host defense versus bacterial and fungal pathogens (**Li et al., 2021**).

Interleukin-17 (IL-17) has several biological functions, elevate protective immunity versus numerous pathogens causing inflammatory pathology over infection and autoimmunity. IL-17-driven inflammation normally controlled by anti-inflammatory cytokines include IL-10, IL-35, TGF $\beta$  and regulatory T cells. IL-17 responses can promote immunopathology in the autoimmunity or infection and also has been involved in the pathogenesis of main other disorders with an inflammatory fundamental, inclusive cardiovascular and neurological diseases (**Mills, 2023**).

In several autoimmune and inflammatory diseases, T helper 17(TH17) cells, recognized by the produce of IL-17, have considered as substantial mediators of the pathological process. IL-17 has pro-inflammatory features and plays a critical role in the activation and conservation of the immune response (**Bettelli et al., 2007**). The combination between liver injury and IL-17 due to hepatic ischemia/reperfusion injury, which activated TH17 cells and upregulated the secretion of IL-17 (**Caldwell et al., 2005**). Elevated IL-17 was associated to hepatic fatty injury and can leads to the advancement from steatosis to steatohepatitis in a mouse model of nonalcoholic fatty liver disease (**Tang et al., 2011**).

A few earlier retrospective cohort studies for predictive indicators of early allograft dysfunction after liver transplantation were displayed in (Table.3). Criteria of EAD for these studies according to **Olthoff's et al. (2010)** are the international normalized ratio

(INR)  $\geq 1.6$  on postoperative day seven or serum total bilirubin (TB)  $\geq 10$  mg/dl, as well as alanine transaminase (ALT) or aspartate transaminase (AST)  $> 2000$  U/L within the first week after surgery. Although the clinical application of these predictive biomarkers has not been verified, there is an urgent need for greater research utilizing molecular biomarkers in conjunction with biochemical indicators since this could result in a more reliable EAD prognosis.

Table 3: Retrospective cohort studies for prognostic markers of early allograft dysfunction following transplanted liver

Citations	N	EAD incidence%	Biomarkers and defined cut off
Hong et al,2013	304	15.8	More than 4.5 mg/dl of serum phosphorus on the second postoperative day
Li et al,2015	234	22.6	Platelet counts $< 68 \times 10^9/L$
Chae et al,2016	104	29.8	Serum brain natriuretic peptide levels during surgery $> 100$ pg/mL
Yang et al,2017	231	38.6	Level of total cholesterol less than 1.42 mmol/L
Kwon et al,2018	148	25.7	Antiphospholipid antibodies
Zhang et al,2018	272	21.6	Albumin-bilirubin Score grade III
Chae et al,2018	260	12.4	Serum cytokines Interleukin-6 and Interleukin-17
Park et al,2019	588	14.1	The ratio of C-reactive protein to Albumin more than 20%
Tao Lv et al,2019	262	16.4	On postoperative day three hepatic artery resistance index less than 0.68
Kwon et al,2019	1960	20.5	Ratio of Neutrophil-to-Lymphocyte $\geq 2.85$
Kwon et al,2020	698	20	Proportion of Von Willebrand factor to protein C more than 8.06
Lee et al,2020	452	13.1	Arterial oxygen content less than 11.8 mL/dL
Hu et al,2021	61	24.6	Level of uric acid $\leq 4.4$ mg/dL
Hung et al,2021	121	26.5	ROTEM derived parameters
Tsai et al,2021	74	29.7	Metabolomics-Circulatory lipids
Singh et al,2022	135	29.6	Hyper perfusion index $\geq 9.97$
Miyachi et al, 2022	199	49	Intraoperative FiO <sub>2</sub> $> 0.5$

Abbreviations: EAD, early allograft dysfunction; ROTEM, rotational thromboelastometry; FiO<sub>2</sub>, fraction of Inspiratory Oxygen.

## Conclusion

This review highlight on liver

transplantation and some of the biochemical markers associated with early graft dysfunction following transplanted liver. Future research on the diagnosis and management of early complication are desperately needed in order to improve outcome.

## Recommendations

Additional prospective studies needed to define and differentiate between the predictors of early allograft dysfunction followed liver transplantation. In addition, uniform inclusion and exclusion criteria that give better understand of the impact of the specific donor or recipient risk factors and predictive newer biomarkers using newer cutoffs through statistical analysis to allow standardized and continuous grading of early complication and predict the risk of graft failure.

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## الملخص العربي

### عنوان البحث: المضاعفات السريرية المبكرة بعد عملية زراعة الكبد من متبرع حي

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تعتبر عملية زرع الكبد العلاج المنقذ للحياة للمرضى الذين يعانون من أمراض الكبد مثل مرض الكبد في المرحلة النهائية أو فشل الكبد الحاد أو سرطانات الكبد الأولية. لقد أصبحت عملية زراعة الكبد من متبرع حي خيار علاج مقبول لحل مشكلة عدم كفاية الأكباد المتبرع بها من المتوفى لعملية زراعة الكبد من متبرع حي. إن تحضير عملية زراعة الكبد من متبرع حي أمر بالغ الأهمية نظرًا لنتائجها الناجحة لكل من المتبرعين والمتلقين. يعد الخلل المبكر في عملية الزراعة من المضاعفات السريرية المهمة التي تؤثر سلبيًا على الطعمون نتائج المريض. إن زيادة تطور خلل الطعم المبكر والارتباط بزراعة الكبد من متبرع حي هو مجال ذو ميزة كبيرة. إن التقدير الوظيفي للكبد المزروع في مرحلة مبكرة بعد الجراحة يعتبر من الأمور المفضلة لدى أطباء زراعة الأعضاء، حيث يعكس النجاح التكنولوجي لزراعة الكبد ويؤثر بشكل كبير على نتائج المتلقي. يتم تعريف خلل الطعم المبكر بأنه حالة وظيفية أولية للكبد المزروع، وهو ما يعرض لخطر معدل الإصابة بالأمراض والوفيات بين المرضى.

الهدف من المقالة:  
هدف المراجعة إلى تسليط الضوء على زراعة الكبد وبعض الدلالات الكيميائية الحيوية المرتبطة بالخلل الوظيفي المبكر في زراعة الكبد من متبرع حي.

الاستنتاج  
زراعة الكبد من الحلول الناجحة لمرضى الفشل الكبدي وهناك بعض العلامات الكيميائية الحيوية المرتبطة بالخلل الوظيفي المبكر في زراعة الكبد من متبرع حي ولكن زراعة الكبد تتطلب أبحاثًا مستقبلية في تشخيص الخلل الوظيفي المبكر مع إمكانية تحسين النتيجة.