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Risk factors of hepatic graft failure, morbidity and mortality after living donor liver transplantation (LDLT): Review Article

Ayman Azzam*

Department of General Surgery, Alexandria University, Alexandria, Egypt

Abstract

Back ground: Liver transplantation is a breakthrough in the modern life**.** With the increase demands on liver transplantation, LDLT was emerged. With more increase in the demands, the donor pool started to be widened and the use of marginal donors started. The factors affect the graft failure become widened and included multiple factors.

Aim and objective: This review extensively put the focus on the risk factors for hepatic graft failure after LDLT. Also, the impact of these factors and their influence on the patients' morbidity and mortality.

Conclusion: Multiple factors were studied as risk factors for graft failure and patients' mortality after LDLT**.** The rate of early graft failure is low. This is due **to** optimum donor selection as regards age, sex, body mass index (BMI) and ABO-compatibility; computer-assisted planning and decision making in donor segmental hepatectomy and optimum GRWR; short cold ischemic time; high level of expertise in the center; and timely detection of vascular, biliary and immunological complications responsible for early graft failure together with early and efficient management. Most of the underlying risk factors for late graft failure include patients with CR which were not responding to treatment and patients with disease recurrence which is unavoidable. Therefore, both these complications constitute real problems in liver transplantation.

Introduction

Liver transplantation (LT) represents the only curative treatment for patients with end-stage liver disease. With improvements in surgical techniques and advances in immunosuppressive therapy, LT has become routine procedure during the past decades [1]. As indications for orthotopic LT have widened [2,3], the need for transplantable organs has increased. Unfortunately, the supply of deceased donor organs has not met the increasing demand. Therefore, expanding the donor pool and reducing waiting list mortality is one of the major challenges today for the liver transplant community [4]. Increasing the frequency of living donor liver transplantations (LDLT) meets both of those challenges [5,6]. With scarcity of deceased donors, LDLT has become the main form of LT especially in Asian countries [7,8]. The success of LDLT in the pediatric population led to improvement of this technique for adult population [9]. Adequate selection of both the donor and the recipient for LDLT are very important factors to prevent mortality and morbidity including graft failure and the need for retransplantation [10,11]. Few studies have investigated factors leading to graft failure especially with LDLT [12,13]. Several risk factors for graft loss after LDLT were identified by researchers as donor age [14], MELD score [15-19], intraoperative blood loss [19-21], warm ischemic time [21], and small for size syndrome [22-25]. Other studies investigated the factors responsible for graft loss and retransplantation namely hepatic artery thrombosis [26,27] primary non-function [26] and hyperacute rejection [28]. Although improving outcomes and survival after LDLT with meticulous selection criteria [9,29], still no definite criteria can predict graft dysfunction or failure.

Graft type and size

In LDLT, the choice of the type and size of the graft is one of the most important aspects of the procedure.

Graft size

Although the safety limit of residual liver volume for donor has not been precisely estimated, it was believed that a normal liver could tolerate right hepatectomy as the residual left lobe constitutes 30.0-40.0% of the total liver mass which is considered safe for the donor [30]. Based on this concept, right lobe graft program was introduced in Kyoto University in February 1998 [31]. In cases where segment 5 and 8 of the right lobe drain mainly in the middle hepatic vein (MHV), right lobe grafts including the MHV (extended right lobe graft) was resorted to, to prevent the congestion of these segments and preserve the functional volume of the right lobe graft and to prevent the occurrence of small-for-size syndrome in the recipient [32]. The increasing use of the extended right lobe grafts was due to the realization of the importance of the inclusion of this vein in the graft whenever it does not affect the venous drainage of residual liver volume in the donor.

Correspondence to: Ayman Azzam, Department of General Surgery, Alexandria University, Alexandria, Egypt, E-mail: aazzam70@yahoo.com

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After the extension of the indications for LDLT to adults, the problem of "small-for-size graft" was encountered. This problem is not found in either cadaveric liver transplantation or in pediatric LDLT. This was partly solved by the introduction of the right lobe graft [31]. However, some cases with right lobe grafts developed poor bile production, delayed synthetic function, prolonged cholestasis and intractable ascites in spite of adequate graft volume. As these symptoms indicate poor graft function in presence of optimum graft volume, it was given the name of "small-for-size syndrome" [33]. Therefore, the "small-for-size syndrome" can be observed not only in "small-for-size graft" but also in optimum or even in large size grafts. Several explanations were introduced to clarify this syndrome and researches where conducted to solve this fatal problem [23]. Several techniques are being explored and innovated in an attempt to ameliorate the impact of small-for-size syndrome. One of the procedures is to obtain larger liver mass by addition of grafts such as auxiliary partial orthotopic LDLT (APOLT) [34], but it has a lot of complications and dual liver grafts [35,36], which is not common as it needs the presence of two available donors which is not always feasible. Other procedures included the MHV to the right lobe graft which may not add liver volume but can improve the graft function by prevention of the congestion of the anterior segment [37]. Injury of the graft may be produced by persistent portal hypertension and portal over perfusion of the graft [38]. Control of portal pressure and graft perfusion may be adopted to prevent graft injury in such cases. This was achieved by innovative techniques such as splenic artery ligation (SPL) [39,40], or permanent portacaval (PC) shunt [41,42].

Graft type

Hepatic steatosis evolved as a risk factor in LDLT. There is consensus that macrosteatosis affects liver graft function and survival more than microsteatosis because it may progress to non-alcoholic steatohepatitis (NASH) and ultimate liver cirrhosis with graft failure [43-46]. Its presence is suspected in overweight or obese donors with a body mass index (BMI) ≥ 25 kg/m^2 [47]. In such donors, CT and ultrasound can be used to estimate hepatic fat [48]. Donors with steatosis have a reduced functional liver mass. It has been proposed that each percentage of hepatic steatosis in the donor decreases the functional graft mass by 1% [49]. This must be factored into the calculation of GRWR. In cadaveric liver transplantation, steatosis has been associated with primary non-function (PNF) and initial poor function that is recoverable [43,44,46]. PNF occurs in as many as 80% of patients with severe steatosis and therefore grafts with more than 60% steatosis represent a contraindication to transplantation [43,50,51]. Initial poor function occurs in approximately 30% of patients receiving livers with moderate steatosis [51]. Several groups have shown that grafts with less than 30% steatosis have results similar to those of transplantation with non-steatotic livers [45,52-54]. In LDLT, Hayashi evaluated the effect of steatosis on graft outcomes and found that grafts with mild to moderate steatosis demonstrated slight disturbances in early graft function, but were similar to controls [55]. Grafts with severe steatosis were associated with poor function and outcome [55]. Similarly, Soejima evaluated the impact of the degree of steatosis in 60 consecutive donors and recipients. One-year graft survival in none, mild and moderate steatosis groups was comparable (85.9%, 80.7%, and 80.0%). He concluded that grafts with moderate steatosis (<50%) can be used if the residual volume in the donor is at least 40% to avoid additional risk related to steatosis [56]. Cho reported similar regeneration ability and early outcome between recipients receiving mild steatotic (≤ 30% macrosteatosis) vs. normal (≤ 5% macrosteatosis) liver grafts. Using biopsies performed 10 days after surgery, he noted that the degree of steatosis decreased to less than 10% in all grafts suggesting that mild steatosis is rapidly reversible after LDLT [57]. Although the use of grafts with mild to moderate steatosis yields comparable results with those without steatosis, it appears risky to use such grafts on a routine basis. Their use are justified when they are not associated with other risk factors. It is recommended that donors with BMI ≥25 should undergo diet control and exercise which permit reduction of liver steatosis allowing a delayed but safer transplantation for both donors and recipients. Liver biopsy is recommended in countries where there is lack of expertise in the evaluation and diagnosis of hepatic steatosis by radiological means. It also serves to detect other pathological conditions in the donor such as hepatitis, fibrosis or cirrhosis, which may be prevalent in these countries. PNF, which is common in cadaveric liver transplantation, did not occur in the present series most likely due to the short cold ischemic time (CIT) in LDLT.

Hepatic grafts from ABO-incompatible donors: is considered as a risk factor in LDLT because of the risk of hyperacute rejection mediated by preformed anti-ABO antibodies [58-60]. ABO-incompatible donors may be the only available source of graft in life threatening situations such as in fulminant hepatic failure (FHF). In countries with limited access to cadaveric donors, the use of grafts from ABO-incompatible living donors occurs more frequently, particularly when the donor source is restricted to immediate relatives [61,62]. Plasmapheresis is effective in decreasing pre-transplantation antibody titers, but it is ineffective in maintaining low post-transplantation antibody titers and fails to prevent death of the patient once hepatic necrosis occurs. Yandza demonstrated that children less than 2 years old had lower anti-ABO antibodies titers and lower morbidity compared to adults [63]. Gugenheim suggested that ABO-incompatible liver transplantation is only justifiable in adult recipients as an emergency [58]. On the contrary, Hanto reported encouraging results in adults [64]. In ABO-incompatible liver transplantation from cadaveric donors, the incidences of preoperative mortality, arterial thrombosis and irreversible rejection and the rate of retransplantation have been reported to be greater than those in ABO-compatible or-identical transplants, irrespective whether the cases were adult or pediatric, emergency or elective transplantation and regardless of the indication for transplantation [58,65-67]. Gordon found reduced graft survival rate in ABO-incompatible liver transplantation from cadaveric donors. Therefore, liver transplantation from ABO-mismatched cadaveric donors has been thought to be justified only in emergency cases especially in children, due to the shortage of appropriate donor grafts [68]. Farges has reported that hyperacute rejection is a complication in adult patients undergoing ABO-incompatible cadaveric liver transplantation [61]. Renard and Andrews also reported hepatic necrosis with hemorrhagic and perivascular parenchymal collapse in pediatric cases [69]. A difference in outcome between adult and pediatric cadaveric liver transplantation has been reported, with pediatric transplants being more successful [70,71]. The reasons for more favorable outcome in children are not totally clear [72,73], but they may be related to lower anti-ABO antibodies levels, [63], or to an immature complement system [74] thus, the factors that initiate hyperacute rejection are absent during early infancy. In contrast, adults undergoing splenectomy in ABO-incompatible liver transplantation to decrease the incidence of hyperacute rejection together with the addition of other immunosuppressive agents in such cases also might contribute to poor outcome in these patients [68,71]. Some centers showed insignificant difference in the results of ABO-incompatible and ABO-compatible grafts as regards the graft failure in LDLT which

can be attributed to the ABO-incompatibility protocol adopted in these centers [75-78]. Although ABO incompatible LDLT may be carried out with relative safety in infants <1 year old using standard immunosuppression, yet, it carries increased risk of graft failure in older patients and should be used only in urgent cases and/or when they are the only available donors.

The donor age and sex: as risk factors in liver transplantation were extensively studied in world literatures. Pittsburgh group studied the effect of donor age and sex on the outcome of grafts in cadaveric liver transplantation. They found that the effect of donor age became evident only when they were older than 45 years. They also found that livers from female donors yielded significantly poorer results, with 2-year graft survival of female donor to male recipient, 55% (range 45% to 67%); female donor to female recipient, 64% (range 54% to 77%); male donor to male recipient, 72% (range 66% to 78%); and male donor to female recipient, 78% (range 70% to 88%) [79]. Ikegami studied the impact of donor age on LDLT. He found that the liver grafts obtained from middle aged (30-50 years old) and older aged donors (>50 years old) recovered their volumes as much as 80% of standard liver volume (SLV) at 1 month, whereas those of younger donors (<30 years old) accelerated volume recovery and also reach as much as 80.0% of SLV in only 1 week after transplantation. These results denote that liver regeneration occurs earlier and proceeds more rapidly in younger livers than in older livers. He also found significant prolongation of prothrombin time values in POD 3 in the grafts obtained from aged donors than those from younger ones [80]. Kimura also reported reduced capacity in protein synthesis in hepatic grafts obtained from aged donors [81]. Old age and female gender should be considered as risk factors in LDLT. They are considered more risky if they are additive such as in old female donors. However, they should not be discarded from donation in the face of shortage of liver donors.

Recipient factors

The recipient status at the time of transplantation: **United Network for Organ Sharing (UNOS) status:** is considered as a risk factor for both graft and patient survival. FHF, which belongs to United Network for Organ Sharing (UNOS) status 1, has reported mortality rate between 70-95% in children depending on the cause of the disease and the age of the patient [82]. Because progression of organ failure and irreversible neurologic damage may occur in pediatric patients with FHF while awaiting a cadaveric allograft, it is crucial that early LDLT be performed without excessive delay in waiting for cadaveric grafts. LDLT as a mode of therapy in FHF in children was first attempted by Tanaka in 1994 [83], who reported on 3 pediatric patients with FHF, all of them received left lobe liver grafts estimated to be 0.8-1.0% of the body weight and were successfully discharged from the hospital. In 1998, the same group reported their results in a series of 11 children with survival rate of 73.0% after a mean follow-up of 28 months (range 13-67 months) [84]. Similar results were reported in pediatric patients from both Eastern [85] and Western centers [86]. Mack in 2001 reported a retrospective study on 19 pediatric patients with FHF associated with multiple organ failure (MOF) comparing the results of LDLT to a similar group of patients who received cadaveric allograft donation (CAD). Patients in the LDLT group had markedly improved survival compared with the CAD group. Thirty-day and six-month survival rates of the LDLT group were 88.0% and 63.0% compared with 45.0% and 27.0% in the CAD group, respectively. He suggested that the difference in survival outcomes was related to the fact that LDLT recipients had decreased waiting times for transplantation and decreased cold ischemia time as compared with the CAD recipients [87]. The application of LDLT in FHF in adults was first addressed by Lo in 1999 who reported that when cadaveric organ donation is scarce, emergency LDLT can be applied to high urgency adult patients [88]. Nishizaki suggested that a high success rate of LDLT and low donor risk could be achieved in adult patients with FHF using a left lobe graft. He reported 15 adult patients with FHF treated with a left lobe graft which corresponded to 23.0-54.0% of recipients' standard liver volume. The overall survival rate was 80.0% with a follow-up period from 3-43 months. He also reported no significant differences in survival outcomes comparing the patients with a liver graft to a standard liver volume ratio of <30.0% and those with a ratio of ≥ 30.0% [89]. In the lights of these studies, it appears that, the results of LDLT in adult patients with FHF were superior to those in pediatric patients. The difference may be related to the cause of the disease, incidence of rejection and the rate of postoperative complications. Testa reported the results of 7 patients who had acute-on-chronic liver failure and underwent urgent LDLT using right lobe grafts. Patient and graft survival rates were only 43.0% at a mean follow-up of 15.1 months [90].

Regarding MELD score: as a risk factor for hepatic graft failure. Freeman in 2003 [91] showed that little lifetime benefit for the recipient is achieved with MELD scores less than 10 and perhaps less than 14. The relative risk for post-transplantation mortality starts to increase for candidates with MELD score greater than 25 at the time of transplantation. Therefore, candidates with MELD score between 14-25 would appear to derive the most lifetime benefit. These would seem to be the ideal candidates for adult LDLT.

Indication of LDLT

Hepatitis B virus related liver disease

Liver transplantation in patients with HBV-related liver diseases is followed by a high incidence of recurrent graft infection and subsequent graft failure [92]. As a result, many transplant centers were reluctant to consider patients with HBV-related liver diseases for transplantation. After the introduction of the prophylaxis protocol against HBV recurrence using a combination of high-dose of HBIG and lamivudine by Markowitz, the results began to improve. He reported on 4 of 10 patients which were HBV-DNA positive before transplantation, all were negative for HBsAg and HBV-DNA at a median follow-up of nearly 1 year [93]. In order to reduce the financial burden of high-dose life-long HBIG, the use of sequential HBIG therapy for 2 years after transplantation followed by lamivudine monotherapy has been shown to be effective in preventing reinfection in patients with a low level of pretransplant viral replication [94].

Hepatitis C virus related liver disease

Liver transplantation in patients with chronic end-stage liver disease caused by chronic HCV-related cirrhosis are reported to be followed by severe graft damage in cadaveric liver transplantation and even more in LDLT [95,96]. It is suggested that the cause of graft damage is the recurrence of HCV infection in the graft. The recurrence of the disease is diagnosed by the presence of elevated ALT, detected HCV-RNA and liver biopsy [97]. An analysis of the UNOS database demonstrated significantly diminished 5-year survival after primary transplantation in HCV-positive patients [98]. The transplant group in the University of California at Los Angeles (UCLA) observed recurrent hepatitis in 86.0% of HCV-infected LDLT recipients compared with only 30.0% of cadaveric transplant recipients. The mean time to HCV recurrence was 4.75 months [95]. Similar outcomes were reported from Colombia University group who reported 80.0% of LDLT recipients developed

recurrent HCV compared with 58.0% of cadaveric recipients (p value <0.05) with mean follow-up of 19 months [96]. It is known that HCV recurrence and progression to fibrosis is enhanced by the use of boluses of methylprednisolone in the management of acute rejection [99]. In order to decrease the rate of recurrence and progression of HCV, Kyoto group began a protocol of steroid free immunosuppression in cases of HCV end-stage liver failure recipients. A monotherapy of tacrolimus without mycophenolate mofetil was used because it has been demonstrated that the administration of mycophenolate mofetil could result in a more sever recurrence [100]. The key point in the management of transplanted patients affected with HCV infection is the regular follow up of transplanted patients to detect early recurrence by PCR and the application of the treatment protocol to guard against the development of liver cirrhosis in the graft and subsequent failure. It is suggested that treatment of LDLT recipients before transplantation may prevent HCV recurrence after transplantation [101]. In a study involving 21 patients receiving a prophylactic treatment by interferon (IFN) and ribavirin (RBV), liver histology was normal in 81.0% of patients one year after transplantation, and virological clearance was observed in 41.0% of patients [102]. Leucopenia and thrombopenia were noted in all studies and resulted in dose reduction in some patients. Moreover, in the early report of Feray, chronic rejection may occur in patients under treatment [103].

Hepatocellular carcinoma

LT in HCC is thought to be a better therapy as compared with resection. This thinking was dependent on the fact that more than 90.0% of cases develop HCC in the setting of underlying liver cirrhosis, most commonly due to chronic hepatitis B or C [104,105]. Resection in such cases is followed by a high rate of development of secondary lesions within few years because of the multicentricity of the tumor [106]. Transplantation is a logical approach in this situation as it can potentially cure both cirrhosis and HCC [107,108]. One of the major downfalls of cadaveric liver transplantation as a treatment for HCC is that patients must wait for a liver [109,110]. This waiting time compromises the outcome of transplantation because of the disease progression may occur during the waiting time. The recent development of adult LDLT provided an alternative source of donor livers for transplantation, which is independent on the waiting time or UNOS criteria. For a patient who has a living donor, a donor organ is not a scarce resource [111,112]. Current selection criteria in cadaveric donor programs are based on a retrospective analysis of tumor characteristics and allocate transplant only to those patients who satisfy Milan criteria [113]. These criteria provide transplantation outcomes that are similar to those of transplantation in patients without HCC. These criteria are based on tumor size and number. Single tumors must be <5cm in diameter, if more than one lesion is present, the maximum number of tumors must be 3 or less and none of them is >3cm in diameter. The rationale behind the use of these criteria is to preserve the outcome in HCC as compared with non-HCC patients so that organ use is optimized [114]. Because LDLT has been a successful and fully accepted treatment for adult patients with end-stage liver disease, interest in this modality as the treatment for HCC has risen. More liberal criteria has been suggested based on the premise that the outcomes of these expanded criteria are similar to those of the more conservative criteria in terms of post-transplantation survival [115-117]. Based on these studies, LDLT was proposed for expanded criteria with little adverse effect on outcome. The pilot study on LDLT for HCC was started in February 1999 in Kyoto University with an approval from the institutional ethical committee with inclusion criteria consisting of otherwise untreatable HCC with complete exclusion of extra-hepatic lesion or macroscopic vascular invasion, irrespective of tumor size and number [13,118]. Some studies demonstrated favorable results in the patients fulfilling these selection criteria and concluded that Milan criteria do not seem to be suitable for selecting HCC patients for LDLT [118,119]. Similar results were reported by Yao, who concluded that the Milan criteria may be expanded with excellent survival in LDLT [120]. From these studies, it is clearly demonstrated that patients with HCC outside the Milan criteria and excluded from cadaveric donor transplantation could survive nearly the same as patients with HCC within Milan criteria in LDLT programs. Therefore, the application of the Milan criteria for all patients with HCC would have denied many patients who can survive after transplantation. Therefore, transplantation is by far the best treatment option for patients with HCC, if a careful search reveals no extra-hepatic disease. In LDLT programs, where the patient has his special living donor, the UNOS and Milan criteria are not necessarily relevant.

The technique of LDLT

LDLT, regarding the technique, is a complex operation as compared to cadaveric LT. A thorough understanding of the segmental anatomy of the liver, the hepatic arterial, hepatic venous, portal venous and biliary ductal systems and the ability to recognize variants in this anatomy are critical to perform LDLT successfully and safely. Various anatomic variations encountered during this procedure has been detailed through careful dissection of cadaveric livers and examination of hepatic corrosion casts [121-123]. In spite of that, many technical complications are still reported in different centers and may be serious enough to lead to both graft failure and death. Hepatic artery thrombosis (HAT) is the most common and the most critical vascular complication [124-126]. It occurs in 12.0% of adult and more than 40.0% of pediatric recipients [126,127]. HAT leads to hepatic necrosis, biliary leakage or strictures and finally recurrent sepsis [128]. Early diagnosis with prompt intervention is essential because urgent retransplantation is required in most cases. Hepatic arterial stenosis (HAS) can be observed in 11.0% of liver recipients. It is usually localized at the site of anastomosis. In most cases, it is caused by technical failure which is responsible for damage of the vascular intima with subsequent necrosis and scar formation. Tight anastomosis can reduce blood flow, which favors arterial thrombosis. In some cases arterial stenosis per se represent an indication of retransplantation [129]. Portal vein thrombosis (PVT) is one of the life threatening complications of liver transplantation, especially when occurs in the immediate postoperative period [130,131]. Acute PVT may lead to portal hypertension or hepatic ischemia with catastrophic sequelae. Late-onset PVT, on the other hand, is generally well tolerated, although it may eventually lead to graft compromise requiring aggressive intervention [132]. Portal vein stenosis (PVS) usually develops slowly after transplantation, and it is suggested by the presence of gastrointestinal varices, ascites and splenomegaly. It is diagnosed by Doppler ultrasonography in asymptomatic cases [133]. Thrombosis or stenosis of the portal venous trunk may be observed in 1.0% to 12.5% liver recipients [126,133,134]. Abnormal blood flow through the portal vein may be caused by technical error, coagulation disorders, previous surgical interventions (splenectomy) or damage of the endothelium of the portal vein during cannulation [126,127,134]. Hepatic venous outflow obstruction may occur due to stenosis and/or thrombosis mainly at the anastomotic site or sites. Several potential mechanisms could be implicated as the cause of anastomotic hepatic vein stenosis. Technical failure is the most likely cause such as tight anastomosis causing purse-string phenomenon,

stitches catching the back wall or additional stitches for hemostasis. Twisting of the outflow vessel of the left lobe graft secondary to its displacement to the empty right liver fossa occurring upon closure of the abdominal wall may be another cause of hepatic venous outflow obstruction [135]. A third cause may be the structural stenosis of the hepatic vein secondary to enlargement of the graft during the process of regeneration. Hepatic venous outflow obstruction may lead to cirrhosis of the graft if such obstruction continues to be present for a long time. The recent introduction of microsurgical techniques for arterial anastomosis in LDLT has greatly reduced the incidence of HAT compared with previous reports [60,135]. From these studies it was concluded that vascular thrombosis occurs mostly during hospital stay and may be responsible for early graft failure, while vascular stenosis appeared late in increasing frequency as the period of follow up increases and may be responsible for of late graft failure [136].

Biliary complications as a risk factor

Biliary complications after LDLT continue to be the most frequent cause of morbidity and may contribute to mortality of recipients. Complications in the form of biliary leaks, bilomas and strictures were reported to occur with an incidence of 10.0% to 30.0% [137-140]. These complications were mostly attributed to ischemia and technical failures [141]. Owing to the prevalence of biliary complications in LDLT, preventive measures were suggested to decrease the rate of these complications. As it is known that ischemic changes around the anastomosis is a major cause of anastomotic stenosis, greater precaution should be taken to preserve the peribiliary plexus around the resected bile duct in the donor.

Hepatic allograft rejection as a risk factor

Despite recent improvements in immunosuppressive therapy, hepatic allograft rejection remains a major cause of morbidity and graft loss in patients undergoing LT [142-145]. Humoral rejection (HR) is a rare complication that occurs early after transplantation and is usually fatal. There is no specific treatment for HR and the only way to save the life of the patient is urgent retransplantation. Therefore, prevention of the condition is essential and may be attained through the selection of ABO-identical or ABO-compatible donors, if possible. Chronic rejection (CR) is an indolent, but progressive form of allograft injury that is usually irreversible and eventually results in the failure of most vascularized solid organ allografts. It is reported that by five years after transplantation, it affects as many as 30-50% of heart, lung, pancreas and kidney allografts recipients, but only 4-8% of patients who undergo liver transplantation [146]. Liver allografts also differ from other solid organs in that CR is potentially reversible. This quality has been generally attributed to liver unique immunobiological properties and the regenerative capacity of bile ducts which are one of the main targets in CR [147-149]. CR can occur within 3 weeks after liver transplantation and was given the name of acute vanishing bile duct syndrome [150]. but commonly occurs after 2 months and usually within 1 year [151,152]. Late onset (later than 1 year) CR is typically seen in inadequately immunosuppressed recipients, either as a result of non-compliance or intentionally attenuated immunosuppression [151]. If the findings indicate a late stage of CR, retransplantation is preferable to too-potent immunosuppression, which may cause fatal infectious complications [151]. CR of a liver allograft may be reversible to some extent. This result was reported in world literature [147,148,153,154]. This reversibility usually occurs before the duct loss or obliterative arteriopathy have become severe. Some patients with CR was found to have experienced one or more episodes of ACR. This may evolve directly from inadequately controlled ACR episodes as reported in some literatures [142,154,155]. The results also show a lower incidence of CR in liver allografts compared to other vascularized allografts. This has been explained by the immunological theories of the so called hepatic tolerogenesity [156]. Graft-versus-host disease (GVHD) is a rare complication that occurs after LT. Smith reported 12 cases of GVHD among 1082 LT done between 1991 and 1998 at Baylor University Medical Center [157]. GVHD is usually a fatal disease and future approaches should focus on its prevention. This can be achieved by HLA matching before LDLT because the donors of all cases of GVHD were of HLA homozygous. Additional risk factors were reported by other authors and include, recipients older than 65 years and recipients of donors more than 40 years younger than the recipients [157].

Infection as a risk factor

The problem of infection in the setting of LT is among the most serious and difficult complications that follow a technically successful LT. Currently infection is the major cause of death after LT [158]. Recipients are susceptible to infections that are normally controlled by the body's intrinsic defense mechanisms. Obligate immunosuppressive therapy required for the prevention and treatment of rejection constitute a major risk factor in these patients and pave the way for opportunistic bacteria, viruses or fungi to cause infections in such patients. The incidence of bacterial infections after LT differs considerably among transplantation centers and ranges between 35.0% and 68.0% [159-163]. The timing of bacterial infection showed that most bacterial infections occurred in the immediate postoperative period and during the hospital stay. The high occurrence of bacterial infections in the early postoperative period was reported in different centers of LD [161,163]. This may be explained by the intense immunosuppressive therapy given during this period to prevent rejection and the presence of bacteremia induced by intra-tracheal tubes, urinary catheters and intravenous lines. Additionally, ischemic and biliary complications of the graft occur more during this period. The danger concerning bacterial infections in LT lies in the difficulty of diagnosis. The usual signs and symptoms of infection may be masked or absent as a result of the patient's immunosuppressed condition [164]. In addition, clinical manifestations of graft ischemia or graft rejection can mimic those of infection. Bacterial infections can be severe enough to result in septic shock, multiple organ failure (MOF) and death. The incidence of invasive fungal infection was reported to be lower than in other centers which reported a range between 4.0% - 48.0% [165-167]. Mortality rate was reported to be 50.0% to 80.0% in the presence of fungal infection [163,165,168]. They stated that prolonged operative time, increased intra-operative transfusion requirements, choledochojejunostomy, prolonged hospitalization, graft failure and retransplantation, vascular and gastrointestinal complications, recurrent bacterial infections and extended use of antibiotics beyond the first week after transplantation were risk factors for the development of fungal infection. They recommended the prophylactic use of intravenous amphotericin B to prevent postoperative fungal infection in these patients. Cytomegalovirus (CMV) infection was reported to be 18.0% to 40.0% of patients [169,170]. Most of CMV infection occurs early usually between 3 and 8 weeks after LT [171-173]. The early occurrence of CMV infection may be related to the intense immunosuppressive therapy during this period to prevent or treat episodes of rejection. Epstein bar virus (EBV) infection came next in frequency to CMV infection. More cases of EBV infection occur late after patient discharge. The real problem in EBV infection is that it is a B cell

lymphotropic virus capable of inducing proliferative changes leading to post-transplantation lymphoproliferative disorder (PTLD) and frank lymphoma. Over-immunosuppressive therapy was considered as a risk factor in the development of PTLD. Therefore, these patients responded well to cessation of immunosuppression together with large doses of intravenous acyclovir. Accurate diagnosis and early treatment of EBV infection remain elusive to guard against development of EBV-associated PTLD. Sometimes this management is not sufficient and the disease may result in patient death [174].

Disease recurrence as a risk factors

Disease recurrence has emerged as an area of major concern as patient survival has increased after LD. Recurrence rates vary greatly depending on the primary liver disease. The majority of conditions for which patients undergo transplantation will recur at some point in time, because a number of end-stage liver diseases are due to host or environmental factors [175-177]. On the other hand, most metabolic liver diseases do not recur after transplantation because they are mainly restricted to the liver and can be said to be truly cured. Some studies found that recurrent disease after LT occurred in 10.0% of long-term survivors [157,178]. The rate of disease recurrence increases as the period of follow up increases. Certain factors have been reported to result in increased rate of HCV recurrence such as high viral load, increased donor age and in the setting of LDLT rather than cadaveric liver transplantation [179]. Combination therapy by PEG-IFN and ribavirin may be well tolerated and beneficial during recurrent HCV infection in liver transplant patients [180]. Recurrence of HBV was reported to occur in 40.0% of patients who undergo liver transplantation and the virus develops resistance to lamivudine therapy [157]. There is now increasing evidence that with the appropriate therapy, recurrence rates may be significantly reduced in HBV recurrence. Other study showed the recurrence rate to be 12.7% [181]. HCC recurrence was detected by continuing elevation of the level of alpha-fetoprotein in the regular follow-up of the patient, confirmed by US detection of the recurrence in the graft. Additional investigations, including chest X-ray and brain scan, proved the presence of metastases. HCC recurrence represents a major risk factor in both graft failure and patient survival. The rate of recurrence of HCC after LT was dependent on the preoperative stage of the disease. Recurrent primary sclerosing cholangitis (PSC) was reported to be 20.0% [182,183] The clinical significance of recurrent PSC is that patients develop biliary strictures and it can mimic ductopenic rejection in presentation. Diagnosis relied on ERCP and liver biopsy. Single, dominant strictures in recurrent PSC are frequently amenable to dilatation. More extensive stricturing may require extensive surgical biliary reconstruction. Recurrent primary biliary cirrhosis (PBC) was reported to occur in 12.0% [184]. The detection was prompted by abnormal liver function tests on routine monitoring. Longer follow-up may be required to determine the clinical significance of recurrent PBC. Recurrent autoimmune hepatitis (AIH) was reported to occur between 25.0-33.0% [185]. The clinical presentation of recurrence is characterized by increased transaminases (particularly AST) coupled with an increase in the serum IgG level and the presence of anti-liver specific proteins or smooth muscle antibodies. Recurrence of AIH can be precipitated by the withdrawal of prednisolone from the immunosuppressive regimen and long-term corticosteroids are usually required in these situations [186].

Problems of Graft failure after LT and risk factors for early and late graft failure

Graft failure after LD remains an important problem as it leads to patient death or retransplantation. Graft failure was reported in the world literature to range between 9.0%-27.0% [187-190]. Graft failure was categorized as early, which occurred within one month, and late, which occurred after one month from transplantation. Primary non-function (PNF) which was reported to be the commonest cause of early graft failure in cadaveric liver transplantation [190], did not occur in LDLT due to the short cold ischemic time. Factors responsible for the low rate of early graft failure in the LDLT; optimum donor selection as regards age, sex, body mass index (BMI) and ABO-compatibility; computer-assisted planning and decision making in donor segmental hepatectomy and optimum GRWR; short cold ischemic time; high level of expertise in the center; and timely detection of vascular, biliary and immunological complications responsible for early graft failure together with early and efficient management. Late graft failure cause were reported in many studies [150,191-193]. Most of the underlying causes of late graft failure include patients with CR which were not responding to treatment and patients with disease recurrence which is unavoidable. Therefore, both these complications constitute real problems in liver transplantation.

Retransplantation as a solution for graft failure and a risk factor for graft failure

In the field of LT, retransplantation may be needed to deal with patients for both early and late graft failure. Hepatic retransplantation is considered a risk factor for both graft and patient survival than primary transplantation. In 2003, Rosen found that, the age, serum bilirubin, creatinine, interval following primary transplantation as well as the UNOS status were predictive factors of outcome in patients with retransplantation [178]. In 2004, Postma studied 55 adult patients with retransplantation [194]. He found that, significant pre-transplant risk factors for unfavorable outcome include indications for transplantation other than HAT (especially CR), high creatinine level, high bilirubin level and low prothrombin level (high INR). He also found that, the era of transplantation affected the survival rate; survival at 1-year and 5-years improved from 56.0% and 48.0%, respectively before 1996 to 89.0% and 81.0%, respectively, after 1996. This is obviously related to the experience gained in overcoming the technical difficulties in dissection of the failing graft and its blood vessels. He concluded that survival rate after retransplantation is improving through the years and is presently quite high approaching the results obtained in elective cases of primary transplantation. Further improvement might be achieved by improvement of renal function before the actual retransplantation. The advances in surgical and medical care of recipients which were achieved in recent years have significantly improved patient and graft survival after the primary transplantation [195]. This situation may give a chance for the original disease to recur in the graft. Therefore, the real problem in the future will be the increase in the number of cases needing retransplantation. Efforts are needed to reduce the risk factors before retransplantation in order to obtain better patient and graft survival. However, this aim may be difficult to obtain because after primary LDLT, donor candidates among the recipient's family will be limited, forcing the selection of marginal donors (older donors, ABO-incompatible donors, small-for-size or steatotic grafts). This situation is undoubtly will be responsible for the significant graft failure and patient mortality obtained in cases of retransplantation.

Mortality after LT

Bacterial infection was a major cause of early patient mortality. Graft failure was the second major cause of mortality. Most of the mortalities occurred during hospital stay. This high rate of hospital mortality may be related to the preoperative status of the patient, the

operative factors (the duration of the operation, blood loss, blood transfusion, cold ischemic time and worm ischemic time) and the intense immunosuppression therapy in the immediate postoperative period. The age of the recipient was a significant factor in mortality. The inferior results in adult patients compared to pediatric patients may be related to the common complications associated with the right lobe grafts usually performed in adult patients as well as the problems of small-for-size grafts. UNOS status 2 A was a significant factor in patient mortality among cases with end-stage liver disease. Retransplantation among patients with graft failure was a significant factor in patient mortality [196]. This may be related to poor preoperative status, difficult surgery and exposure to the complications of intense immunosuppressive therapy. Right lobe graft was a significant factor in patient mortality. This may be due to the high rate of vascular and biliary variations in the right lobe grafts, technical difficulties in the process of transplantation and the high incidence of postoperative complications.

Summary and Conclusion

Multiple factors were studied as risk factors for graft failure**.** Factors responsible for the low rate of early graft failure in the LDLT include optimum donor selection as regards age, sex, body mass index (BMI) and ABO-compatibility; computer-assisted planning and decision making in donor segmental hepatectomy and optimum GRWR; short cold ischemic time; high level of expertise in the center; and timely detection of vascular, biliary and immunological complications responsible for early graft failure together with early and efficient management. Most of the underlying risk factors for late graft failure include patients with CR which were not responding to treatment and patients with disease recurrence which is unavoidable. Therefore, both these complications constitute real problems in liver transplantation.

It is important to remember that successful LT does not return a patient to normal. Rather a new disease "a transplanted liver" replaces the former disease. However, this new state allows patients a chance of both long-term survival and a more normal life style than were possible during the late stages of their liver disease. After LT patients must take immunosuppressive medications for the remainder of their lives. Discontinuation of the prescribed medications may lead to rejection and rapid deterioration in the patient's condition.

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