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ORIGINAL ARTICLE

Complementary Roles of Cadaveric and Living Donor Liver Transplantation in Acute Liver Failure

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Abstract

Background Living donor liver transplantation may complement cadaveric transplantation in acute liver failure (ALF) patients.
Methods Between 2008 and 2017, 89 patients were treated for ALF; 15 patients (17%) recovered with intensive care treatment; 31 (35%) died without transplant. The records of the remaining 43 patients (median (range) age: 14 (1–62)) who underwent transplantation were evaluated.
Results The etiologic factors were toxic agents (10; mushrooms: 8; herbs: 2), hepatitis viruses (7; A: 1; B: 6), Wilson's disease (7), autoimmune hepatitis (4), and Budd-Chiari syndrome (2); 13 cases were idiopathic. Cadaveric organs (whole, split, reduced) were transplanted to 32 patients; 11 patients underwent living donor transplantation. One patient (2%) died of septic shock on the second postoperative day. Bacterial infection was the most common early (< 3 months) complication in the remaining patients (31/42; 74%), followed by delirium (5/42; 12%) and acute rejection requiring steroid pulse (5/42; 12%). Seven other patients died during median (range) follow-up of 94 (14–142) months: various infections (5), leukemia (1), and acute myocardial infarction (1). The 1-, 5-, and 10-year survival rates were 100%, 96%, and 92% in children and 94%, 82%, and 65% in adults respectively.
Conclusions Cadaveric organ sharing and transplantation from living donors when appropriate yield a high survival rate, despite high early morbidity, in ALF patients whose conditions deteriorate despite intensive care treatment. Efforts to eliminate preventable causes of acute liver failure will lead to more efficient use of health care resources.

Keywords Cadaveric donor · Living donor · Mushroom poisoning · Hepatitis A · Hepatitis B · Wilson's disease

Introduction

Acute liver failure (ALF) is a rapidly progressive, life-threatening condition with a diverse etiology. Developments in specific treatments and intensive care methods have resulted in significant improvements in survival rates. Still, liver transplantation is the only treatment option for a subset of patients.[1,2] It yields satisfactory 1- and 5-year patient survival rates of approximately 85% and 75% respectively in adults and 91% and 86% in children but is limited by the availability of cadaveric organs at a short notice.[3,4] Living donor liver transplantation is a useful alternative, especially in regions

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with insufficient deceased organ support.[5–10] Although successful results have been reported, concerns about donor safety and ethical issues persist.[8,9,11–13]

In this report, we communicate our experience on the complementary roles of cadaveric and living donor liver transplantation in acute liver failure and make recommendations for a more efficient use of health care resources.

Patients and Methods

Between 2008 and 2017, 89 patients were treated for ALF; 15 patients (17%) recovered with intensive care treatment; 31 (35%) died without transplant. The records of the remaining 43 patients who underwent transplantation were evaluated. This is a retrospective study on the data of the patients who were treated at our hospital according to the best practices of the study period. Our IRB waives the need for ethical approval for these observational studies. The research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013). The content of this manuscript complies with all the rules of the "Call for an end to unethical transplant practices" by The Transplantation Society (Transplantation.2019; 103:647.) and The Declaration of Istanbul on Organ Trafficking and Transplant Tourism (Transplantation. 2008; 86:1013.).

Institutional Approach To Potential Candidates for Emergency Liver Transplantation

All acute severe hepatitis patients with an INR level higher than 1.5 were consulted immediately with the liver transplantation unit. They and their families were informed on the possibility liver transplantation, including from living donors, but also assured by their attending physicians and the transplant surgeon that maximum effort would be spent to avoid a liver transplant. Treatments with proven or possible benefit were given: antiviral agents for hepatitis B; penicillin G, carbon-filter dialysis, and plasmapheresis for mushroom poisoning; plasmapheresis for Wilson's disease; and in the second half of the study period, N-acetyl cysteine perfusion in idiopathic cases. Patients who required plasmapheresis or progressed to ALF as defined below or had ALF at admission were treated in the intensive care unit.

Definition of Acute Liver Failure

In adult patients, the standard definition of ALF was used: the development of jaundice and coagulopathy followed by hepatic encephalopathy in a patient without preexisting liver disease; acute deterioration of Wilson's disease was included as well.[2] In pediatric patients, ALF may be diagnosed in the absence of encephalopathy.[1] However, all pediatric patients who underwent liver transplant in this series had obvious neurologic symptoms.

Prioritized Allocation of Cadaveric Organs for ALF Patients in Turkey

A petition is sent online to the Organ and Tissue Department of the Ministry of Health that sends it online to three independent referees who must respond in 2 h. Consensus among 3 referees is mandatory for the prioritized allocation of all donated livers in the country to a particular center. The absence of preexisting liver disease (except Wilson's disease) and the presence of at least grade 2 encephalopathy are mandatory for all patients, including children. The approved petition must be renewed every 2 days, depending on the status of the patient with maximum possible extension to 10 days.

Decision to Perform Living Donor Liver Transplantation

In principle, all patients were considered for cadaveric transplantation. In small children, the suitability of an available cadaveric organ for splitting was considered.[14] Even when a suitable living donor was ready, transplantation was not usually performed until the potential recipient required endotracheal intubation. In such instances, an emergency cranial CT was performed to exclude severe brain damage before proceeding to surgery.

Living Donor Preparation

Actual preparation was started whenever the INR of the potential recipient exceeded 2. The most recent version of the donor preparation at our institution is summarized in Table 1. Except for minor improvements during the study period, this protocol was conducted in all potential donors regardless of recipient status except for liver biopsy: under emergency conditions, this took approximately 36–40 h. This time frame did not usually allow myocardial scintigraphy (required in all potential donors who were diabetic or older than 40 years of age), resulting in exclusion of some donors due to incomplete preparation. Still, it was possible in patients with acute/subacute presentation (interval between the onset of jaundice and encephalopathy between 7 days and 24 weeks), in contrast with the hyperacute cases (less than 7 days).[2] Because CT volumetry tends to overestimate right lobe volume,[17] a correction factor of 0.8 was used and a graft weight/body weight ration greater than 1% was required transplantations for ALF in adults. Routine liver biopsy is the norm at our institution. This was performed as a frozen section in emergency cases and this diversion from the standard procedure was included in the consent form.

Preoperative Care

Prophylactic antibiotic treatment was not given routinely to acute severe hepatitis cases and patients with mild encephalopathy. In patients with clinical, biochemical, and microbiologic findings of infection and in patients who required endotracheal intubation, cultures were taken; empirical treatment (usually ampicillin-sulbactam) was initiated and modified if necessary, according to clinical course and laboratory results. In the other patients, antibiotic treatment (usually ampicillin-sulbactam) was started just before the operation. Antifungal prophylaxis (in the earlier years: liposomal amphotericin in children and fluconazole in adults; in the more recent years: fluconazole for all patients) was started before the operation and continued for 10–14 days in the absence of documented infection.

Surgical Technique

Standard techniques of cadaveric and living donor liver transplantation were used.[18–21]

Table 1 Summary of living donor preparation

1-Up to 4th-degree relatives; age: 18–60
2-Detailed history and physical examination
3-Blood group compatibility (group A2 donors accepted); HLA "suitability" (to avoid GVHD)
4-Standard biochemical tests, infectious agent tests, and autoantibodies*
5-Leiden and protrombin mutations, proteins C and S,ATIII, antiphospholipid antibodies
6-Spirometry, echocardiography and if diabetic or older than 40 years, myocardial perfusion scintigraphy
7-CT angiography and volumetry
8-MRI-MRCP
9-Upper and if older than 50 years, lower gastrointestinal endoscopy; mammography in women older than 50
10-Psychiatric evaluation
11-Indocyanine green clearance test
12-Routine liver biopsy as a final step

GVHD, graft-versus-host disease: patients receiving partial livers from blood-related donors, inevitably have some common HLA antigens with the donor. Under particular HLA combinations in which the passenger lymphocytes in the liver graft recognize some host HLA antigens as foreign but the host lymphocytes cannot detect any foreign HLA antigens on the donor lymphocytes—the so-called donor-dominant one-way HLA matching—the risk of fatal GVHD is very high[15,16]

*Glucose, urea, creatinine, Na, K, Cl, Ca, Mg, P, complete blood count, AST, ALT, LDH, ALP, GGT, total and direct bilirubin, serum protein electrophoresis, cholesterol, triglycerides, prothrombin time, activated partial thromboplastin time, fibrinogen, ferritin, AFP, CEA, CA 19-9, CA 12-5, fT4, TSH, ceruloplasmin, VDRL-RPR, anti-HIV, anti-HAV IgG, HBsAg, anti-HBsAg, anti-HBc IgM and IgG, HBV DNA, anti-HCV, HCV-RNA, anti-CMV IgM and IgG, AKL IgM and IgG, ANA, AMA, ASMA, p-ANCA

Postoperative Care

Generally, standard immunosuppression with steroid and tacrolimus was performed. In patients with suspected but undocumented infection, the dose of steroid at reperfusion (500 mg in adults, 10 mg/kg in children) was reduced to 1 mg/kg and immunosuppression was withheld postoperatively for 48 h. Tacrolimus trough levels were adjusted to 8–10 ng/mL. Rapamycin or, more recently, everolimus was used in selected patients with acute kidney injury. Abdominal fluid samples were taken at the beginning (if present) and end of the operation. Protocol cultures were taken on the first (blood, tracheal aspirate, urine) and second postoperative days (abdominal drain fluid) as well as before urinary catheter and abdominal drain removal. In the absence of documented or suspected infection, antibiotics were stopped after INR decreased to a level below 1.5.

Survival Analysis

Survival rates were calculated according to the Kaplan-Meier method.

Results

Sixteen patients were male and 27 were female. Median (range) age was 14 (1–62) years. Seventeen patients were adults and 26 were children (≤ 17 years of age). The median (range) age of the children was 9 (1–16).

Thirty-five patients (81%) (14 adults and 21 children) were intubated at the time when the decision to transplant was made.

The underlying diseases of the transplanted patients are summarized in Table 2. Toxic hepatitis due to wild mushrooms or herbal tea (consumed for the purpose of weight loss) was the most frequent underlying cause of ALF.

Grafts

Cadaveric liver transplantation was performed in 32 patients, including 4 children who received ex situ split (3) or reduced (1) left lateral sections. The reduced graft was prepared by

Table 2 Etiology of acute liver failure in the transplanted patients

Toxic agents (mushrooms 8, herbal tea 2)	10
Viral hepatitis (HBV 6, HAV1)	7
Wilson's disease	7
Autoimmune hepatitis	4
Fulminant Budd-Chiari syndrome	2
Cryptogenic	13

performing a right trisectionectomy with hilar preservation to remove a large hydatid cyst in the right lobe. Eleven patients received grafts from living donors: 7 left lateral sections and 4 right lobes without the middle hepatic vein.

Living Donors

Six of the 11 living donors were discharged without complications.

Three donors experienced a biliary fistula (International Study Group of Liver Surgery Grade B).[22] Endoscopic sphincterotomy was necessary in one patient; the fistula was self-limited in the other two patients, but one of them required vancomycin treatment for methicillin-resistant coagulase-negative streptococci (drain fluid culture result) because small residues in deep locations caused fever.

One patient had a small fluid collection that caused mild fever; it was not suitable for percutaneous drainage and was treated by ampicillin-sulbactam.

One donor experienced an episode of respiratory difficulty that was evaluated as having a low-moderate probability for pulmonary embolism. The findings of Doppler ultrasound of the lower extremities, echocardiography, and CT-angiography were unremarkable. She had no preoperatively identified risk factor; still, she was given low-molecular-weight heparin for 6 months.

Early Mortality

An adult patient who received a cadaveric graft for ALF due to hepatitis B died with a functioning graft in clinical picture of septic shock on the second postoperative day; the 90-day mortality was 1/43 (2%).

Early Complications (in the First 90 Days)

The complications summarized in Table 3 are briefly described below:

Bacterial infection (proven and suspected) was the most common complication (74%); the diagnosis was made with positive culture results from blood, urine, tracheal aspirate-sputum and abdominal fluid samples, clinical course (general condition, liver dysfunction that cannot be accounted for by other factors), and biochemical markers of infection (leukocyte count, C-reactive protein and procalcitonin). Abdominal fluid cultures gave at least one positive result in 21 patients (50%); in 11 patients (27%), culture of the abdominal fluid samples yielded a bacterium that was not detected in other samples from the same patient, was resistant to the antibiotic (if any) the patient was receiving, and led to a change in treatment.

Delirium episodes in the early postoperative period were successfully treated with haloperidol and no long-term neurologic sequelae developed.

Table 3 Complications in the first 3 months (excluding the patient who died on POD 2)

Bacterial infections (proven and suspected)	31 (% 74)
Acute rejection requiring steroid pulse	5 (% 12)
Delirium	5 (% 12)
Catheter-related complications*	2 (% 5)
Roux-Y bleeding (self-limited)	2 (% 5)
Acute kidney injury requiring hemodialysis	1 (% 2)
Aplastic anemia	1 (% 2)
Cecal perforation	1 (% 2)
Fungal brain abscess	1 (% 2)
Fungal urinary tract infection	1 (% 2)
Nonanastomotic hepatic artery stenosis due to kinking	1 (% 2)
Refractory right-sided pleurisy due to tacrolimus	1 (% 2)
Severe posttransplant brain injury	1 (% 2)
Tetraparesia	1 (% 2)
Thrombocytopenia requiring IVIG	1 (% 2)
Thrombotic thrombocytopenic purpura	1 (% 2)
Tracheal stenosis	1 (% 2)

*Femoral pseudoaneurysm and subclavian vein thrombosis

POD, postoperative day; *IVIG*, intravenous immunoglobulin

Duct-to-duct reconstruction of the biliary tree was preferred (n:33). A Roux-Y reconstruction was performed in 10 patients; two of these patients experienced self-limited gastrointestinal bleeding episodes possibly from the jejunojejunostomy.

One child with "idiopathic" ALF developed aplastic anemia, possibly due to the same unidentified virus afflicting the liver and was barely saved from bone marrow transplantation. However, he could not receive proper immunosuppression for long periods and eventually developed chronic rejection that required retransplantation at 14 months posttransplant.

Cecal perforation could be related to pressure necrosis due to Jackson-Pratt drain abutting the edematous bowel; it was treated by a temporary colostomy.

Fever and anisocoria led to cranial imaging that showed a 1.5-cm lesion suspected to be a fungal abscess; fluconazole was switched to voriconazole (amphotericin B caused a severe allergic reaction) and the clinical findings resolved.

Kinking of the long graft artery was detected in the second postoperative month, in a 43-year-old woman who underwent cadaveric transplantation. Attempts at dilation and stenting unfortunately resulted in thrombosis. Collateral circulation to the liver developed eventually but MRCP showed secondary sclerosing cholangitis with a complex stricture at the hilus. After the initial months, she became asymptomatic except for rare cholangitis attacks under ursodeoxycholic acid treatment. She survived 116 months and died of acute myeloid leukemia.

An adult patient who underwent cadaveric liver transplant for ALF due to hepatitis B developed severe right-sided

pleurisy that required tube thoracostomy twice to avoid a mediastinal shift; an exhaustive investigation into the likely causes (cardiac, hepatic, infectious) was futile; eventually switching from tacrolimus to cyclosporine led to marked improvement in 5 weeks and eventual resolution.

A 17-month-old girl underwent living donor liver transplantation for cryptogenic ALF. Her preoperative CT showed moderate-to-severe brain edema but no evidence of herniation. The operation was uneventful but severe brain damage requiring prolonged intensive care occurred. She is currently at home but requires close supportive care.

A 9-year-old boy underwent cadaveric transplantation for mushroom poisoning after 5 days of endotracheal intubation. During hilar dissection, after ligation and division of the hepatic arteries and the common hepatic duct, the anesthesiologist reported that pupillary reflex disappeared and the pupillae had become fixed dilated. A decision whether to abort or proceed had to be made. The liver from a 72-year-old donor had been sent by plane from a distant city and taken to the operation table. It was unlikely that the liver could be used in another recipient. The operation was continued. The graft showed good early function. However, the pupils remained dilated until 10 h after abdominal closure. Then, dilation started to resolve and the pupillary reflex returned. He regained consciousness and was extubated on the 4th postoperative day. However, he was tetraparesic. He was admitted to the ward on the 7th postoperative day. Full functional recovery could be achieved with 4 weeks of intense physical rehabilitation, and he was discharged to his home on the 40th postoperative day.

Tacrolimus may be implicated in the thrombotic thrombocytopenic purpura; plasmapheresis yielded a successful outcome and tacrolimus was switched to cyclosporine.

Tracheal stenosis was ascribed to prolonged intubation and was successfully treated with removable stents.

Long-term Follow-up

Median range follow-up was 94 (14–42) months. The 1-,5-, and 10-year survival rates were 100%, 96%, and 92% in children and 94%, 82%, and 65% in adults respectively.

During long-term follow-up, retransplantation was successfully performed in two patients. One of these was the patient with aplastic anemia described above. The other patient, a 12-year-old boy, underwent emergency cadaveric liver transplantation for cryptogenic ALF. At 6 years posttransplant, he developed biochemical abnormalities that were ascribed initially to redundancy and functional stenosis of the duct-duct reconstruction. ERCP and stenting were ineffective. Liver biopsy showed chronic liver disease due to overlap syndrome (autoimmune hepatitis and primary sclerosing cholangitis); reexamination of the initial explant showed massive necrosis that obscured very occasional areas of periductal concentric fibrosis. The original diagnosis was revised as autoimmune hepatitis. He underwent successful retransplantation with a right lobe from a living donor.

Seven other patients died in the second (pneumonia one patient, fungal infection precipitated by ATG treatment for steroid-resistant rejection one patient), third (sepsis), fifth (sepsis), seventh (pneumonia), and tenth (acute myeloid leukemia one patient, acute myocardial infarction one patient) posttransplant years. Compliance-related problems contributed to the delays in the final admissions of two patients: the patients who died of pneumonia in the second year and sepsis in the third year. All brothers of the first patient (a single, 28-year-old man) and the husband of the second patient were drug addicts; to the best of our information, the patients were not. In other words, their social support was not optimal. Within the limited time available, it was decided that we could collaborate with the parents of the first patient in his return to normal life. The second patient has postpartum Budd-Chiari syndrome; she had given birth to a healthy child. It was decided that her parents would support her. She made an unsuccessful suicide attempt in the third year and did not adhere to psychiatric treatment.

Discussion

One disturbing aspect of this otherwise successful series is that about one-third of the patients died without transplant. This is due to three factors. First, the number of liver transplant centers in Istanbul increased to 16 during the study period and 12 of these are foundation university or private hospitals. During the first half of the study period, some of these hospitals were reluctant to accept severe hepatitis patients without potential living donors because the cadaveric donation rate in Turkey was very low. In other words, the transplantation probability of a patient at a government university hospital was comparatively lower than the probability at other institutions due to referral/admission bias. The recent increase in the donation rate (to approximately 7–8 per million population) and competition between centers possibly led to a more relaxed policy and consequently, a more random distribution of patients, except for small children who are accepted by a limited number of centers. The second reason is that the detailed donor preparation summarized in Table 1 was conducted diligently except for the liver biopsy. In practical terms, there was usually not enough time to exclude coronary heart disease in potential donors who were diabetic or older than 40 years of age. Death due to myocardial infarction, of a 39-year-old donor [23] with a negative stress EKG test, shows that absolute safety is not possible but supports our policy of using myocardial perfusion scintigraphy. Third, ABO incompatible transplantation was not performed due to concerns about the already high infection rate. There were unfortunately no blood group A2 donors whom we accept as "blood group-compatible" if there are no other candidates.[24]

Infection, the most common early complication was observed in approximately 74% of the cases but was not associated with early mortality. At an initial glance, this seems counterintuitive. However, the high figure probably results from two factors: first, ALF is a strong predisposing factor even before surgery.[1,2] In the ELTR database, "infections were the major cause of death/graft failure".[3] Second, aggressive surveillance, including abdominal fluid cultures, resulted in the improved detection of clinically insidious infections but allowed early and aggressive intervention (antibiotics, reduction, or even cessation of immunosuppression). Abdominal fluid cultures are included in the clinical protocols of many transplant centers. However, the published experience on the actual results is limited.[25] A positive culture result was the main finding that led to a change in treatment in 11 patients. In other words, a significant complication would have been missed if surveillance had been limited to blood, urine, and tracheal aspirate/sputum cultures. A potential weakness is that a culture result positive for a highly susceptible gram-positive microorganism was evaluated as clinically insignificant (contamination during sampling), reflecting a risk of overdiagnosis (data not shown). Measurement of the abdominal fluid neutrophil count and LDH level, as reported by Sanada et al., may be confounded by postoperative inflammation in the first postoperative day but may be useful after the fifth postoperative day.[25]

Postoperative delirium is a recognized complication of liver transplantation; it is associated with parameters reflecting higher disease severity.[26,27] Therefore, it is not surprising that it was observed in 5 (12%) of the patients in this series.

The experience reported here demonstrates 4 weaknesses of liver transplantation in the treatment of ALF:

1. The point of no return in terms of neurologic recovery has not been defined.[28–30] Although the presence of severe brain edema increases the risk of posttransplant brain injury, neurologic recovery is possible in half of the cases.[29] A child who had moderate-to-severe brain edema but not brain death had severe posttransplant brain injury although the graft from the living donor functioned immediately after implantation. Another child whose pupillary reflex was lost during the operation regained consciousness in a tetraparesic state on the 4th postoperative day; he fortunately achieved full functional recovery with intensive physical therapy. Of course, if the disappearance of the light reflex had been noted in the intensive care unit, transplantation would have been cancelled.
2. Sometimes the liver is not the only organ involved. One child with "idiopathic" ALF developed aplastic anemia, possibly due to the same unidentified virus afflicting the liver [31,32] and was barely saved from bone marrow transplantation. However, he could not receive proper immunosuppression for long periods and eventually developed chronic rejection that required retransplantation.
3. In many cases, the histological picture is so severe that clues to the original disease process obscured by the extensive necrosis or may be practically absent. One patient developed cirrhosis 6 years after transplant. In retrospect, examination of the original sections revealed subtle clues of an overlap syndrome.
4. The psychiatric evaluation is compromised by the possibility of encephalopathy at admission. Also, time constraint is a problem for both psychiatric evaluation and assessment of social support. In some instances, the transplant team feels compelled to "give the benefit of doubt," i.e., to proceed with transplantation in the face of warning signs that would lead to further investigations in the elective setting. This problem has been recorded in 8% of the patients in the ELTR database.[3]

It has been argued that living donor liver transplantation in ALF creates an ethical hazard because the donor candidate does not have enough time to fully contemplate on the implications of their decisions.[11] Also, time constraints may compel the transplant team to skip some of the components of the regular donor preparation. In the series reported here, all preparations in the standard preparation were but liver biopsy was modified; a frozen section was used.

Finally, 24 of the 43 recipients had a preventable underlying disease. Better public education on mushroom poisoning and weight loss supplements would be effective. "Universal" vaccination for hepatitis A and B is an achievable goal in Turkey because the government provides unrestricted health insurance for all children. Family planning would be effective in decreasing the frequency of Wilson's disease or at least early identification of the patients at the asymptomatic stage.

Conclusion

Improved cadaveric organ sharing, use of split grafts when possible, and transplantation from living donors in appropriate situations yield a high survival rate, despite high early morbidity, in acute liver failure patients whose condition deteriorates despite intensive care treatment. Efforts to eliminate preventable causes of acute liver failure will lead to more efficient use of health care resources.

Data Availability Data will be made available to the referees if required.

Author contribution Study conception and design: İÖ, HAY, ÖD, SK
Acquisition of data: all authors
Analysis and interpretation of data: all authors
Drafting of manuscript: İÖ
Critical revision of manuscript: all authors

Code availability Not applicable

Declarations

Ethics approval This is a retrospective study on the data of the patients who were treated at our hospital according to the best practices of the study period. Our IRB waives the need for ethical approval for these observational studies. The research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013). The content of this manuscript complies with all the rules of the "Call for an end to unethical transplant practices" by The Transplantation Society (Transplantation.2019;103:647.) and The Declaration of Istanbul on Organ Trafficking and Transplant Tourism (Transplantation. 2008 ;86:1013.).

Consent for publication All patients gave permission for anonymous publication of their data at the time of admission to the hospital.

Consent to participate All patients gave consent for treatment at our hospital. This is a retrospective analysis of standard clinical practice at our hospital.

Competing interests The authors declare no competing interests.

References

1. Lutfi R, Abulebda K, Nitu ME, Molleston JP, Bozic MA, Subbarao G (2017). Intensive care management of pediatric acute liver failure. J Pediatr Gastroenterol Nutr. 64:660-670. https://doi.org/10.1097/MPG.0000000000001441.
2. Stravitz RT, Lee WM (2019). Acute liver failure. Lancet.394(10201):869-881. https://doi.org/10.1016/S0140-6736(19)31894-X.
3. Germani G, Theocharidou E, Adam R, Karam V, Wendon J, O'Grady J et al (2012). Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol. 57:288-296. https://doi.org/10.1016/j.jhep.2012.03.017.
4. Kwong A, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA et al. (2020).OPTN/SRTR 2018 Annual Data Report:Liver. Am J Transplant. 20 Suppl S1:193-299. https://doi.org/10.1111/ajt.15674.
5. Kılıç M, Aydin U, Noyan A, Arıkan Ç, Aydoğdu S, Akyıldız M et al. (2007) Live donor liver transplantation for acute liver failure. Transplantation. 84:475-479. https://doi.org/10.1097/01.tp.0000276987.55382.e2
6. Yamashiki N, Sugawara Y, Tamura S, Nakayama N, Oketani M, Umeshita K et al. (2012) Outcomes after living donor liver transplantation for acute liver failure in Japan: results of a nationwide survey. Liver Transpl.18:1069-1077. https://doi.org/10.1002/lt.23469.
7. Yankol Y, Ertugrul M, Kanmaz T, Mecit N, Ocak I, Durmaz O, Acarli K,et al. (2016)Management of pediatric acute liver failure in a region with insufficient deceased donor support: A single-center experience. Exp Clin Transplant.14:535-541. https://doi.org/10.6002/ect.2015.0008.
8. Gupta A, Asrani SK. (2019) Role of living donor liver transplantation in acute liver failure. Liver Transpl. 25:1308-1309. https://doi.org/10.1002/lt.25610.
9. Pamecha V, Vagadiya A, Sinha PK, Sandhyay R, Parthasarath K, Sasturkar S et al. (2019) Living donor liver transplantation for acute liver failure: Donor safety and recipient outcome. Liver Transpl. 25:1408-1421. https://doi.org/10.1002/lt.25445.
10. Sahin TT, Sarici KB, Kilci B, Koç C, Otan E, Karakaş S et al. (2019) Factors influencing mortality following liver transplant in acute liver failure: A single center experience. Exp Clin Transplant. https://doi.org/10.6002/ect.2019.0096
11. Marino IR, Doyle HR.(2002) Living donor in urgent cases: ethical hazard? Liver Transpl 8:859-860. https://doi.org/10.1053/jlts.2002.35187.
12. Erim Y, Beckmann M, Kroencke S, Valentin-Gamazo C, Malago M, Broering D et al. (2007) Psychological strain in urgent indications for living donor liver transplantation. Liver Transpl.13:886-895. https://doi.org/10.1002/lt.21168.
13. Levitsky J, Gordon EJ. (2020) Living donor liver transplantation when deceased donor is not possible or timely: Case examples and ethical perspectives. Liver Transpl 26:431-436. https://doi.org/10.1002/lt.25708.
14. Valentino PL, Emre S, Geliang G, Li L, Deng Y, Mulligan D et al. (2019) Frequency of whole-organ in lieu of split-liver transplantation over the last decade: Children experienced increased wait time and death. Am J Transplant. 19:3114-3123. https://doi.org/10.1111/ajt.15481.
15. Kiuchi T, Harada H, Matsukawa H, Kasahara M, Inomata Y, Uemoto S et al (1998). One-way donor-recipient HLA-matching as a risk factor for graft-versus-host disease in living-related liver transplantation. Transpl Int. 11 Suppl 1:S383-384.
16. Kamei H, Oike F, Fujimoto Y, Yamamoto H, Tanaka K, Kiuchi T (2006). Fatal graft-versus-host disease after living donor liver transplantation: differential impact of donor-dominant one-way HLA matching. Liver Transpl.12:140-145.
17. Yoneyama T, Asonuma K, Okajima H, Lee KJ, Yamamoto H, Takeichi T et al. (2011) Coefficient factor for graft weight estimation from preoperative computed tomography volumetry in living donor liver transplantation. Liver Transpl.17:369-372. https://doi.org/10.1002/lt.22239
18. Klintmalm GBG, Busuttil RW Recipient hepatectomy and grafting. In: Busuttil RW and Klintmalm GBG,eds. In: Transplantation of the Liver. 3rd ed. Philadelphia:Elsevier-Saunders; 2015:600-610.
19. Tanaka K, Inomata Y. Living donor transplantation in children. In: Busuttil RW and Klintmalm GBG,eds. In: Transplantation of the Liver. 3rd ed. Philadelphia:Elsevier-Saunders; 2015:642-658.
20. Lo CM, Chan SC. Adult living donor right hepatectomy and recipient operation. In: Busuttil RW and Klintmalm GBG,eds. In: Transplantation of the Liver 3rd ed. Philadelphia:Elsevier-Saunders; 2015:667-675.
21. Vilca-Melendez, Heaton ND. Split liver transplantation for pediatric and adult recipients. In: Busuttil RW and Klintmalm GBG,eds. In: Transplantation of the Liver 3rd ed. Philadelphia:Elsevier-Saunders; 2015:690-701.
22. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L et al. (2011) Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery.149:680-688. https://doi.org/10.1016/j.surg.2010.12.002.
23. Polido W Jr, Hoe LK, Siang NK, Chah TK.(2007) Acute myocardial infarction after live donor liver surgery. Liver Transpl.13:154-156. https://doi.org/10.1002/lt.21002.
24. Kluger MD, Guarrera JV, Olsen SK, Brown RS Jr, Emond JC, Cherqui D. (2012). Safety of blood group A2-to-O liver transplantation: an analysis of the United Network of Organ Sharing database. Transplantation.94:526-531. https://doi.org/10.1097/TP.0b013e31825c591e.
25. Sanada Y, Kawano Y, Urahashi T, Ihara Y, Wakiya T, Okada N et al. (2015) Examinations of ascites from prophylactic drains can predict intra-abdominal infections after living donor liver

transplantation. Pediatr Transplant. 19:595-604. https://doi.org/10.1111/petr.12549.
26. Wang SH, Wang JY, Lin PY, Lin KH, Ko CJ, Hsieh CE et al. (2014) Predisposing risk factors for delirium in living donor liver transplantation patients in intensive care units. PLoS One. 9: e96676. https://doi.org/10.1371/journal.pone.0096676.
27. Lee H, Oh SY, Yu JH, Kim J, Yoon S, Ryu HG. (2018) Risk factors of postoperative delirium in the intensive care unit after liver transplantation. World J Surg. 42:2992-2999. https://doi.org/10.1007/s00268-018-4563-4.
28. Chan G, Taqi A, Marotta P, Levstik M, McAlister V, Wall W et al. (2009) Long-term outcomes of emergency liver transplantation for acute liver failure. Liver Transpl.15:1696-1702. https://doi.org/10.1002/lt.21931.
29. Tan WF, Steadman RH, Farmer DG, Hong JC, Busuttil RW, Apinyachon W et al. (2012) Pretransplant neurological presentation and severe posttransplant brain injury in patients with acute liver failure. Transplantation. 94:768-774. https://doi.org/10.1097/TP.0b013e3182620596.
30. Yang HR, Thorat A, Jeng LB, Hsu SC, Li PC, Yeh CC, et al.(2018) Living donor liver transplantation in acute liver failure patients with grade IV encephalopathy: Is deep hepatic coma still an absolute contraindication? A successful single-center experience. Ann Transplant. 23:176-181. https://doi.org/10.12659/AOT.907274.
31. Aydoğdu S, Tümgör G, Karapınar DY, Karapınar B, Arıkan Ç, Kılıç M et al.(2011) Severe aplastic anemia following liver transplantation in a patient with non-A-E fulminant hepatitis. Turk J Gastroenterol. 22:337-340. https://doi.org/10.4318/tjg.2011.0222.
32. Di Giorgio A, Sonzogni A, Piccichè A, Alessio G, Bonanomi E, Colledan M et al. (2017) Successful management of acute liver failure in Italian children: A 16-year experience at a referral centre for paediatric liver transplantation. Dig Liver Dis. 49:1139-1145. https://doi.org/10.1097/MPG.0000000000000593.