ORIGINAL ARTICLE

Liver transplantation in patients with sickle cell disease: possible but challenging—a cohort study

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SUMMARY

The liver is frequently affected in patients with sickle cell disease (SCD), but few reports have described liver transplantation (LT) in patients with SCD. We present a thorough analysis of the largest single-center series of LT in patients with SCD and the first systematic review. There were 21 patients with a median age of 37.6 years. LT was performed for acute liver failure related to the sickling process (57%) or electively for end-stage liver disease (43%). Prior to LT, 13 patients (62%) were in the intensive care unit and required mechanical ventilation (33%), vasopressor therapy (24%), renal replacement therapy (10%), or molecular adsorbent recirculating system therapy (19%). Post-LT morbidity and mortality were 95% and 33%, respectively. Patient survival at 1 and 5 years were 58.3% and 41.7%, respectively, in the urgent group and 88.9% and 77.8%, respectively, in the elective group. A total of 22 transplant patients with SCD are described in 20 articles in the literature. The 1- and 5-year patient survival rates for the 18 evaluable patients were 75% and 65%, respectively. LT improves survival in patients with SCD and acute liver failure or end-stage liver disease but is associated with high morbidity during the early postoperative course.

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Introduction

Sickle cell disease (SCD) is the most common monogenic disease worldwide, affecting more than 300 000 newborns each year [1]. There are approximately 100 000 people with SCD in the United States and 3 million worldwide [2]. SCD is an inherited multiorgan disorder characterized by the presence of pathologic hemoglobin S. In SCD, the presence of abnormal erythrocytes (i.e., sickle cells) leads to hemolytic anemia and vaso-occlusive crises affecting all tissue and organs. In developed countries, SCD has evolved into a debilitating chronic disorder with significant morbidity due to organ damage. The liver is one of the affected organs, causing sickle hepatopathy, which pathologically involves sickling within hepatic sinusoids and leads to vascular stasis and localized hypoxia. However, SCD hepatopathy covers a wide variety of pathologies, both acute and chronic, that occur as a consequence of the sickling process, including gallstone disease, hypoxic liver injury, hepatic sequestration, venous outflow obstruction, hepatic crises, and sickle cell intrahepatic cholestasis (SCIC) [3]. SCIC is a severe subtype, though the outcome of acute SCIC has been vastly improved by exchange blood transfusion (EBT); in chronic SCIC, there is limited evidence for EBT programs as a therapeutic option. Moreover, clinicopathological features are aggravated by liver iron overload that results from cumulative red cell transfusions and by associated liver diseases such as autoimmune and post-transfusional hepatitis C. Altogether, these liver diseases can be very severe and irreversible, leading to the discussion of liver transplantation as a salvage therapy. In practice, LT can be indicated in two settings [4]: acute liver failure mimicking fulminant hepatitis and end-stage chronic liver disease. Data regarding liver transplantation (LT) in patients with SCD are limited to mostly case reports (Table 1) [5-24]. Because of the paucity of data available regarding the indications for LT and perioperative outcomes as well as the lack of long-term follow-up in most reported cases, the present study entailed a thorough analysis of a large single-center experience of LT in patients with SCD.

Patients and methods

All consecutive patients with SCD listed for deceased donor LT who eventually underwent transplantation from 1990 to 2018 at the Liver Transplantation Unit (Henri Mondor University Hospital, Créteil, France) were retrospectively analyzed. All patients were previously followed in the adult SCD referral center of our institution [25,26]. The study was approved by the hospital's ethics committee, and the database was officially registered with the French Data Protection Authority (Commission Nationale Informatique et Liberté; Registration Number: 1699340). The present study complies with the guidelines endorsed by the STROBE consortium [27].

LT indication and graft allocation

The patients with transplant were divided into two groups. The first group included patients who underwent urgent LT (ULT) due to severe acute liver failure; for these patients, the transplantation occurred within 4 days following the listing. The second group included patients who underwent elective LT (ELT) for chronically decompensated underlying liver disease. The grafts were allocated following the "liver score" mainly based on the Model for End-Stage Liver Disease (MELD) score [28].

Perioperative management

All patients were managed by a multidisciplinary team including hepatologists, hematologists specialized in the management of SCD, anesthesiologists/intensivists, and LT surgeons. All transplantations were performed with deceased donor grafts and using standard surgical techniques. The perioperative anesthetic strategy was extrapolated from nontransplant surgery [29] and French guidelines for the management of adult SCD, originating from our center [26], and aimed to achieve optimal oxygenation, hydration, perfusion, thermoregulation and analgesia.

Red blood cells, plasma, and platelets were transfused as dictated by the results of repeated blood tests and, during surgery, constant communication with the surgeons regarding coagulopathy and hemorrhage in the operative field. Transfusion and blood exchange transfusions were adapted to maintain the hemoglobin (Hb) S fraction at $< 30\%$ and the Hb level at between 8 and 10 g/dl during the entire perioperative period.

Our immunosuppression protocol regarding transplanted patients with SCD has been previously described [16]. Immunosuppression included calcineurin inhibitor-based, mycophenolate mofetil or rabbit antithymocyte globulin (day 0–4). The blood calcineurin inhibitor levels should be maintained at the lowest dose in combination with induction therapy and mycophenolate mofetil.

Perioperative prophylaxis for bacterial, viral, and fungal infections was applied as indicated for high-risk patients [30]. Multimodal analgesia relied on nefopam and/or opioids.

Table 1. Studies reporting liver transplantation in patients with sickle cell disease.

First author, year	Cases	Sex, age (years)	Urgent versus elective	Indication for LT	Hb type	Target Hb-S post-LT	Outcome
Olivieri, 1994* [21]	1	M, 26	Urgent	Iron cirrhosis	Hb-S β thalassemia	NA	Alive, 18 months
Kindscher, 1995 [17]	1	F, 47	NA	HCV cirrhosis	HbSS	<30%	Alive, 3 months
Lang, 1995 [18]	1	M, 11	Elective	Biliary cirrhosis	HbSS	<20%	Alive, 24 months
Lerut, 1999 [19]	1	F, 42	NA	Cryptogenic cirrhosis	Hb-S β thalassemia	<10%	Alive, 30 months
Emre, 2000 [12]	1	M, 6	NA	ALF due to SCIC	HbSS	<20%	Died (sepsis), 6 months
Gilli, 2002 [14]	1	M, 22	Elective	SCIC	Hb-S β thalassemia	<20%	Alive, 24 months
Ross, 2002† [23]	1	M, 49	Urgent	ALF due to SCIC	HbSS	<20%	Died (pulmonary embolism), 22 months
Van den Hazel, 2003 [24]	1	M, 23	Elective	Secondary hemochromatosis	HbSS	<20%	Alive, 5.5 years
Baichi, 2005 [8]	2	F, 26–27	Urgent (n = 1) Elective (n = 1)	ALF due to SCIC Primary sclerosing cholangitis	HbSS	<10%	Died (abdominal bleeding and multiorgan failure), 35 days Died (cerebral hemorrhage and multiorgan failure), 85 days
Delis, 2007 [11]	1	F, 19	Elective	HBV cirrhosis	HbSS	NA	Alive, 17 months
Meekel, 2007 [20]	3	NA, 8–17	Urgent (n = 1) Elective (n = 2)	ALF due to SCIC (n = 1) SCIC (n = 1), HCV + SCIC (n = 1)	NA	<25%	Died (subdural hematoma, n = 1), 6 years Alive (n = 2), NA
Berry, 2007 [9]	1	NA, 17	NA	Autoimmune cirrhosis	HbSS	NA	Died postoperatively, NA
Greenberg, 2009 [15]	1	F, 30	Urgent	ALF due to unknown origin	HbSS	<30%	Alive, 28 days
Perini, 2010 [22]	1	M, 37	Urgent	Iron and HCV cirrhosis	Hb-S β thalassemia	<30%	Died (intracerebral hemorrhage), 5 months
Blinder, 2013 [10]	1	M, 37	Elective	Chronic SCIC	HbSS	<30%	Alive, 12 months
Gardner, 2014 [13]	1	M, 33	Elective	Chronic SCIC	HbSS	<30%	Alive, 24 months
Alder, 2016 [7]	1	F, 5 months	NA	Recurrent episodes of cholangitis after Kasai procedure	NA	NA	Alive, 6 months
Loh, 2018 [6]	1	M, 24	Elective	Primary sclerosing cholangitis	HbAS	NA	Alive, NA
Kwun Lui, 2018 [5]	1	M, 29	Urgent	ALF due to SCIC	HbSS	NA	Alive, 7 months

ALF, acute liver failure; F, female; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplantation; M, male; NA, not available; SCH, sickle cell hepatopathy; SCIC, sickle cell intrahepatic cholestasis.

Note that the present series included six patients described in our previous publication (Hurtova *et al.* [16]).

*Combined heart transplantation.

†Combined kidney transplantation.

Perioperative data were retrieved from the prospectively maintained databases of the Agence Nationale de Biomédecine (CRISTAL database) and our center. Data in these files were available as of April 2019. The donor risk index (DRI) score [31] and balance of risk (BAR) score [32] were calculated.

The presence of organ failure was classified according to a modified version of the CLIF-SOFA scale [33]. The types of organ failure evaluated were as follows: (i) circulatory failure, defined as the use of a vasopressor (epinephrine, norepinephrine, or dopamine); (ii) respiratory failure, defined as being on mechanical ventilation; (iii) renal failure, defined as serum creatinine > 170 μmol/l or the need for renal replacement therapy; (iv) coagulation failure, defined as an International Normalized Ratio (INR) ≥ 2.5 or a platelet count < $20 \times 10^3/mm^3$; (v) cerebral failure, defined as hepatic encephalopathy grade 3–4; and (vi) liver failure, defined as total bilirubin> 204 μmol/l. The number of organ failures was dichotomized as ≤ 2 or < 2.

Postoperative morbidity and mortality were assessed within 90 days of transplantation. Postoperative morbidity was classified according to the Clavien–Dindo classification system [34]. Primary nonfunction was defined as immediate graft failure, with no discernible cause leading to death or urgent retransplantation. Early allograft dysfunction was defined as in Oltoff *et al.* [35]. Acute cellular rejection is considered to require increased immunosuppression [36].

Systematic review

A systematic review of the literature pertaining to LT for SCD was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study selection criteria were defined before initiating data collection to ensure the identification of studies eligible for the analysis. All studies in which the primary objective was to describe LT in SCD patients were retrieved and analyzed.

The literature search was performed in the following online databases: MEDLINE (through PubMed), Embase, Google Scholar, Scopus, and KoreaMed. To increase the probability of identifying all relevant articles, a specific research equation was formulated for each database using the following keywords and/or MeSH terms: "liver transplantation", "orthotopic liver transplantation", "liver transplant", "transplantation and sickle cell anemia", "sickle cell anemia", "sickle cell disease", "sickle cell", and "sickle beta-thalassemia" (Fig. S1). In addition, the reference lists from eligible studies and relevant review articles (not included in the systematic review) were crosschecked to identify additional records. The literature search was performed in April 2019, and no time restriction was applied. Only studies written in English or French that met the selection criteria were reviewed. We pooled data from all individually documented patients to assess the overall patient and graft survival after LT for SCD.

Statistical analysis

Continuous variables are presented as medians (ranges) or numbers (%). Comparisons of variables in patients at the time of LT between patients who underwent ULT or ELT were performed using the Mann–Whitney test for continuous variables and chi-squared tests for categorical variables. Overall survival was defined as the interval from the date of LT to the date of death or the date of last follow-up. Survival curves were plotted by the Kaplan–Meier method and compared using log-rank tests. Data were analyzed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA). All tests were two-tailed, and results with a *P* value lower than 0.05 were considered statistically significant. No patient was lost to follow-up.

Results

From 1990 to 2018, 29 consecutive patients with SCD were listed for LT. Eight patients were withdrawn from the waiting list due to improvement under blood exchange (four patients) or death (three patients with multiorgan failure and one with massive stroke).

Characteristics of SCD patients at the time of LT

The study population (Fig. 1) included the remaining 21 patients with transplant, with 12 (57%) undergoing ULT and 9 (43%) undergoing ELT. The patient characteristics at the time of transplant are summarized in Table 2. There were 13 male and eight female adult patients, with a median age of 37.6 years. The SCD type was homozygous S/S in 12 patients (57%), Sß° thalassemia in seven patients (33%), and heterozygous S/C in two patients (10%). In their past history, all had at least one vaso-occlusive crisis, 20 (95.2%) had received multiple blood transfusions, 7 (33%) had at least one episode of acute chest syndrome, and 5 (24%) and 6 (28%) had undergone cholecystectomy or splenectomy, respectively.

The median preoperative level of Hb-S was 26% (10–35). Twenty patients (95%) received preoperative exchange blood transfusion to achieve preoperative Hb-S < 30%: 11 (92%) in the case of acute liver failure and

9 (100%) in the case of elective LT. At least one underlying additional liver disease was present in 17/21 patients (81%): all of the patients in the ELT group and 8/12 (67%) in the ULT group.

At the time of LT, 13 patients (62%) were intensive care unit (ICU) bound, 5 (24%) were hospital bound, and 3 (14%) were at home. In the study population, the median MELD score, DRI, and BAR score were 34, 1.77, and 15, respectively, and 15 patients had at least 2 organ failures. All the above-reported values were higher in the subset of patients with ULT compared to the subset of patients with ELT, but the difference reached statistical significance only for the BAR score and number of patients with at least 2 organ failures.

The study population represented 2% of the single first transplants performed at our center ($n = 1051$, including 991 ELT and 60 ULT) and 0.5% of the cohort of adult patients ($n = 4000$) followed at our national SCD reference center during the study period.

Intraoperative data

Intraoperative data are described in Table S1. The median transfusion volume of red blood cells was eight units. There was no significant difference between the ULT group and ELT group for any of the intraoperative variables studied.

Postoperative mortality (90 days)

Early post-transplant outcomes are summarized in Table 3. Five patients died within 90 days (90-day mortality rate = 24%) of transplantation, with a median delay of 13 (3–56) days. The primary complications leading to death were portal vein thrombosis, acute rejection, SCD crisis, primary nonfunction, and stroke, with one case each. At the time of death, all five patients had a combination of multiple organ failure and sepsis. Four of these patients were in the ULT group (4/12, 33%); one was in the ELT group (1/9 11%). Twenty patients experienced 82 complications within 90 days of LT (morbidity rate = 95%), with a median of four complications (range 0–7 complications). Severe complications (grade III or IV) occurred in seven patients in each group. As shown in Table 2, the most frequent complications were infectious (71%), neurological (66%), renal (62%), and vascular (19%) events. In the entire study population, the median stay in the ICU was 21 (2–89) days, and the median hospital stay was 36 (2–79) days.

Long-term survival

Among the 16 patients surviving more than 90 days and with a mean follow-up period of 45.8 (0–138) months, three patients died at 15, 16, and 46 months

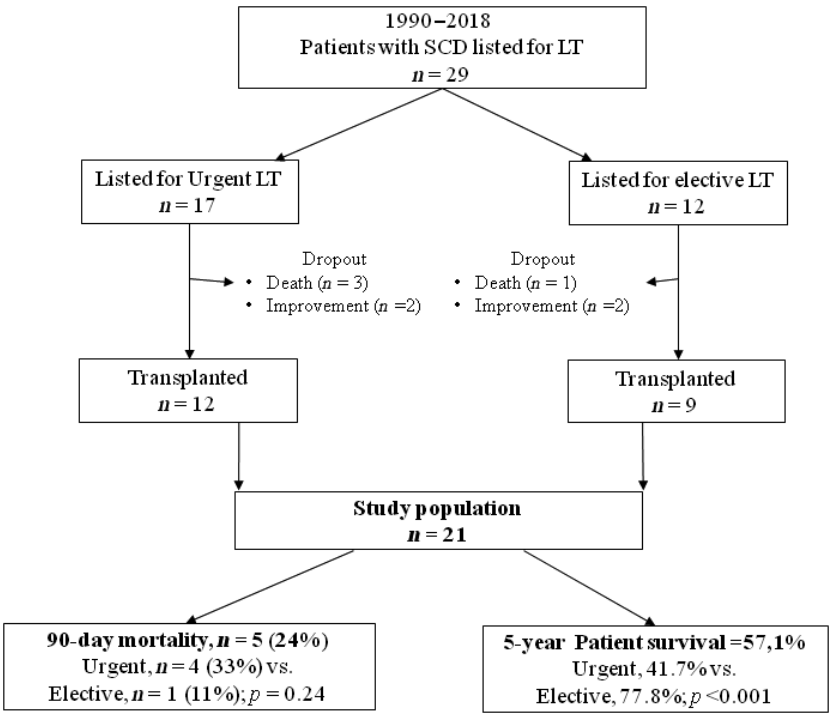

Figure 1 Flowchart.

Table 2. Clinical and biological characteristics at the time of liver transplantation.

	Total (n = 21)	Urgent LT (n = 12)	Elective LT (n = 9)	P value
Clinical data				
Age (years)	38 (19–48)	39 (19–48)	38 (23–45)	0.29
Sex male/female	13 (62)/8 (38)	8 (67)/4 (33)	5 (56)/4 (44)	0.60
Body mass index (kg/m^2)	20 (15–26)	23 (19–26)	19 (15–24)	0.13
SCD type				
Sβ°thalassemia	7 (33)	5 (42)	2 (22)	0.20
S/C	2 (10)	2 (17)	0 (0)	
S/S	12 (57)	5 (42)	7 (78)	
SCD history				
Vaso-occlusive crisis	17 (81)	9 (75)	8 (88)	0.60
Acute chest syndrome	7 (33)	4 (33)	3 (33)	0.99
Exchange blood transfusion	20 (95)	11 (92)	9 (100)	0.37
Underlying liver disease*				
HBV	4 (19)	2(17)	2 (22)	0.74
HCV	6 (43)	4 (33)	2 (22)	0.57
Cirrhosis with iron overload	8 (38)	5 (42)	3 (33)	0.69
Autoimmune hepatitis	3 (14)	1(8.3)	2 (22)	0.37
Primary sclerosing cholangitis	2 (10)	0 (0)	2 (22)	0.08
MELD score	34 (16–40)	38 (16–40)	30 (16–40)	0.22
MELD> 30	13 (62)	8 (75)	5 (55)	0.60
MELD = 40	7 (33)	6 (50)	1 (11)	0.06
DRI score	1.77 (1.24–3.12)	1.82 (1.4–3.12)	1.6 (1.24–2.9)	0.51
BAR score	15 (6–25)	16.5 (70–21)	10 (6–18)	0.03
Location before liver transplant				
Home	3 (14)	0 (0)	3 (33)	0.03
Ward or intensive care unit	18 (86)	12 (100)	6 (66)	
Organ failures prior to liver transplant				
Encephalopathy	13 (62)	9 (75)	4 (44)	0.15
Acute renal failure	13 (62)	9 (75)	4 (44)	0.15
Renal replacement therapy	2 (10)	1 (8)	1 (11)	0.83
Mechanical ventilation	7 (33)	5 (42)	2 (22)	0.35
Vasopressor	5 (24)	4 (33)	1 (11)	0.24
≥2 organ failures	15 (71)	12 (100)	3 (33)	0.002
Biological parameters				
INR	2.3 (1–15)	2.9 (1.3–15)	1.7 (1–3.2)	0.06
Total bilirubin (μmol/ml)	411 (50–1320)	416 (50–768)	411 (139–1320)	0.54
Aspartate aminotransferase (IU/l)	162 (65–13 364)	280 (65–13 364)	135 (105–4049)	0.16
Alanine aminotransferase (IU/l)	80 (28–8461)	178 (30–8461)	71 (28–658)	0.27
Creatinine (μmole/ml)	139 (24–344)	178 (72–305)	79 (24–344)	0.17
Hemoglobin (g/dl)	8.7 (5.8–10.6)	8.2 (7.2–9.4)	8.9 (5.8–10.6)	0.60
Platelet count (×10^9/l)	128 (32–930)	112 (95–930)	131 (48–283)	0.99

Data are expressed as the median (range) or number of patients (%).

ALF, acute liver failure; BAR, balance of risk; DRI, donor risk index[32]; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, internationalized ratio; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; SCD, sickle cell disease.

*Some patients had multiple liver diseases.

after LT due to stroke, unknown cause, and septicemia, respectively. The patient survival rates were 71.4% and 57.1% at 1 and 5 years, respectively. Three patients underwent retransplantation within 1 year: one on postoperative day 2 for primary nonfunction (this patient subsequently died, as mentioned above), one at 4 months for late hepatic artery thrombosis (alive and well at 7 years postretransplantation), and one at 3.5 months for multiple intrahepatic biliary strictures without hepatic artery thrombosis (alive and well at 5 years postretransplantation). The 1- and 5-year graft survival rates were 66% and 52%, respectively. Patient

survival rates at 1 and 5 years were 58.3% and 41.7%, respectively, in the ULT group and 88.9% and 77.8%, respectively, in the ELT group ($P = 0.55$).

Despite close follow-up and blood exchange, 10 of 16 patients who survived beyond day 90 (63%) developed at least one SCD crisis, including in the chest, bones, brain, and liver.

Pooled analysis of the literature

Overall, 22 patients (17 adults and five children) from 20 articles, excluding our six previously published cases [16], met the inclusion criteria and were selected for systematic review (Fig. S1). Most studies were case reports (18/20, 90%), and the remaining 2 (10%) [8,20] included two and three patients. The characteristics of these 22 patients are provided in Table 1.

Among the 18 evaluable patients, there were 11 male and seven female patients (sex was not indicated for four patients), with a median age of 26 years ranging from 6 months to 49 years. The SCD type was S/S in 13 patients and Sß° thalassemia in seven patients, S/C in one patient, and S/A in one patient (type was not mentioned for four patients). Seven (39%) of the 18 evaluable patients underwent emergency LT within the context of sickle cell hepatopathy.

Eleven patients (11/22, 50%) had coexisting chronic liver disease, including viral cirrhosis ($n = 3$), primary sclerosing cholangitis ($n = 2$), iron overload ($n = 3$), biliary cirrhosis ($n = 1$), cryptogenic cirrhosis ($n = 1$), and autoimmune hepatitis ($n = 1$). Three patients died within 3 months after LT, resulting in a mortality rate of 14% (3/22). The causes of 90-day mortality were intra-abdominal bleeding and multiorgan failure and intracerebral hemorrhage and multiorgan failure. The mean follow-up duration for the 18 evaluable patients was 19 months (range, 1–72). Fifteen patients were alive at the end of follow-up, with ranged from 28 days to

Table 3. Postoperative outcomes.

	Total ($n = 21$)	Urgent LT ($n = 12$)	Elective LT ($n = 9$)	*P* value
90-day mortality, *n* (%)	5 (24)	4 (33)	1 (11)	0.24
Surgical complications				
Reoperation	4 (19)	3 (25)	1 (11)	0.42
Early retransplantation	3 (14)	2 (17)	1 (11)	0.71
Biliary complications	3 (14)	2 (17)	1 (11)	0.71
Arterial thrombosis/stenosis	4 (19)	2 (17)	2 (22)	0.74
Portal vein thrombosis	0	0	0	
Outflow block	0	0	0	
Medical complications				
Primary nonfunction	1 (5)	1 (8)	0 (0)	0.37
Delayed graft function	8 (38)	5 (42)	3 (33)	0.69
Pulmonary complications	10 (48)	7 (58)	3 (33)	0.25
Respiratory support, days	5 (0–55)	10 (0–55)	3 (0–45)	0.031
Neurological complications, *n* (%)	16 (76)	11 (91)	5 (55)	0.06
Delirium	12 (57)	8 (67)	4 (44)	0.89
Seizure	4 (19)	2 (17)	2 (22)	0.74
PRESS syndrome	3 (14)	2 (17)	1 (11)	0.71
Acute renal failure, *n* (%)				
Overall	13 (62)	(58)	5 (55)	0.89
Requiring replacement therapy	6 (29)	4 (33)	2 (22)	0.57
Cardiovascular, *n* (%)	8 (38)	6 (50)	2 (22)	0.19
Infection, *n* (%)	15 (71)	11 (91)	4 (44)	0.02
Bacterial	12 (57)	9 (75)	3 (33)	0.06
Fungal	3 (14)	2 (17)	1 (11)	0.71
Viral	2 (10)	1 (8)	1 (11)	0.83
Acute rejection	3 (14)	3 (25)	0 (0)	0.1
ICU stay (days)	21 (2–89)	25 (2–89)	17 (2–63)	0.21
Hospital stay (days)	36 (2–79)	36 (11–89)	25 (2–63)	0.34

ICU, intensive care unit; LT, liver transplantation; PRESS, posterior reversible encephalopathy syndrome; RRT, renal replacement therapy.

Data are expressed as the median (range) or number of patients (%).

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5.5 years. The post-LT 1-, 3-, and 5-year patient survival rates in the 18 evaluable patients were 75%, 65%, and 65%, respectively.

Discussion

The present retrospective analysis of the largest single-center series of consecutive LT in patients with SCD suggests that regardless of the urgent elective indication, LT is a life-saving procedure with high postoperative mortality and morbidity rates, particularly in those undergoing transplant in an urgent setting.

How can these results be considered? From the patient's point of view, it is clear that overall, the patients in this series as well as those in the literature benefited from the transplant. The MELD score is a predictor of short-term mortality, and the values were particularly high in the ULT group. In general, patients with an indication for LT and associated organ failure have a poor prognosis. The patient population with ACLF is a good example. In the present series, 15/21 patients had at least two organ failures defined according to SOFA criteria, which are those of the ACLF definition. Finally, some patients in the ULT group had fulminant hepatitis-like presentation that met Clichy's criteria. The spontaneous prognosis of patients with these criteria is very poor without LT.

From the clinician's point of view, the results are not good. Perioperative mortality is high, particularly in those undergoing emergency transplantation. Indeed, the 5-year survival of emergency transplant patients is below 50%, which in the field of LT is the minimum acceptable survival. All of this makes sense because the patients had organ failure and a high BAR score and because the causative disease—sickle cell disease—is not alleviated in any way by transplantation. Neurological complications following LT were very frequent. In addition to the acknowledged neurotoxicity of immunosuppressants, the direct adverse effect of general anesthesia, or the sequelae of hepatic encephalopathy, we may hypothesize that the underlying frequent infraclinical brain injury in SCD patients might decrease the threshold for neurological complications [37]. In our series, 63% of patients surviving the postoperative period developed SCD crisis, demonstrating that the course of SCD logically does not appear to be modified by LT [4]. Recurrent sickle cell hepatopathy in the liver graft has been reported only in two patients [12,19]. The maintenance of an Hb level < 30% was the mainstay of our perioperative management strategy. The reported target Hb-S level varied from < 10% to < 30% (Table 3). Overall, the perioperative management strategy was extrapolated from that of nontransplant surgery in SCD patients, which has already been extensively described [38-44]. Finally, as cited above, some patients have a fulminant presentation, and the short-term mortality after transplantation is high in this setting (approximately 30% in the European Liver Transplant Registry, http://www.eltr.org/, as assessed in January 2020). The survival of SCD patients with elective transplantation is better, and the results are similar to those obtained for the general population of transplant recipients. The important difference is that regardless of whether the transplant was an emergency, the patients in this series were young (38 years) and that results are typically better than the average results obtained in a general population of transplant recipients with an average age of 60 years. Furthermore, the patients in this series received a good graft, as evidenced by the DRI.

In the present series, the outcomes of LT were not only influenced by the associated chronic liver diseases and the number of organ failures prior to LT, but also by the high rate of post-LT complications in particular infectious and neurological complications. Several potential ways may be discussed to improve LT outcomes. The cumulative experience with LT in SCD patients may lead to a better knowledge of these specific post-LT complications. These led us to propose the following strategies in the pre-LT period including (i) infection screening protocol particularly before transplanting recipients with acute liver failure and (ii) pre-existent cerebral vascular lesions screening protocol including magnetic resonance imaging of the central nervous system whenever possible to assess the presence of SCD-related cerebral vasculopathy susceptible to decrease the threshold for neurological complications, and in the perioperative post-LT period including (i) prophylactic antibiotics and anti-fungal therapies, (ii) combination of induction therapy (by polyclonal or monoclonal antibodies) and mycophenolate mofetil should permit to delay the introduction of a calcineurin inhibitor and maybe the incidence of neurological complications, and (iii) prophylactic anti-seizure therapy.

Our study had some limitations: (i) Given the limits of any retrospective study, type 2 error due to sample size cannot be ruled out with regard to the comparisons between the ULT and ELT groups. The main example is 90-day mortality, with a rate of 33% for ULT vs. 11% for ELT. The difference was not statistically significant, although there was an absolute difference of 22%, (ii) the absence of ontological homogeneity in the literature hampered a thorough review, and (iii) as there is a

tendency to report successful cases and not those in which the patients did not survive, a significant reporting bias cannot be ruled out, especially for the review, which was based on mostly case reports.

Aggressive management of SCD might obviate LT, as reported here. In parallel, the subset of patients listed who were forced to drop out because death or worsening condition precluded LT and the subgroup of patients for whom LT is futile [45] remain to be identified in this specific population of patients.

In conclusion, this study showed that LT is rarely indicated in patients with SCD. LT is indicated for two clinical phenotypes, ULT and ELT. Neurological complications were particularly frequent. Although the results obtained following ELT were acceptable, improvement is needed for results with ULT.

Authorship

EL, CL, CF and DA: conceived and designed the study. EL, ALQ, BR, JCM and FE: contributed to acquisition of data. EL, CL, CF, CS and DA: analyzed and interpreted the data and drafted the manuscript. EL, CL, CF, CS, ALQ, BR, JCM, FE, CD, DC, AH, FG, PB and DA: revised and approved the manuscript.

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Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Search strategy.

Table S1. Intraoperative events.

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