REVIEW ARTICLE

Liver transplantation for sickle cell disease: a systematic review

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Abstract

Background: Sickle cell disease is a group of autosomal recessive disorders characterised by haemolytic anaemia. Liver is one of the most affected organs, ranging from liver tests alterations to acute liver failure for which liver transplantation is the only life-saving treatment.

Methods: This study aims to make a systematic review of the current literature to evaluate indications, timing, and results of liver transplantation for patients affected by SCD.

Results: Twenty-nine patients in total were reported worldwide until 2018, the average patient age is 28.7 (0.42–56), all patients have a pre-transplant diagnosis of SCD. Cirrhosis at transplantation was present in six-teen (n = 16, 55.1%) patients. In ten patients (n = 10, 34.5%), acute liver failure arises from healthy liver and presented sickle cell intrahepatic cholestasis. Eleven patients (n = 11, 39.2%) died, three (n = 3, 10.7%) in the first postoperative month, and seven (n = 7, 25%) in the first year. Mean follow-up was 27 months (range: 7–96), one-year overall survival was 48.7%.

Discussion: Liver transplantation for SCD has been increasingly reported with encouraging results. Indications are presently reserved for acute liver failure arising both in healthy liver and end-stage liver disease.

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Introduction

Sickle cell disease (SCD), also known as sickle cell anaemia (SCA) or drepanocytosis, is a group of inherited autosomal recessive disorders described for the first time in the 1910s.[1] SCD is predominantly characterised by haemolytic anaemia secondary to the premature breakdown of red blood cells. Its genetic origin and genetic variants were discovered in 1949.[2] The disease is caused by an inherited substitution of valine for glutamic acid at position 7 of the haemoglobin beta gene within the chromosome 11p15.5.[3,4] The mutation is a single-nucleotide polymorphism (SNP) within the code where the codon GAG is changed for GTG in the β-globin gene. This leads to an amino acid change with consequent structural modification of the normal haemoglobin HbA to the pathologic HbS.[5] In heterozygous subjects, only one allele is affected and at least one gene can produce the correct protein, with minor clinical manifestations. SCD can be included in the wider group of haemoglobinopathies. In this cluster of diseases, HbS in one allele can be combined with a mutation on the second allele such as: β-thalassemia, HbC, HbD, HbA.[6] In this new conformation, haemoglobin S (HbS) is polymerised, producing a sickle-shaped red blood cell (RBC).[7,8] The decreased elasticity of the RBCs results in a weaker structure and reduces their ability to properly deform during their passage through microcirculation. In addition, RBCs oxygen precipitation increases HbS polymerisation, although the normal shape should be re-established when O_2 tension is restored. The average RBC

mean lifetime in SCD is 10–20 days as compared to the 90–120 days of the healthy ones.[9] When two alleles have the S mutation (S/S configuration), the disease is clinically defined SCA. The Global Burden of Disease indicates that in 2015 forty-four millions of people worldwide were affected by SCD, with 114,800 deaths every year.[10] Life expectancy is between 40 and 60 years[11] considering all the different types of SCDs. Diagnosis is usually made during neonatal screening, and first clinical manifestations typically appear in the 4th–5th month postpartum. The resulting chronic haemolytic anaemia due to the premature RBC breakdown is associated with a recurrent painful vaso-occlusive crisis (VOCs), systemic inflammation,[12,13] sepsis, splenomegaly, and final multiple organ failure. Liver is one of the most affected organs with different patterns of organ injury. Clinical manifestations in liver can range from simple liver tests alterations to acute liver failure (ALF) mainly due to intrahepatic vascular occlusion and infarction. Sickle cell intrahepatic cholestasis (SCIC), the most severe form of sickle cell hepatopathy, has been described by Green *et al.*, in 1953.[14] It is characterised by the sickling of red blood cells within hepatic sinusoids with consequent localised hypoxia, stasis, and infarction. Ballooning of the hepatocytes determines a direct back hypertension obstructing bile passage towards the intrahepatic ducts. This causes acute and severe cholestasis, and it is often associated with renal failure, coagulopathy, and neurological manifestations. SCIC is clinically characterised by acute right upper quadrant pain, fever, jaundice, neurological abnormalities, and liver failure.[15] Mortality is high (up to 40%) in spite of supportive care and exchange blood transfusions. In 1980, Sheehy introduced and reported the first successful use of exchange transfusion for SCIC.[16] Khurshid, in a series of 26 patients presenting with SCIC, reported a decreasing mortality from 38% to 17% after exchange transfusion.[17] Despite this aggressive treatment, ALF with progressive encephalopathy may develop, frequently associating multiple organ failure. This acute presentation has an estimated incidence of 10%[18] and can lead to fulminant hepatic failure,[19] accountable for 64% of deaths.[20,21] Chronic liver disease is often an consequence of iron overload[6] or viral hepatitis, which can occur after multiple transfusions.[22] Intrahepatic and extrahepatic bile duct stones, as well as gallbladder stones, are also frequent and have different associations with acute and chronic cholangitis. Liver transplantation is the only life-saving treatment for liver failure, arising both in healthy liver or in chronic liver disease. Nevertheless, transplantation does not treat the disease but its clinical manifestations, therefore SCD can recur. In the peri-transplantation period, prevention of new SCD crisis and possible graft dysfunction is often obtained maintaining the haemoglobin S fraction concentrations lower than 20%.[23] The first liver transplantation for SCA with favourable outcomes was performed by Lang *et al.* in 1995.[24] The aim of this study was to make a systematic review of the relevant current literature to evaluate the indications, timing, and results of liver transplantation for patients affected by SCD.

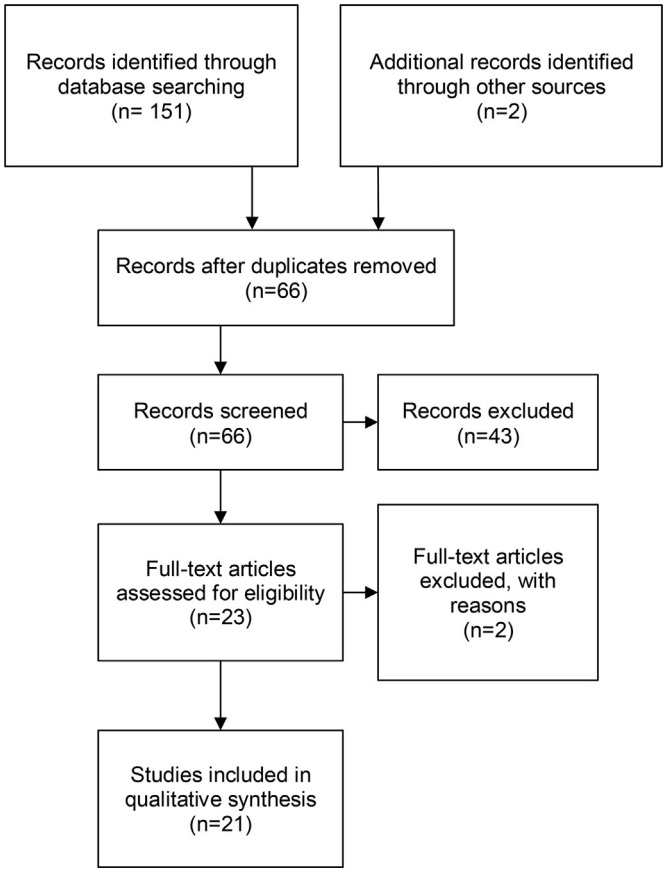
Material and methods

Electronic bibliographical databases (namely MEDLINE, PubMed, EMBASE, and Scopus) were searched. The following terms and rules were used for the search: [sickle cell disease AND liver transplantation], [sickle cell anaemia AND liver transplantation], [drepanocytosis AND liver transplantation]. Results were filtered in the English language and until September 2018. Prospective and retrospective cohort studies, patient series, and patient reports were included and used for quantitative and qualitative synthesis of data according to the PRISMA criteria (Table 1). A total of 150 articles were initially found, adding one more article, the title of which did not match the requirements although it was eligible for the analysis. Eighty-seven articles were excluded because of duplicates and 43 articles were also excluded because they were not liver transplant clinical cases with SCD. Twenty articles were finally included.

Results

A total of 29 patients who underwent LT for SCA worldwide are present in the current literature (Table 2), and single centre

Table 1 Flow diagram



series or case reports are the available contributions. Average patient age is 28.7 (0.4–56), twelve patients (n = 12, 41.8%) were female, fourteen patients (n = 14, 48.2%) were male, three (n = 3) were not specified. All patients had a pre-transplant diagnosis of SCD. Fourteen patients (n = 14, 48.2%) had a S/S genotype, six (n = 7, 24.1%) an S/β genotype, three (n = 3, 10.7%) an S/C type, and one (n = 1) a S/A and S/D type. In three patients, the information was not available. Fourteen patients (n = 14, 48.2%) had SCIC as an indication to LT. In this group, eight of them (n = 8, 57.14%) had an S/S genotype. Cirrhosis at transplantation was present in sixteen (n = 16, 55.1%) patients. In ten patients (n = 10, 34.5%), acute liver failure arose from a healthy liver and those patients presented SCIC as the main clinical feature. In all cases, intraoperative and postoperative blood exchange transfusions were used to lower the HbS level concentration, with a reported value ranging from 10,3% to 69,6%. Eleven patients (n = 11, 39.2%) died, three (n = 3, 10.7%) in the first postoperative month, and seven (n = 7, 25%) in the first year. Causes were cerebrovascular accident, sepsis, and recurrent SCIC in one patients (n = 9, 9%). One patient (n = 1, 3.5%) died on postoperative day 10 for acute rejection, another one developed recurrent hepatitis C virus-related cirrhosis and died 11 years after LT. All patients received standard immunosuppression according to the local protocol. In one patient, a second liver transplantation was performed, and in another one a third liver transplantation was also reported with final exitus. Only one patient (n = 1, 3.5%) received combined liver and kidney transplantation. Follow-up was available in fourteen patients with a mean of 27 months (range: 7–96). The longest reported survival was 11 years for a patient who died of recurrent hepatitis C virus-related cirrhosis. Considering alive patients, the longest survival reported was 8 years. The one-year survival was 48.27%. Three patients were reported alive with no available follow-up.

Table 2 Articles and number of patients per year reviewed

Authors	Year	Age	Gender	Origin	Genotype	Chirrosis	HbS %	Outcome	Reference
Lang *et al*.	1995	11	M	N/A	SS	N	0.2	Alive 2 POY	24
Kindscher *et al*.	1995	47	F	N/A	SS	Y	0.3	Died cerebral hemorrhage	33
Lerut *et al*.	1999	42	F	Italian	Sβ	Y	0.6	Alive 30 POM	34
Emre S. *et al*.	2000	6	M	Black	SS	N	10.3	Died 5 POM Spesis	28
Gilli *et al*.	2002	22	M	N/A	Sβ	Y	12.6%	Alive 3 POM	35
Ross A.S. *et al*.	2002	49	M	Afro-american	SS	N	52	Died 22 POM pulmonary embolus	36
V. D. Hazel *et al*.	2003	23	M	Caucasian	SS	Y	19	Alive 5.5 POY	37
M. M. Baichi *et al*.	2005	26	F	Afro-american	SS	Y	69.6	Died 1 POM recurrent SCIC	38
M. M. Baichi *et al*.	2005	27	F	Afro-american	SS	N	15.1	Died 1 POM sepsis	
Delis	2006	19	F	Caucasian	SD	Y	33.8%	Alive after 17 POM	39
Mekeel K. L. *et al*.	2007	8	N/A	N/A	N/A	N	<25	Died 6 POY cerebral accident	19
Mekeel K. L. *et al*.	2007	17	N/A	N/A	N/A	N	<25	Alive 5 POY	
Mekeel K. L. *et al*.	2007	17	N/A	N/A	N/A	N	<25	Alive 5 POY	
Greenberg *et al*.	2009	30	F	Afro-american	SS	N	0.26	Alive 28 POD LT	40
Perini *et al*.	2010	37	M	N/A	Sβ	Y	0.39	Died 2 POM cerebral accident	41
Hurtova M. *et al*.	2011	36	M	Carabbean	Sβ	Y	31.7%	Died 11 POY HCV Cirrhosis	32
Hurtova M. *et al*.	2011	37	M	Carabbean (Mali)	Sβ	Y	N/A	Died 4 POY Sepsis	
Hurtova M. *et al*.	2011	32	M	Mauritaria	Sβ	Y	N/A	Alive 8 POY	
Hurtova M. *et al*.	2011	47	F	Algeria	SC	Y	N/A	Died 10 POD rejection	
Hurtova M. *et al*.	2011	43	F	Mali	SS	Y	N/A	Died 6 POM lukoencelopathy and infections	
Hurtova M. *et al*.	2011	43	F	Carabbean	SS	N	N/A	Alive 42 POM	
Tomaino J. *et al*.	2011	16	F	N/A	SC	Y	<30%	Alive 2 POY	42
Blinder M.A. *et al*.	2013	37	M	Afro-american	SS	Y	<30%	Alive 12 POM	43
Gardner K. *et al*.	2014	33	M	Afro-Caribbean	SS	Y	<30%	Alive 2 POY	23
Gillis JH *et al*.	2015	56	F	Afro-american	SC	Y	0.44	N/A	44
Laura A. *et al*.	2016	0.42	F	N/A	SS	N	<30%	N/A	45
Loh Ps *et al*.	2018	24.00	M	Nigerian	SA	N	0.35	N/A	46
Lui S. K. *et al*.	2018	29.00	M	Afro-american	SS	N	48.2%	Alive 7 POM	27
Racho R *et al*.	2019	19.00	M	Afro-american	Sβ	N	41.9%	N/A	25

Discussion

Liver involvement in sickle cell disease is characterised by different patterns of organ injury with clinical manifestations ranging from simple liver tests alterations during a VOCs to ALF secondary to intrahepatic cholestasis and parenchymal infarction.[25–27] Long-term treatment with blood transfusion exchange is often the trigger for the development of chronic liver disease, such as hepatitis C virus-related cirrhosis, secondary haemochromatosis, and secondary sclerosing cholangitis, frequently associated biliary complications. Severe ALF in patients affected by SCD is a rare event, and its prevalence has been reported to be 0.55% in a cohort of 2000 patients in a referral centre.[27] SCIC, one of the most severe forms of liver involvement, is the most common indication to urgent liver transplantation. No definite criteria exist for the diagnosis of SCIC, but severe hyperbilirubinemia is the striking feature. In the present review of the literature, LT was reported in 29 patients, ~69% of them aged more than 20 years, and in ~55% of cases patients presented with an underlying cirrhosis. The high prevalence of chronic liver disease is probably due to the fact that at present the management of SCD has improved with longer patient survival. As a consequence, patients are more susceptible to secondary complications of the disease as previously showed. Half of the patients had a S/S genotype, known to be the most severe form of the disease. However, any combination of the S gene was reported in transplanted patients. SCIC and infarction can arise in healthy livers and can be accountable for ALF necessitating urgent transplantation, as reported in the present review in 34.5% of patients. Postoperative mortality is mainly due to sepsis, cerebrovascular accident, and recurrence of sickle cell liver disease. Two patients had a second transplantation, and a 6-year-old child a third transplantation with final *exitus*. In these patients, the indication to re-transplantation was intrahepatic vascular complication secondary to SCD crisis, namely arterial and venous thrombosis. As transplantation is the treatment of a severe manifestation of the disease, but SCD can recur, involving liver or other organs. The only available long-term follow-up report is a 44.5% 10-year survival in a single centre series of six patients,[27] with the longest reported survival of 11 years for one patient who finally died for recurrent hepatitis C virus-related cirrhosis. Although LT appears to be feasible with acceptable results, there is still no consensus on indication, timing, and management of SCD specific issues. Regarding indications, it is accepted that a young patient with acute liver failure, especially in a healthy liver, may benefit from a life-saving treatment such as transplantation. Differences among centres and countries exist. In the UK, for instance, end-stage liver disease as a consequence of SCD is not an accepted indication for LT.[28] Results are still not comparable to common indications for LT. Thus, it is recommended to perform LT in a context where haematologists with an expertise of SCD management are present to optimise perioperative medical treatment. Results are still not comparable to common indications for LT. Anyways, it has to be considered that these patients are transplanted in conditions comparable to those of fulminant hepatitis, and so the corresponding results should be looked for in this subgroup of LT indications. The survival rates suggest that both LT for SCD and for fulminant hepatitis are not so dissimilar, except for patients affected by SCD transplanted in a setting of acute liver failure, condition associated to worse survival and increased mortality at 1-year.

The European Liver Transplant Registry, LT for fulminant hepatitis is associated with a postoperative mortality rate of 30% and with 1-year, 5-year and 10-year survival rates of 72%, 66% and 60% respectively.[29] In 2020 the 1-year survival rate of 88%, 3-years survival rate of 70% and 5-years survival rate of 58% were reported in USA in SCD patients.[30] In the same year Levesque *et al.* reported a series that considered LT for SCD in two settings: urgent LT (ULT) and eligible LT (ELT). The authors showed for the first group a 1-year survival of 58% (ULT), and 88% (ELT) for the second one. The 3-years survival rate was reported of 41 for ULT and 77% for ELT.[31] Another consideration is that the experience of the different centres is improving according to the increasing number of patients treated. Moreover, a better multidisciplinary work between haematologists, hepatologists, and surgeons, is allowing for a rapid recognition and treatment of specific SCD-related complications. Comorbidities influence results as well, SCD patients can suffer both from the conditions associated with chronic liver disease and with the ones related to SCD. The largest reported series is the one of Hurtova *et al.*, where both a liver transplantation centre and a SCD referral centre were present.[32] These authors observed that even if sickle cell crises recurred after LT, they were usually milder and less frequent in comparison with those which occurred before them. They argued that the absence of associated advanced liver disease could be a protective factor, as well as the prevention of SCD treatment-related complications. They proposed to switch from a systematic blood transfusion programme to therapy with recombinant erythropoietin when Hb was less than 8 g/dL and to associate hydroxyurea. Moreover, the incidence of cerebrovascular events in the postoperative period are probably associated with the microvascular alterations due to SCD. This should be prevented by a careful attention on the haemoglobin drop and HbS increasing in the post-LT period. Concerning the possible prevention of these types of complications, they suggest a careful pre-transplant assessment of cerebral vascular lesions with MRI, a delayed introduction of a calcineurin inhibitor, with low concentrations, and in combination with mycophenolate mofetil (MMF). Patients with SCD have a theoretically high risk of allograft rejection because of their frequent anti-HLA sensitisation, their ethnicity, and their young age. In the same study, Hurtova, showed that when an episode of SCIC takes place, a second and more severe episode, which may potentially lead to fatal hepatocellular failure, may be anticipated. These authors suggest that LT can be performed at an early stage.

But it is highly recommended to perform it after a careful evaluation of comorbidities, discarding other possible causes of ALF which can be potentially managed with medical treatment.

Conclusions

Liver transplantation (LT) for sickle cell disease (SCD) has been increasingly reported with encouraging results. Indications are currently reserved for ALF arising both in a healthy liver or in chronic liver disease. Careful screening of SCD-related systemic complications is fundamental and a close collaboration with haematologists is required for perioperative management. Considering the specificity of the disease, these patients should be addressed, whenever possible, to referral centres both for SCD and LT.

Authors' contributions

Emanuele Felli and Giuseppe Maria Ettorre designed the research; Riccardo Memeo and Eric Felli performed the research; Valerio Giannelli and Eric Felli analysed the data; Emanuele Felli, Riccardo Memeo, and Eric Felli wrote the manuscript; Emanuele Felli, Eric Felli, Valerio Giannelli, Marco Colasanti, Riccardo Memeo, Adriano Pellicelli, Edoardo Maria Muttillo, Michele Diana, and Giuseppe Maria Ettorre reviewed the manuscript, Giuseppe Maria Ettorre supervised the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

None declared.

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