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Evaluation of survival of sickle cell patients after liver transplantation at the Henri Mondor Hospital in Créteil (HHM) in France: A Retrospective cohort study

Abstract

Background: Hepatic cholestasis is very common in sickle cell disease, thus requiring liver transplantation; but this technique is not practiced in the developing world. The objective of this study was to evaluate the survival of sickle cell patients after liver transplantation followed at the Henri Mondor Hospital in Créteil (HHM) in France.

Methods: Historical cohort study conducted in 24 sickle cell patients followed at the Henri Mondor hospital in Créteil in France during the period from 1991 to 2019. The clinical, biological and evolutionary parameters were studied. Patient survival was described by Kaplan Meier curves and risk factors for death were sought by Cox regression.

Results: Among the 24 sickle cell patients who underwent a liver transplant, 11 had died, representing a mortality rate of 45.8%. Their average age was 35.7±8.6 years, female sex ratio 1M/2F. Malnutrition accounted for 25%, 58.3% of patients were homozygous, in hepatic presentation, 45.8% were grade 0 and 54.2% grade I-V. Ascites, hepatic encephalopathy and high risk according to the MIELD score had influenced death ($p<0.05$). The median time to intervention was longer in the deceased ($p<0.001$), on the other hand, the duration of follow-up was shorter in the deceased ($p<0.001$). After adjustment, male gender (HRa: 3.95 95% CI: 1.42-9.00), homozygous status (HRa: 3.92 95% CI: 1.61-5.12), encephalopathy 2.70 (1.41-7.01), MELD score high risk (3.20 (1.26-5.66) and time to intervention ≥ 3 days (HRa: 2.96 95% CI: 1.89-6.78) were the independent predictors of sickle cell mortality.

Conclusion: the death rate is high in transplanted sickle cell patients; it is influenced by the state of the liver, the time to intervention and the homozygote state.

Keywords: sickle cells, liver transplantation, survival, mortality

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Introduction

Sickle cell disease was one of the first human genetic diseases to be identified and is caused by the presence of pathological hemoglobin S (HbS) in homozygous (HbSS) patients, resulting in the formation of sickled erythrocytes under deoxygenated conditions.[1] This disease is most prevalent in the African American population and intravascular sickling of red blood cells causes hemolysis, vaso-occlusive crises and severe pain. While the diagnosis of SCD foreshadowed a poor prognosis, due to several complications including the most formidable hepatic complication.[1–3] Acute sickle cell intrahepatic cholestasis is a severe condition that can progress to acute liver failure associated with 50% mortality; some cases respond to exchange transfusion, but an estimated 17% are refractory to exchange transfusion with transplantation as the only survival option.[4-7] Repeated attacks on the liver can lead to chronic liver disease and cirrhosis. Thus, chronic liver disease and cirrhosis are often multifactorial in these patients.[8,9] Despite these data suggesting that many patients with sickle cell disease are at risk of developing liver failure, the role of liver transplantation (LT) in sickle cell disease is limited.[5,7,10–12] Transplantation has been more frequently described in the literature, and historically, patients with SCD have been associated with an increased risk of mortality after liver transplant.[13,14] However, more recent studies have shown survival comparable to that of diabetic kidney transplant recipients, with improved survival after liver transplantation.[15] The objective of this study was to evaluate the survival of sickle cell patients after liver transplantation followed at the Henri Mondor Hospital in Créteil (HHM) in France.

Material and methods

Study design and participants

The data collected concerned 24 patients followed at the Henri Mondor Hospital in Créteil (HHM), included in the Assistance Publique des Hôpitaux de Paris (APHP). These patients were followed mainly by the hepatology department and the Red Blood Cell Genetic Diseases Unit (UMGGR). The data used were extracted from the APHP platform using crystal software.

The inclusion period was between January 1991 and December 2019 for patients meeting the following criteria: suffering from major sickle cell syndrome (SS, SC, S α thalassemia, S ß thalassemia); have severe sickle cell liver disease (total bilirubin > 200 mol/L and/or TP < 50% and/or GGT > 400 IU/L); be at least 18 years old and have available liver histopathology analysis (liver biopsy and explant puncture). For each patient, the following groups of data were collected: data concerning the natural history of sickle cell disease, sickle cell liver disease, liver transplantation and postoperative follow-up were collected retrospectively, sociodemographic data, data on the phenotype sickle cell disease as well as the different hemoglobin levels, data on the medical history, the cofactors of hepatic morbidity as well as the clinical presentation of the patient; data on medical treatments, biological parameters, liver histology provided before and after liver transplantation and data on clinical evolution, vital status (living or deceased patients).

Statistical analyses

The analyzes were carried out using SPSS for Windows version 21 software. For the quantitative variables with a Gaussian distribution, the descriptive statistics used were the mean and standard deviation, while the non-normally distributed data were described by the median and their interquartile space (IQS). The proportions of the different modalities were expressed as a percentage for the qualitative variables. Pearson's chi-square or Fischer's exact test was used to compare the proportions, Student's t test compared the means, while Mann Whitney's U test was used to compare the medians. Kaplan Meir's method was used to describe overall patient survival. The log Rank test was then performed to verify the significance for each of these comparisons. The date of liver transplantation was considered the original date for all patients, while the date of the latest news varied according to the vital status of the patient. For deceased patients, it corresponded to the day of death, while for the living subject it corresponded to the point date. Predictors of mortality were sought using the stepwise Cox regression test. For all the tests used, the value of $p<0.05$ was the threshold of statistical significance.

Results

Vital patient outcomes

Of the 24 sickle cell patients who underwent liver transplantation, 11 had died a mortality rate of 45.8% (Figure 1).

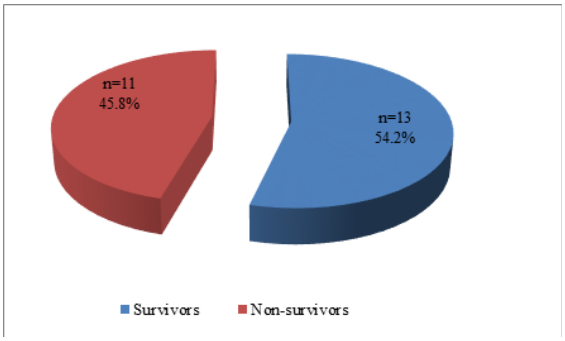

Figure 1 Distribution of patients according to vital outcome

General characteristics of patients and vital outcome

Mean age of sickle cell patients was 35.7 ± 8.6 years, the majority of them were female sex ratio 1H / 2F, men decided significantly more than women (p = 0.043). Undernutrition accounted for 25%, 58.3% of patients were homozygous with a significantly higher frequency of death among them than heterozygous (p=0.036). In the hepatic presentation, 45.8% were grade 0 and 54.2% grade I-V. It was observed that grade I-V patients died more than those of grade 0 (p=0.032). Ascites, hepatic encephalopathy and high risk according to the MIELD score had a significant influence on patient death ($p<0.05$). The median time to intervention was significantly longer in the deceased patients than in the living ($p<0.001$), on the other hand, the duration of follow-up was significantly shorter in the deceased than in the living ($p<0.001$) (Table 1).

Patient survival

Female patients tended to have better survival compared to male patients, with a statistically significant difference (p=0.004) (Figure 2). The comparison of the survival curves of sickle cell patients, according to the time to intervention, showed that survival was significantly (p=0.005) shorter in sickle cell patients operated on beyond 3 days than in those operated on before 3 days (Figure 3). Heterozygous sickle cell patients tended to have better survival compared to homozygous sickle cell patients, with a statistically significant difference (p=0.038) (Figure 4).

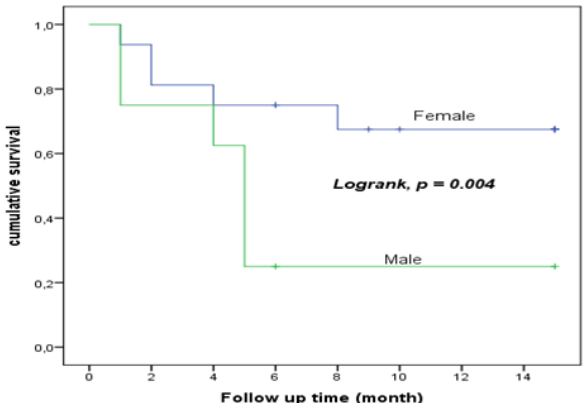

Figure 2 Survival Curves of COVID-19 patients according to gender

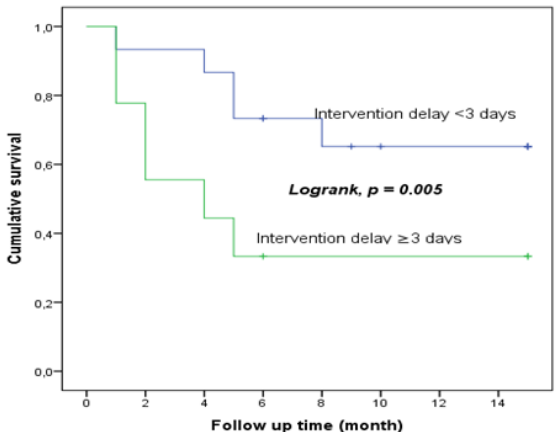

Figure 3 Survival Curves of COVID-19 patients according to intervention delay

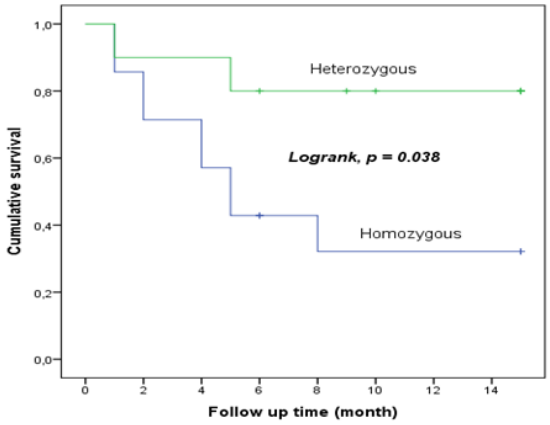

Figure 4 Survival Curves of COVID-19 patients according to sickle cell type

Predictors of mortality

In univariate analysis, male gender, homozygous status, ascites, encephalopathy, high-risk MELD score and time to surgery greater than 3 days were the predictors of sickle cell mortality. After adjustment, male gender (aHR: 3.95 95% CI: 1.42-9.00), homozygous status (aHR: 3.92 95% CI: 1.61-5.12), encephalopathy 2.70 (1.41-7.01), MELD score at high risk (aHR : 3.20 95%CI :1.26-5.66) and time to intervention greater than 3 days (aHR: 2.96 95% CI: 1.89-6.78) were the independent predictors of mortality in sickle cell patients (Table 2).

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Table 1 General characteristics according to vital outcome

Variable	Over all n=24	Survivors n=13	Non-survivors n=11	p
Age, years	35.7±8.6	37.0±6.3	34.2±10.8	0.438
range				0.625
<40 years	15 (62.5)	8 (61.5)	7 (63.6)	
≥40 years	9 (37.5)	5 (38.5)	4 (36.4)	
Gender				**0.043**
Female	16 (66.7)	11 (84.6)	5 (45.5)	
Male	8 (33.3)	2 (15.4)	6 (54.5)	
BMI	20.4±3.3	20.6±2.8	20.1±3.9	0.590
Malnutrition	6 (25.0)	3 (23.1)	3 (27.3)	
Normalweight	18 (75.0)	10 (76.9)	8 (72.7)	
Sickle cell type				**0.036**
Homozygous	14 (58.3)	5 (38.5)	9 (81.8)	
Hetrozygous	10 (41.7)	8 (61.5)	2 (18.2)	
CVO Frequency/years				0.223
<4	10 (41.7)	4 (30.8)	6 (54.5)	
≥4	14 (58.3)	9 (69.2)	5 (45.5)	
Transfusions				0.590
<4	6 (25.0)	3 (23.1)	3 (27.3)	
≥4	18 (75.0)	10 (76.9)	8 (72.7)	
Hepatic presentation				**0.032**
Stage 0	11 (45.8)	7 (53.8)	4 (36.4)	
Stage I-IV	13 (54.2)	6 (46.2)	7 (63.6)	
Mechanical ventilation	17 (70.8)	9 (69.2)	8 (72.7)	0.605
Ascite	13 (54.2)	6 (46.2)	7 (63.6)	**0.032**
EH	13 (54.2)	6 (46.2)	7 (63.6)	**0.003**
MELD	31.3±9.0	31.5±9.1	30.9±9.3	0.869
Risk patients				**0.005**
Low	12(50.0)	7(53.8)	5(45.5)	
High	12(50.0)	6(46.2)	6(54.5)	
EER preop	16(66.7)	9(69.2)	7(63.6)	0.556
Na+	138.7±4.6	138.7±5.7	138.7±3.6	0.999
Hb , g%	8.1±1.5	7.8±1.7	8.3±1.3	0.458
TP	36.5 (24.5-62.0)	33.5 (19.0-58.0)	47.5 (24.5-80.0)	0.342
INR	2.0 (1.0-3.0)	2.0 (1.0-4.0)	1.5 (1.0-3.5)	0.817
Bilbin	659.0 (259-953)	803.5 (453.5-1320.0)	375.5 (195.5-935.0)	0.233
GGT	101.5 (45.0-418.0)	98.5 (41.0-365.5)	209.5 (37.0-558.0)	0.456
PAL	200.5 (119.5-410.0)	180.0 (92.0-431.5)	252.0 (123.5-920.5)	0.384
AST, UI/L	138.5 (119.5-206.5)	152.0 (105.0-206.5)	135.0 (119.5-10067.0)	0.157
ALT, UI/L	70.5 (43.0-132.0)	60.0 (36.5-180.0)	77.5 (40.0-2868.0)	0.261
Creatinine, mg/dl	142.5 (64.5-231.5)	167.0 (64.5-250.0)	116.0 (34.5-272.5)	0.794
Ferritine	1811 (451-2788)	2056.0 (451.0-4356.5)	1299.5 (157.0-2672.0)	0.328
WB cell/mm^3	15000 (10100-23550)	14750.0 (6960-21800)	18750 (10100-26650)	0.377
Hb S, g%	34.6 (19.5-49.2)	25.4 (17.0-42.3)	49.2 (3.3-67.3)	0.426
Platelet, cell/mm^3	151.5 (103.0-232.0)	128.0 (76-265)	185 (103-593)	0.334
Intervention delay	0.5 (0.0-4.0)	0 (0-2.5)	4.0 (0.0-13.0)	**<0.001**
<3 days	15 (62.5)	10 (76.9)	5 (45.5)	
≥3 days	9 (37.5)	3 (23.1)	6 (54.5)	
Follow-up time (months)	6.0 (4.5-12.5)	15.0 (8.0-15.0)	4.0 (1.0-5.0)	**<0.001**

Discussion

The aim of this study was to assess the survival of sickle cell patients after liver transplantation followed at the Henri Mondor Hospital in Créteil (HHM) in France. Of the 24 sickle cell patients followed in this hospital establishment, 14 or 58.3% were homozygous. Overall mortality after transplantation was 45.8% lower than surviving patients (54.2%). This improvement in the survival of sickle cell patients reflects the impact of implementing regular patient follow-up and early management strategies with treatment and prophylaxis. From a clinical point of view, the results of this study are not good. Mortality is high after transplantation. Indeed, the 5-year survival

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of transplanted patients is around 50%, which in the field of liver transplantation is a minimally acceptable survival. This all makes sense because the patients had organ failure and a high MELD score; and more sickle cell disease is not eradicated by liver transplantation. The MELD score is a predictor of short-term mortality; in this study, high-risk patients actually had high mortality. This could also be explained by organ failure more common in patients (jaundice, hepatic encephalopathy, ascites and renal failure).

Table 2 Predictors of mortality in sickle cell transplant recipients

Factor	Univariate analysis		Multivariate analysis	
	p	HR	p	aHR
Gender				
Female		1		1
Male	0.001	3.06 (1.91-6.27)	**0.004**	3.95 (1.42-9.00)
Sickle cell type				
Heterozygous		1		1
Homozygous	0.006	4.25 (1.91-9.87)	**0.015**	3.92 (1.61-5.12)
Ascites				
No		1		1
Yes	0.042	2.64 (1.48-5.67)	0.646	1.39 (0.34-5.67)
Hepatic encephalopathy				
No		1		1
Yes	0.034	3.48 (1.43-5.06)	**0.046**	2.70 (1.41-7.01)
MELD				
Low risk		1		1
High risk	0.005	3.31 (1.40-4.28)	**0.015**	3.20 (1.26-5.66)
Intervention delay				
<3 days		1		1
≥3 days	0.007	3.00 (1.90-9.97)	**0.004**	2.96 (1.89-6.78)

This study showed that patients over 40 died more than those under 40, but the difference was not statistically significant. Our results are consistent with these studies, which show that the peak incidence of death has shifted to older age groups, probably due to the introduction of birth screening, prevention and management of complications during the first years of life.[16–20]

Our study shows a 5-year survival superior to that observed by Hurtova et al. who reported a survival rate of 44.4%[21] against 54.2% for our study. The difference could be explained by the method of survival evaluation used. However, our study used the Kaplan Meir method while that of Hurtova et al proceeded by the actuarial method. The study by Mekeel et al. presented a maximum survival rate at 5 years, with 100% of transplant patients living within this period.[22] However, this study only involved 3 sickle cell liver transplant patients. The other nuance is the age of the patients. Mekeel et al had worked with children whose ages ranged between 8 and 17 years, while our study focused on adults whose ages ranged between 18.9 and 50 years. The study by Baichi et al focused on 2 patients, who died one month after transplantation,[23] i.e. a survival rate of 0% at 5 years. This study is similar to ours in that it concerns adults who were 26 and 27 years old. Caution in the comparison remains in the size of the sample which remains very small. Other studies had focused on adult patients but in the form of case reports. These include van den Hazel et al whose study involved a 23-year-old adult patient who had survived the 5-year threshold.[24] Blinder et al's study of a 37-year-old adult patient who had survived 3.5 years after transplantation,[10] the study by Gilli et al. on a 22-year-old adult patient who had survived 2 years,[25] the study by Perini et al. on a 37-year-old adult patient who had survived 5 months after transplantation.[26]

The survival of heterozygous transplanted sickle cell patients is better, and the results are similar to those obtained for the general population of transplant recipients in France.[27] The survival of women, that of patients who underwent liver transplantation in less than 3 days was better. The reason for such a result is explained by the early control of the patient's condition, preventing progression to serious complications.[28] In multivariate analysis, male sex, duration of transplantation greater than 3 days, homozygous subjects, hepatic encephalopathy and high risk of MELD score were the factors emerging as predictors of mortality during liver transplantation. Organ dysfunction could explain the deaths of these categories of patients.

Our study had some limitations: (i) Given the limitations of any retrospective study, type 2 error due to sample size cannot be ruled out with respect to comparisons between survivors and deceased, (ii) the lack of ontological homogeneity in the literature hindered a thorough review, and (iii) as there is a tendency to report both survived and deceased cases, a bias could be reported, especially for the review, which was mainly based on case reports.

Conclusion

This study showed that the survival of transplant patients was similarly better than the death rate. This mortality is associated with male sex, hepatic complications, duration of transplantation and organ failure (MELD score).

Declaration

Author's contributions

JJM and ANN participated in protocol elaboration, data collection, and analysis and wrote the manuscript; CD, FM and AWYT reviewed the manuscript.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the National Health Ethics Committee of the DRC under Approval No.239/CNES/BN/PMMF/2021.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

Not applicable.

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Conflicts of interest

The authors declare no potential conflicts of interest relevant to this article.

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