PRELIMINARY EVALUATION OF THE EFFECTIVENESS OF AUTOLOGOUS BONE MARROW STEM CELL THERAPY IN SUPPORTING THE TREATMENT OF BILIARY ATRESIA

Nguyen Pham Anh Hoa[1,✉], Hoang Tuan Khang[1]
Pham Duy Hien[1], Nguyen Thanh Binh[1,2], Dang Thi Ha[1], Bach Thi Ly Na[1]
Pham Thi Hai Yen[1], Tran Duc Tam[1], Phan Hong Long[3], Vu Manh Hoan[1]
Nguyen Duc Hanh[1], Nguyen Duc Thanh[3], Tran Thi Thu Huyen[1]
[1]Vietnam National Children's Hospital
[2]Hanoi Medical University
[3]University of Medicine and Pharmacy, Vietnam National University

Biliary atresia (BA) is a rare hepatobiliary disorder. Stem cell therapy is expected to serve as a supportive treatment to slow fibrosis progression. This study aimed to assess the therapeutic efficacy and the safety of the Kasai procedure combined with autologous bone marrow stem cell (ABMSC) infusion. From May 2021 to December 2024, 82 pediatric BA patientswho underwent the combined treatment at Vietnam National Children's Hospital were enrolled. The mean age at surgery was 76.8 ± 12.6 days. No severe complication occurred during stem cell harvesting or follow-up time frame. The successful bile drainage rate at 6 months post-surgery was 58.5%. Post-operatively, transaminase levels gradually declined and stabilized from 12 months. GGT levels peaked at 3 months ($p < 0.001$), then declined from 6 months and stayed stabilized. PELD scores improved significantly. Liver tissue elasticity increased gradually until 12 months (14.6 ± 4.5kPa) and then stabilized. Mean post-surgical survival was 34.3 ± 1.7 months, and 30-month survival rate was 64.7%. Portal hypertension occurred in 55% of patients, mostly in those with high-dose MSC therapy. Despite benefits achieved in liver function improvement, progressive cirrhosis remains a challenge, necessitating further research on optimizing stem cell therapy in BA treatment.

Keywords: Biliary atresia, Kasai operation, autologous bone marrow stem cells, treatment outcomes, safety.

I. INTRODUCTION

Biliary atresia (BA) is a progressive inflammatory disorder triggering bile duct obstruction, thus leading to liver cirrhosis and end-stage liver disease.[1] The Kasai procedure remains the primary treatment for bile drainage but is only a temporary solution. Cirrhosis still continues to progress even after Kasai surgery, so liver transplantation is the definitive treatment for patients with biliary atresia who have reached end-stage liver disease. Nevertheless, many children, especially in developing countries, could not afford liver transplantation due to the shortage of donors, the high cost, and the long-term dependence on immunosuppressant medication. Numerous studies worldwide have highlighted the role of stem cells (SCs) in the treatment of chronic liver diseases and cirrhosis, with the hope to slow fibrosis progression and extend the waiting period before liver transplantation.[2-5] However, research on its efficacy in the pediatric BA population remains limited. This study evaluates

Corresponding author: Nguyen Pham Anh Hoa
Vietnam National Children's Hospital
Email: dranhhoa@nch.gov.vn
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the preliminary effectiveness and safety of ABMSC therapy as a supportive treatment of biliary atresia at Vietnam National Children's Hospital.

II. MATERIALS AND METHODS

1. Subjects

The patients diagnosed with biliary atresia are based on the following inclusion and exclusion criteria.

Inclusion Criteria

- Infants between 30 and 100 days old with a confirmed intraoperative diagnosis of BA.
- Liver biopsy confirming the diagnosis of BA.
- Informed consent was obtained from the legal guardians.

Exclusion Criteria

- Prior Kasai procedure.
- Severe cardiovascular, renal, gastrointestinal, or central nervous system diseases.
- Total parenteral nutrition within two weeks before surgery.
- Unexplained infections, bleeding disorders, or thrombosis.
- Poor-quality bone marrow samples or abnormal cells.
- Inability to provide required biological samples or adhere to follow-up.

2. Methods

This interventional study was conducted from May 1, 2021, to December 18, 2024, at the Vietnam National Children's Hospital with a convenience sample of 82 eligible patients.

Research Methodology

Eligible BA patients underwent ABMSC collection and infusion concurrently with the Kasai procedure. Bone marrow was harvested through anterior iliac crest puncture under general anesthesia, with an estimated volume of 10 ml/kg. Liver function test improvement, bile drainage efficiency, and the degree of fibrosis were evaluated.

Study parameters and variables

The collected data included age at surgery, gender, weight, average follow-up time, and stem cell-related parameters, such as mesenchymal stem cell (MSC) dose. Additionally, early intraoperative and postoperative complications were monitored, along with clinical and laboratory parameters, including serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), albumin, international normalized ratio (INR), liver stiffness measurement via elastography, and ediatric End-Stage Liver Disease (PELD) score. These parameters were assessed preoperatively and at 3, 6, 12, 18, 24, and 30 months after the operation.

Successful bile drainage (6 months after operation) was defined if patients had normal stool color, jaundice resolution, and serum total bilirubin < 34 mmol/L.

The PELD score is calculated as follows:

PELD score = 0.48 × ln(Bilirubin, mg/dL) + 1.857 × ln(INR) − 0.687 × ln(Albumin, g/dL) + 0.436 (if age < 1 year) + 0.667 (if the history of growth failure is positive).

Table 1. Comparison table of liver fibrosis staging measured by elastography ultrasound (kPa) and METAVIR according to Philips' recommendations

Liver fibrosis classification	METAVIR	kPa
Normal	F0	2.0 – 4.5
Mild fibrosis	F0 – F1	4.5 – 5.7
Moderate fibrosis	F2 – F3	5.7 – 12.0
Severe fibrosis	F3 – F4	12.0 – 21.0

Methods to measure MSC count in bone marrow aspiration:

- Counting the number of mesenchymal stem cells using flow cytometry with the BD Facs Canto machine.

- Using the mesenchymal stem cell counting reagent kit (Human MSC Analysis Kit 50 tests/ box, Lot: 3354146) from BD Company.

- Based on the expression and non-expression of specific markers:

+ Positive (≥ 95%): CD73, CD90, CD105.

+ Negative (≤ 2%): CD14 or CD11b, CD79a or CD19, CD34, CD45, HLA-DR.

The reagent for positive control evaluation was hMSC Positive Isotype Control Cocktail and for negative control evaluation was hMSC Negative Isotype Control Cocktail. MSC dose = Volume of bone marrow-derived stem cell mass × Number of MSC cells/kg body weight × 1000.

Portal Hypertension: Diagnosis based on the following symptoms.

- Clinical signs: The patient presents with symptoms of chronic liver disease accompanied by one or more of the following: splenomegaly (enlarged spleen), collateral circulation, ascites, or gastrointestinal bleeding.

- Paraclinical assessments were evaluated indirectly through:

+ Doppler ultrasound to assess liver parenchyma, portal vein diameter, collateral circulation around the umbilical region, and reversed or abnormal portal vein flow.

+ Upper gastrointestinal endoscopy to detect esophageal varices.

+ Platelet counts less than 125 G/L.

Data analysis was performed using SPSS software version 20.0. Descriptions with percentages, mean, and standard deviation were analyzed, and comparative testing using a student's T-test was performed. A p-value of less than 0.05 was considered statistically significant. The Kaplan-Meier survival analysis was used to estimate the survival function.

3. Research ethics

The study was approved by the Ethics Committee of the Institute of Child Health Research, Vietnam National Children's Hospital (No. 986/BVNTW-VNCSKTE on May 26, 2021).

III. RESULTS

A total of 82 patients diagnosed with BA met the eligibility criteria and were included in the study. The mean age at surgery was 76.8 ± 12.6 days, ranging from 40 to 98 days, with a female-to-male ratio of 1.16:1. The mean weight was 5.07 ± 0.65 (kg), and the average follow-up time was 22.6 ± 13.3 months (6 - 42 months).

A mean volume of 66.7 ± 12.4 mL bone marrow aspirate was collected with a mean harvesting duration of 11.3 ± 2.6 minutes. The average MSC cell count per kilogram of body weight was 5.25 ± 5.08 × 10^3 cells. All 82 patients successfully received ABMSC therapy in conjunction with the Kasai procedure. The average volume of processed SC administered to each patient was 11.4 ± 1.5mL. The portal vein was the primary injection site in 64.6% of cases, while 35.4% of patients were infused SC through the round ligament vein. Our results demonstrated that the portal vein route is feasible and safe for children with BA.

During bone marrow aspiration, 20.9% of patients experienced hypotension, and 13.9% had hypothermia. All patients required intraoperative blood transfusion when hemoglobin (Hb) levels dropped below 9 g/ dL. Notably, there were no significant adverse event related to the stem cell infusion or follow-up time after the operation.

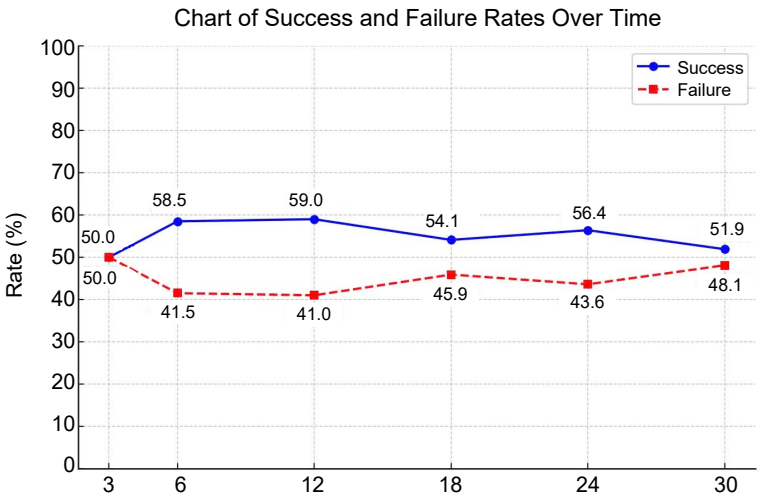

Chart 1. Successful biliary drainage rate at different follow-up time points

The success rate was 58.5% at 6 months post-surgery (with mean serum total bilirubin level was 117.8 ± 142.1 mmol/L compared to 168.1 ± 42.1 pre-operative) and remained stable throughout subsequent time points.

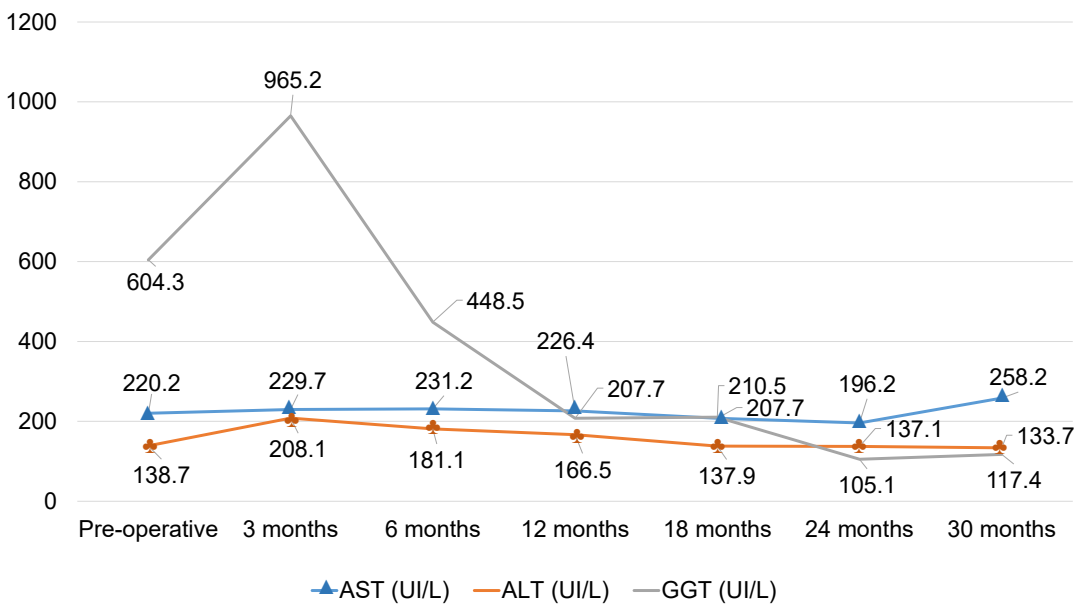

Chart 2. Changes in AST, ALT, and GGT levels over time

AST levels remained relatively stable during the first 6 months, while ALT increased significantly. GGT levels peaked at 3 months post-surgery ($p < 0.001$) and showed a gradual decline from 6 months onward. From 12 months, AST and ALT levels decreased and stabilized over time. Meanwhile, GGT demonstrated a marked reduction following surgery. Values are presented as mean ± standard deviation (SD).

Table 2. Changes in PELD score over time

Timepoint	PELD score (Mean ± SD)	*p*-value
Pre-surgery (n = 82)	8.5 ± 4.5	-
3 months post-surgery (n = 82)	3.6 ± 9.1	$p_{03} < 0.001$
6 months post-surgery (n = 79)	5.1 ± 11.8	$p_{06} = 0.012$
12 months post-surgery (n = 54)	3.2 ± 14.0	$p_{012} = 0.007$
18 months post-surgery (n = 42)	-1.7 ± 11.2	$p_{018} < 0.001$
24 months post-surgery (n = 41)	-0.7 ± 11.0	$p_{024} < 0.001$
30 months post-surgery (n = 33)	-1.9 ± 8.3	$p_{030} < 0.001$

The PELD score improved significantly after the operation, with a remarkable decrease observed from 3 months onward. Statistical significance was achieved at multiple time points ($p < 0.05$).

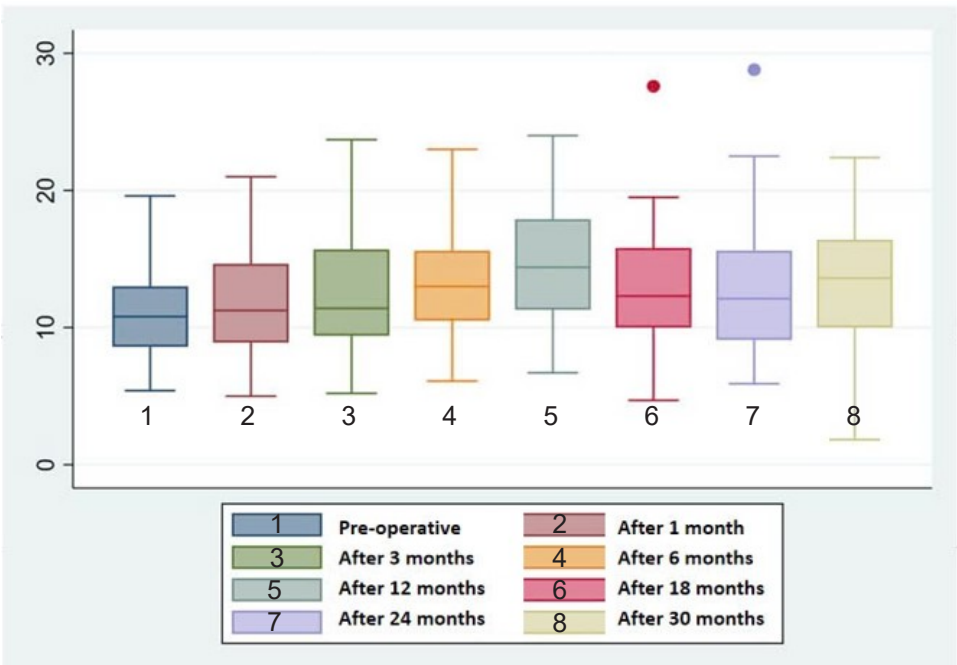

Chart 3. Changes in liver elasticity (EQI kPa) over time

Liver stiffness gradually increased post-surgery, peaking at 12 months (14.6 ± 4.5kPa). Afterward, the elasticity values gradually declined and stabilized, reaching 13.2 ± 5.3kPa at 30 months post-surgery.

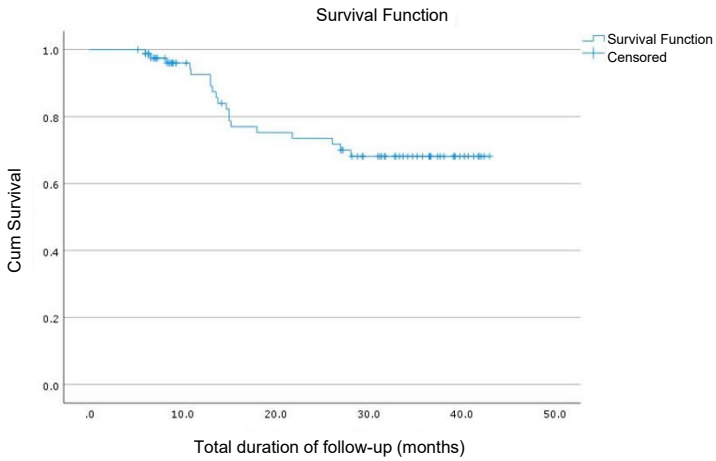

Chart 4. Overall survival time after surgery

The chart depicts overall survival following surgery, with a mean survival of 34.3 ± 1.7 months. Survival probability gradually declined, with the sharpest decrease occurring between 12- and 24-months post-surgery. At the 30-month time point, the cumulative survival was 64.7%.

Table 3. MSC dose and portal hypertension incidence after treatment

Presence of Portal Hypertension	MSC dose (n, %)		p-value
	≤ 3 x 10^3/kg	> 3 x 10^3/kg	
6 months post-surgery	9 (25.0%)	16 (37.2%)	0.245
12 months post-surgery	12 (46.2%)	21 (75.0%)	*0.03*
18 months post-surgery	8 (38.1%)	14 (66.7%)	0.064
24 months post-surgery	11 (52.4%)	13 (65.0%)	0.412
30 months post-surgery	16 (43.2%)	25 (55.6%)	0.267

Portal hypertension occurred in 55% of patients, with a mean onset time of 9.3 ± 6.3 months. Patients receiving MSC doses > 3 × 10^3 cells/kg had a higher incidence of portal hypertension, with a statistically significant difference at 12 months post-surgery (p = 0.03).

IV. DISCUSSION

The mean age at surgery for the 82 patients in this study was 76.8 ± 12.6 days, higher than the 57 days reported in Gutierrez's study.[6] The female-to-male ratio was approximately 1.16:1, consistent with findings from both domestic and international studies.

Adverse events associated with ABMSC therapy were primarily related to bone marrow harvesting, including hypotension and thrombotic complications. In pediatric anesthesia, intraoperative hypotension is defined as a 20 - 30% systolic blood pressure reduction from baseline.[7] In this study, 20.9% of patients experienced transient hypotension post bone marrow aspiration, likely due to preoperative fasting-induced dehydration, bowel preparation, Propofol anesthesia, and

caudal epidural anesthesia. These cases were managed with fluid resuscitation and red blood cell transfusion when Hb levels fell below 90 g/L, ensuring hemodynamic stability before proceeding with the Kasai procedure. To mitigate MSC-associated thrombosis risk, a filtration system (500µm and 200µm) was used to remove impurities from the bone marrow aspirate before stem cell isolation. ABMSC infusion was administered slowly (1mL per minute) to reduce the risk of thrombosis. Clinical monitoring and Doppler ultrasound detected no thrombosis or other complications during bone marrow harvesting or post-infusion follow-up.

As shown in Chart 1, the successful bile drainage rate was 58.5% at six months post-surgery and remained stable throughout follow-up time points. This was higher than previous rates reported by Lo Anh Tinh (57.38%) and Emad Hamdy Gad (33.7%).[8,9] While no direct evidence confirms stem cell regeneration in the biliary system, improved bile drainage may result from MSCs' immunomodulatory, anti-inflammatory, and fibrosis-inhibiting properties and CD34+ cell regenerative potential. Additionally, MSC-secreted cytokines and growth factors, such as hepatocyte growth factor (HGF), may enhance liver tissue regeneration and improve liver function.[10] Bilirubin levels declined in the first six months post-Kasai surgery with mean serum total bilirubin level of 117.8 ± 142.1 mmol/L compared to 168.1 ± 42.1 pre-operative. Still, they did not remain consistently low in the long term, likely due to progressive liver fibrosis, recurrent cholangitis, or waning stem cell therapeutic effects. Repeated stem cell infusions may be required to maintain long-term benefits. The duration of stem cell effectiveness depends on liver damage severity, stem cell type and dose, and delivery method. The intra-arterial infusion may enhance targeted hepatic delivery, while intravenous infusion ensures broader distribution. Several studies, including those by Sharma (2011), Khan A. (2008), and Fu-Sheng Wang (2012), have demonstrated that stem cell therapy significantly improves liver function within 7 days to 1 month post-treatment.[11-13] However, these effects were generally transient and lasted only for 12 to 24 months. This improvement was observed in patients who received both CD34+ cells and MSCs.

Regarding hepatic enzyme markers, AST and ALT are critical indicators of liver function and hepatocellular damage. Chart 2 shows no significant change in AST and ALT levels before and after surgery combined with stem cell infusion. GGT levels increased slightly in the early months post-surgery, likely due to biliary tract injury caused by surgical intervention in the biliary tree. Nevertheless, the GGT level started to decline after 6 months and continued this trend until 12 months after surgery, indicating gradual stabilization and improvement in bile drainage. These findings align with those of Lo Anh Tinh (2018), further supporting the potential therapeutic role of stem cell therapy in biliary atresia treatment.[9]

Animal studies have demonstrated that MSCs can slow liver fibrosis progression and even reverse fibrotic changes through various paracrine signaling mechanisms. These mechanisms work by inhibiting hepatic stellate cell (HSC) activation, reducing collagen production, and directly degrading extracellular matrix (ECM) components.[10] The PELD score, widely used to assess and predict disease progression in pediatric patients, helps classify and prioritize liver transplant candidates based on severity. As shown in Table 2, there was a significant improvement in PELD scores within three to six months post-surgery, with the

average PELD score dropping from 8.5 pre-operatively to 3.6 at three months ($p < 0.001$) and further decreasing to -1.9 at the 30-month timepoint. These findings are consistent with a meta-analysis by Wenming Lu (2023), which reviewed 11 clinical trials on chronic liver disease patients treated with MSCs. The study concluded that MSC therapy significantly improved albumin levels at 2 weeks, 1 month, 3 months, and 6 months after treatment while showing statistically significant improvements in MELD scores at 1, 2, and 6 months post-infusion.[14]

In clinical practice, most BA patients already have biliary cirrhosis at the time of surgery, and fibrosis continues to progress even after a successful Kasai procedure. With its anti-inflammatory and anti-fibrotic properties, stem cell therapy offers a promising approach to delaying cirrhosis progression. However, its effectiveness is dependent on several factors, including stem cell type, administration route (portal vein, hepatic artery, peripheral intravenous…), and duration of action. This underscores the importance of long-term monitoring and potential booster stem cell infusions to sustain therapeutic effects. Although liver biopsy remains the gold standard for fibrosis assessment, its invasive nature and associated risks make repeated procedures impractical. As a result, non-invasive imaging techniques, such as elastography, have become valuable tools. Studies have shown that elastography has high sensitivity and specificity in fibrosis assessment, comparable to the METAVIR scoring system.[7] As illustrated in Chart 3, our study utilized EQI to monitor liver stiffness, a key fibrosis marker. Results showed a gradual increase in EQI from 11.3kPa preoperatively to a peak of 14.6kPa at the 12-month timepoint post-surgery, reflecting ongoing fibrosis progression. However, EQI values subsequently declined to 13.2kPa in 30 months ($p < 0.05$), suggesting a stabilization of fibrosis progression over time. This supports the hypothesis that stem cell therapy, particularly MSCs, may help mitigate fibrosis progression. Given that MSCs exert anti-fibrotic effects by inhibiting HSC activation, reducing collagen deposition, and degrading ECM, these mechanisms may have contributed to reducing and stabilizing liver stiffness.[10]

Several studies worldwide have demonstrated the effectiveness of SC and MSC therapy in improving survival outcomes. A study by Lin et al. (2017) involving 56 patients with chronic HBV hepatitis who received bone marrow-derived MSCs at doses ranging from 1.0 to 10×10^5 cells/kg weekly for four consecutive weeks reported a significantly higher cumulative survival probability at 6 months in the MSC-treated group (73.2%) compared to the control group (55.6%, $p = 0.03$), along with improved liver function.[15] Similarly, Sharma et al. (2010) found that the 12-month survival rate was higher in the group treated with SC (36.4%) compared to the control group, suggesting that SC therapy may prolong survival in children with cirrhosis due to BA.[12] As illustrated in Chart 4, our study's mean overall survival time was 34.3 months, with a cumulative survival probability of 64.7% at 30 months post-surgery. A study by Qiao et al. (2015) analyzed 244 BA patients after Kasai surgery and reported a mean survival time of 41.2 months, with cumulative survival probabilities of 61.1% at 3 years and 43.3% at 5 years, respectively.[16] This difference suggests that stem cell therapy may offer a potential survival benefit, raising hopes of prolonging survival in BA patients.

Our findings indicated that ABMSC therapy contributed to improved liver function in BA patients post-Kasai surgery, with sustained

effects observed up to 30 months post-treatment. Key indicators such as bilirubin, GGT, AST, ALT, albumin, and PELD scores reflected significant hepatic function recovery, which may help extend the liver transplant waiting period. However, some patients still exhibited progressive liver fibrosis, as evidenced by rising elastography (Elasto) scores over time. This suggests that SC therapy supports liver function maintenance but does not completely halt fibrosis progression.

Table 3 revealed that the average time to the onset of portal hypertension was 9.3 months post-surgery in our study. This unexpected result raised concerns that rather than reducing the risk of portal hypertension, stem cell therapy might have accelerated its onset. Furthermore, patients who received MSC doses greater than 3×10^3 cells/kg had a higher incidence of portal hypertension, with a statistically significant difference at 12 months post-surgery ($p = 0.03$). Based on the proposed mechanism of SCs, a hypothesis for this finding was suggested. Firstly, the portal vein was used as the site for SC infusion, which may have had a direct impact on the vein, a structure inherently vulnerable in patients with BA, potentially increasing the risk of early-onset portal hypertension. Secondly, SCs may promote rapid hepatocyte proliferation, but uneven cellular growth could disrupt the hepatic microvascular architecture, leading to increased portal venous resistance at an earlier stage. Furthermore, SCs stimulate blood flow within the portal circulation. However, if the collateral circulation has not yet fully developed, excessive hepatocyte proliferation could compress the hepatic microvasculature, disrupt intrahepatic blood flow, and contribute to the early development of portal hypertension.

V. CONCLUSION

No serious complication was observed during bone marrow stem cell harvesting and in the follow-up period. There was a significant improvement in clinical and laboratory parameters, including bile drainage status, GGT, and PELD score, as well as stabilized liver elasticity. Stem cell therapy demonstrated potential benefits in prolonging survival, with a cumulative survival probability of 64.7% at 30-month post surgery. These findings suggest that ABMSC therapy may serve as a promising supportive treatment for congenital biliary atresia, although long-term monitoring and further research are needed to optimize its effectiveness and mitigate potential risks.

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Conflict of interest: None.

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