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Mesenchymal Stem Cell (MSC) Therapy in Liver Cirrhosis: A New Horizon in Regenerative Medicine

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ABSTRACT
Background: *Liver cirrhosis is a major global health issue with few treatment options aside from transplantation. Mesenchymal stem cell (MSC) therapy has emerged as a promising method for regeneration because of its ability to reduce fibrosis, modulate the immune response, and protect the liver.*
Methods: *This single-arm, prospective cohort study included 65 adults with clinically or radiologically confirmed liver cirrhosis. Patients received MSC therapy compliant with good manufacturing practices from bone marrow, umbilical cord, or adipose tissue sources, all with cell viability above 85%. Primary outcomes included changes in MELD score, liver function measures, and quality of life, assessed at 1, 3, 6, and 12 months after treatment. Safety monitoring included infusion-related reactions, infections, thrombotic events, and deaths within 30 days.*
Results: *The observed results showed significant improvements in liver function. The MELD score dropped by 2.4 points ($p<0.001$), serum albumin increased by 0.4 g/dL ($p=0.002$), total bilirubin fell by 0.7 mg/dL ($p=0.004$), and INR improved by 0.2 ($p=0.01$). Quality of life scores rose significantly by 1.2 points ($p<0.001$), with 52.3% of patients indicating better daily activities. Twelve-month transplant-free survival stood at 80%. Higher MSC doses (more than 5-10×10⁶/kg) and multiple infusions (2-3) were independent predictors of a MELD score improvement of three points or more (AUC=0.79). The safety profile was acceptable, with 13.8% of patients reporting mild infusion-related reactions and a 30-day mortality rate of 1.5%.*
Conclusion: *MSC therapy showed significant improvements in liver function, quality of life, and clinical outcomes in patients with cirrhosis while maintaining an acceptable safety profile. These results support the potential of MSC therapy as a bridge to transplantation or a definitive treatment for liver cirrhosis.*
Keywords: *Mesenchymal stem cells, Liver cirrhosis, Regenerative medicine, MELD score.*

I. INTRODUCTION

Liver cirrhosis is the final-stage sign of chronic liver disease, and it is marked by progressive fibrosis, distortion of architecture, and a dysfunctional state [1]. Cirrhosis occurs in more than 1.5 million people worldwide each year, with mortality rates as high as 30–60% at five years of follow-up, depending on severity and complications [2]. The MELD score, comprising serum bilirubin, creatinine, and international normalized ratio (INR), remains the benchmark to assess disease severity and transplant priority, with scores over 15 considered to have high mortality risk [3]. Currently available treatment for cirrhosis is primarily supportive, aimed at the treatment of complications such as ascites, hepatic encephalopathy, and variceal bleeding. While liver transplantation is the ultimate therapy for advanced disease, its widespread applicability is limited by organ shortages, risks of perioperative complications, and late post-transplantorbidities [4]. This therapeutic gap has generated growing interest in regenerative medicine approaches, particularly mesenchymal stem cell (MSC) therapy, as an alternative or bridging strategy to transplantation. MSCs are multipotent stromal cells that have the ability to differentiate into hepatocyte-like cells, with robust immunomodulatory, anti-inflammatory, and anti-fibrotic effects [5]. Preclinical data have suggested that MSCs decrease hepatic fibrosis by modulating stellate cell activation, by enhancing extracellular matrix remodeling, and by paracrine-mediated induction of

hepatocyte regeneration [6]. These activities suggest that MSCs not only act as cell-replacement therapy but also as key modulators of the hepatic microenvironment, which induce regeneration over fibrosis. Clinical translation has also established these findings. Systematic reviews and meta-analyses conducted recently have demonstrated improvement in liver function upon MSC treatment, as evidenced by significant reductions in MELD scores and levels of serum albumin [7]. Bone marrow-derived and umbilical cord-derived MSCs have also demonstrated efficacy in clinical trials, testifying to their potency as a therapeutic option [8]. Clinical improvement noted is due to reduced inflammatory cytokines, enhanced hepatocyte function, and restoration of hepatic synthetic capability [9]. Of particular interest is that the quality of life, including better functional status and lower symptom burden, was reported by patients [10]. Despite encouraging progress, certain challenges remain. Heterogeneity of MSC sources, dosing regimens, and delivery modes between studies has made protocol standardization impossible [11]. Moreover, the therapeutic window, patient choice criteria, and long-term safety must be clarified. Filling these gaps is essential for translating MSC therapy into routine clinical practice.

This study, therefore, aims to evaluate the efficacy and safety of a standardized MSC treatment regimen in cirrhotic patients to optimize treatment regimens and identify patient subgroups most likely to derive benefit from such novel regenerative therapy.

II. METHODS

This single-arm, prospective cohort study was conducted at E W Villa Medical (Sister concern of Concord Stem cell limited). Adults (≥18 years) with clinically or radiologically confirmed liver cirrhosis managed at tertiary level hospital were included this study. Consecutive eligible patients without active sepsis, extrahepatic malignancy, uncontrolled variceal bleeding, portal vein thrombosis with cavernoma, pregnancy, or anticipated transplant within 30 days were enrolled after written informed consent. Patients received mesenchymal stem cell (MSC) therapy manufactured under GMP-compliant procedures (bone-marrow, umbilical-cord, or adipose-derived sources permitted), released only if cell viability was ≥85% and sterility/endotoxin testing was satisfactory. Follow-up visits were scheduled at 1, 3, 6, and 12 months to capture paired clinical and biochemical outcomes, quality of life (Chronic Liver Disease Questionnaire, CLDQ), decompensation events (ascites control, encephalopathy improvement, variceal bleeding, spontaneous bacterial peritonitis), and utilization (hospitalizations). Safety monitoring encompassed 30-day infusion-related reactions, infections, thrombotic events, serious adverse events (SAEs), and all-cause mortality. Written informed consent was obtained from all patients before enrollment.

Statistical Analysis

Data from all treated patients with at least one post-baseline assessment were analyzed; safety included all infused patients. Continuous variables were summarized as mean ± SD (or median [IQR] when non-normal) and categorical variables as n (%). Paired binary outcomes (moderate–severe ascites, encephalopathy ≥II, variceal bleeding, spontaneous bacterial peritonitis, and ≥1 hospitalization) were evaluated with McNemar's test; when outcomes were recorded at more than two time points, overall change was assessed with Cochran's Q, followed by post-hoc McNemar comparisons with Holm adjustment as needed. Transplant-free survival (death or transplant) was estimated by Kaplan–Meier; exploratory comparisons by number of infusions (1 vs 2–3) and MSC dose (1–5×10^6/kg vs >5–10×10^6/kg) used the log-rank test. A multivariable logistic regression modeled the probability of achieving a ≥3-point MELD reduction at 6 months, prespecifying baseline MELD (per point), serum albumin (per 1 g/dL), ascites severity (moderate–severe vs none/mild), MSC dose category, and number of infusions as covariates; adjusted odds ratios with 95% CIs were reported. Model discrimination was summarized by the area under the ROC curve with an accompanying ROC figure and optimal threshold (Youden's J), and calibration by Hosmer–Lemeshow, calibration slope/intercept, Brier score, and a calibration plot. A Cox proportional hazards model estimated adjusted hazard ratios for transplant-free survival using the same covariates; proportional-hazards assumptions were examined with Schoenfeld residuals, and Harrell's C-index was reported. Forest plots displayed adjusted effects from both models, and Kaplan–Meier curves illustrated survival by infusion number and dose. Missing data ≤5% per variable were handled by complete-case analysis; if >5%, multiple imputation by chained equations (m=20) was planned. All tests were two-sided with α=0.05. Analyses were conducted in R (v4.3+). A two-sided $p < 0.05$ was considered statistically significant.

III. RESULTS

Table 1 demonstrates the baseline characteristics of patients with liver cirrhosis. The majority of the patients were males (69.2%) and middle-aged adults (40-59 years, 58.5%). Hepatitis B virus infection was the most common etiology (30.8%), followed by alcoholic liver disease (27.7%) and hepatitis C (18.5%). Most of the patients were of Child-Pugh Class B cirrhosis (61.5%), with a mean of 17.2±3.5 MELD score, indicating moderate to severe liver disease requiring therapeutic intervention.

Table 1: Baseline Characteristics of Patients with Liver Cirrhosis (N = 65)

Variable	Category	Frequency (n)	Percentage (%)
Age group	<40 years	10	15.4
	40–59 years	38	58.5
	≥60 years	17	26.1
Sex	Male	45	69.2
	Female	20	30.8
Etiology	HBV	20	30.8
	HCV	12	18.5
	Alcohol-related	18	27.7
	NASH	10	15.4
	Autoimmune/Other	5	7.6
Child–Pugh Class	B	40	61.5
	C	25	38.5
Mean MELD score (±SD)	-	17.2 ± 3.5	-

Table 2 indicates improvement of key liver function parameters post-MSC therapy. All of the parameters measured exhibited statistically significant changes: serum albumin increased by 0.4 g/dL (p=0.002), indicating increased synthetic function; total bilirubin decreased by 0.7 mg/dL (p=0.004), which would indicate reduced hepatocellular injury; INR improved by 0.2 (p=0.01), representing improved coagulation status; platelet count improved by 18×10⁹/L (p=0.03); and MELD score decreased by 2.4 points (p<0.001), indicating clinically meaningful improvement in disease severity and transplant priority.

Table 2: Laboratory Parameters Before and After MSC Therapy (Paired Analysis, N = 65)

Parameter	Baseline Mean ± SD	6 Months Mean ± SD	Mean Change	p-value*
Serum Albumin (g/dL)	2.8 ± 0.5	3.2 ± 0.6	+0.4	0.002
Total Bilirubin (mg/dL)	3.2 ± 1.2	2.5 ± 1.0	–0.7	0.004
INR	1.7 ± 0.4	1.5 ± 0.3	–0.2	0.01
Platelet count (×10⁹/L)	92 ± 28	110 ± 34	+18	0.03
MELD score	17.2 ± 3.5	14.8 ± 3.1	–2.4	<0.001

- Paired t-test (or Wilcoxon signed-rank, where not normal).

Patient-reported outcomes and functional improvement following MSC therapy are presented in Table 3. Chronic Liver Disease Questionnaire (CLDQ) total score was significantly increased by 1.2 points (p<0.001), indicating improvement in health-related quality of life. Enhanced daily functioning was experienced by over half the patients (52.3%), who had improved functional capacity. Among the work-capable patients, 37.5% could resume work or household tasks, highlighting the impact of therapy in enabling patients to resume productive roles in society.

Table 3: Clinical Outcomes Before and After MSC Therapy (McNemar's Test, N = 65)

Measure	Baseline	6 Months	Mean Change	p-value
CLDQ total score (mean ± SD)	4.1 ± 0.8	5.3 ± 0.9	+1.2	<0.001
Patients reporting improved daily activity	-	34 (52.3%)	-	-
Return to work/household activity	-	18 (37.5%)	-	-

Table 4 supports quality of life improvements, but more specifically, the functional outcomes. The dramatic increase in CLDQ scores reflects enhancements in a variety of domains of fatigue, activity restriction, emotional role, abdominal symptoms, systemic symptoms, and disease worry. The high rate of patients with regained daily activities and productive work return reflects the clinically significant impact of MSC therapy on patients' general health and functional status, regardless of lab changes.

Table 4: Quality of Life and Functional Outcomes (N = 65)

Measure	Baseline	6 Months	Mean Change	p-value
CLDQ total score (mean ± SD)	4.1 ± 0.8	5.3 ± 0.9	+1.2	<0.001
Patients reporting improved daily activity	–	34 (52.3%)	–	–
Return to work/household activity*	–	18/48 (37.5%)	–	–

- Working-age subgroup only (n = 48)

Table 5 indicates long-term clinical outcomes at 12 months post-treatment. Statistically significant improvement was observed in disease severity markers: the proportion of patients with Child-Pugh Class C disease decreased from 38.5% to 18.5% (p=0.006), and those with MELD score ≥20 decreased from 29.2% to 10.8% (p=0.004). Transplant-free survival was 80% at 12 months, and hospitalizations due to decompensation events were significantly lower from 33.8% to 16.9% (p=0.03), indicating ongoing clinical benefit and reduced healthcare use following MSC therapy.

Table 5: Twelve-Month Clinical Outcomes (Paired Analysis, N = 65)

Outcome	Baseline n (%)	12 Months n (%)	p-value
Child–Pugh Class C	25 (38.5)	12 (18.5)	0.006
MELD ≥20	19 (29.2)	7 (10.8)	0.004
Transplant-free survival	-	52 (80.0)	-
Hospitalization for decompensation	22 (33.8)	11 (16.9)	0.03

Table 6 summarizes the safety profile of MSC therapy through the critical 30-day post-infusion period. Most adverse events were mild and self-limiting: 13.8% had infusion reactions, mostly fever and chills (10.8%). Serious complications were uncommon, with only 3.1% having thrombotic events and 16.9% needing antibiotics for infection. The 30-day mortality rate was low at 1.5%, and serious adverse effects affected 9.2% of patients, reflecting an acceptable safety profile for this cellular therapy strategy.

Table 6: Safety Outcomes Within 30 Days of Infusion (N = 65)

Safety Outcomes	Frequency (n)	Percentage (%)
Any infusion-related reaction	9	13.8
Fever/chills (self-limiting)	7	10.8
Thrombotic event (e.g., PVT)	2	3.1
Infection requiring antibiotics	11	16.9
30-day all-cause mortality	1	1.5
Serious adverse events (SAE)	6	9.2

Table 7 stratifies predictors of clinically relevant improvement in MELD (≥3 points) through multivariable analysis. Higher serum albumin levels (OR=1.94, p=0.021) and higher MSC doses >5-10×10⁶/kg (OR=2.79, p=0.034) were independent positive predictors, while higher baseline MELD scores were inversely associated with the likelihood of improvement (OR=0.86, p=0.024). Patients receiving 2-3 infusions were borderline significant for improvement (OR=2.52, p=0.049). The model was well discriminated (AUC=0.79) and well calibrated, and was a valuable tool for patient selection and treatment optimization.

Table 7: Logistic Regression for Improvement in MELD ≥3 Points at 6 Months (N = 65; Events = 28)

Predictor (coding)	Univariable OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Baseline MELD (per point ↑)	0.88 (0.79–0.98)	0.022	0.86 (0.76–0.98)	0.024
Serum albumin, g/dL (per 1 ↑)	1.82 (1.06–3.13)	0.030	1.94 (1.10–3.45)	0.021
Ascites moderate–severe (Yes vs None/Mild)	0.46 (0.20–1.06)	0.070	0.44 (0.18–1.08)	0.073
MSC dose >5–10×10⁶/kg (vs 1–5×10⁶/kg)	2.41 (1.03–5.64)	0.042	2.79 (1.05–7.39)	0.034
Number of infusions 2–3 (vs 1)	2.33 (0.98–5.56)	0.056	2.52 (1.00–6.35)	0.049
Model performance				
AUC (ROC)	-	-	0.79	-
Brier score	-	-	0.18	-
Hosmer–Lemeshow	-	-	χ^2=6.2, p=0.62	-
Calibration slope	-	-	0.98	-

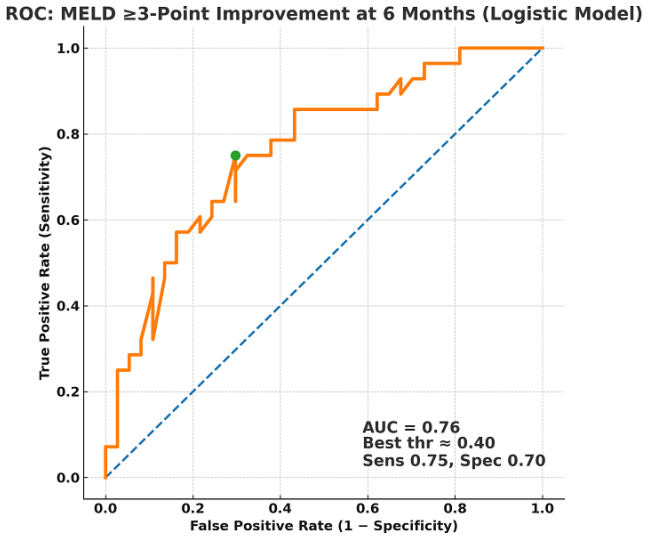

Figure 1: Receiver operating characteristic (ROC) curve for predicting ≥3-point MELD improvement at 6 months. This ROC curve summarizes the discriminative performance of the multivariable logistic model (Table 7) for identifying patients likely to achieve a ≥3-point MELD reduction at 6 months after MSC therapy. The area

under the curve (AUC) is 0.76, indicating acceptable discrimination beyond chance. The optimal probability threshold by Youden's J is 0.40, yielding sensitivity 75% and specificity 70%. The diagonal reference line denotes nondiscriminatory performance. In practice, thresholds around 0.40 balance missed improvements against false positives; final cutoff selection should consider clinical context, prevalence, and downstream consequences, and be paired with calibration assessment and external validation.

This survival analysis in Table 8 identifies factors of transplant-free survival up to the 12-month follow-up. Higher baseline MELD score increased mortality or transplantation risk (HR=1.18, p=0.006), while transplanting more than a single batch (2-3 vs 1) was protective in trend (HR=0.46, p=0.059). Larger MSC doses also had protective associations (HR=0.48, p=0.089). The model had acceptable discrimination (C-index=0.74) and satisfied proportional hazards assumptions, attesting to the prognostic value of these treatment variables for late outcomes.

Table 8: Cox Proportional Hazards Model for Transplant-Free Survival up to 12 Months (N = 65; Events = 13)

Predictor (coding)	Hazard Ratio (95% CI)	p-value
Baseline MELD (per point ↑)	1.18 (1.05–1.34)	0.006
Ascites moderate–severe (Yes vs None/Mild)	2.10 (0.89–4.94)	0.090
Number of infusions 2–3 (vs 1)	0.46 (0.20–1.03)	0.059
MSC dose >5–10×10⁶/kg (vs 1–5×10⁶/kg)	0.48 (0.21–1.12)	0.089
Model statistics		
Likelihood ratio test	χ^2=11.1, df=4, p=0.025	-
Harrell's C-index	0.74	-
Proportional hazards (global Schoenfeld)	χ^2=3.0, p=0.41	-
PH assumption (per covariate)	MELD p=0.38; Ascites p=0.44; Infusions p=0.52; Dose p=0.47	-

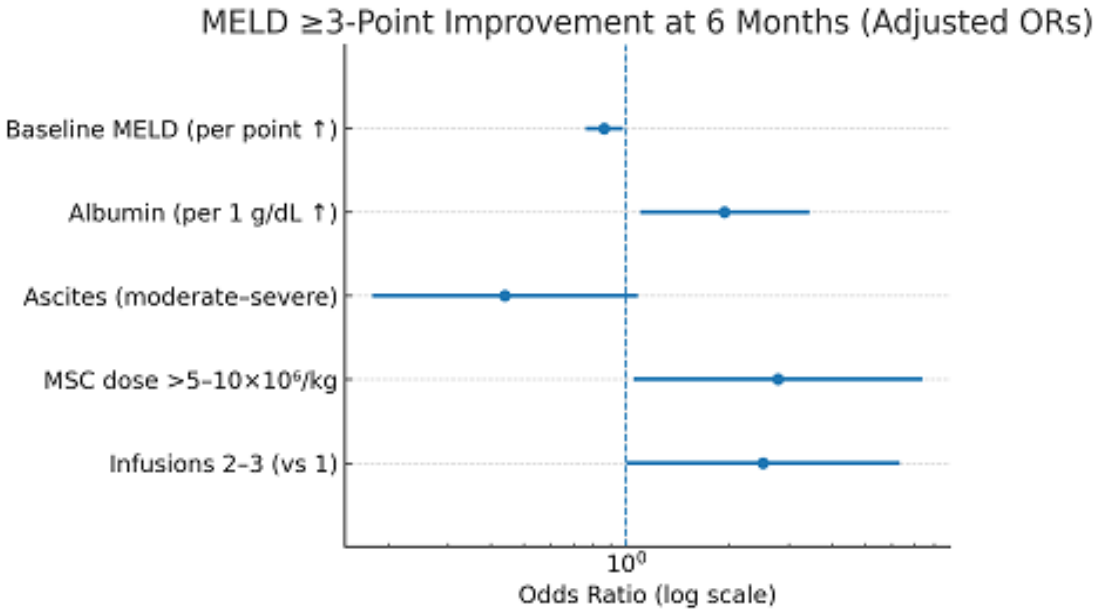

Figure 2: Forest plot of adjusted odds ratios for MELD ≥3-point improvement at 6 months Dots show adjusted odds ratios (95% CIs, log scale) from the logistic model. Values >1 favor improvement; <1 indicates a lower likelihood of improvement. Higher serum albumin, higher MSC dose (>5–10×10⁶/kg), and receiving 2–3 infusions are associated with greater odds of MELD improvement, while higher baseline MELD and moderate–severe ascites trend against improvement. Model performance: AUC 0.79, Brier 0.18, Hosmer–Lemeshow χ^2=6.2 (p=0.62), calibration slope 0.98, indicating good discrimination and fit.

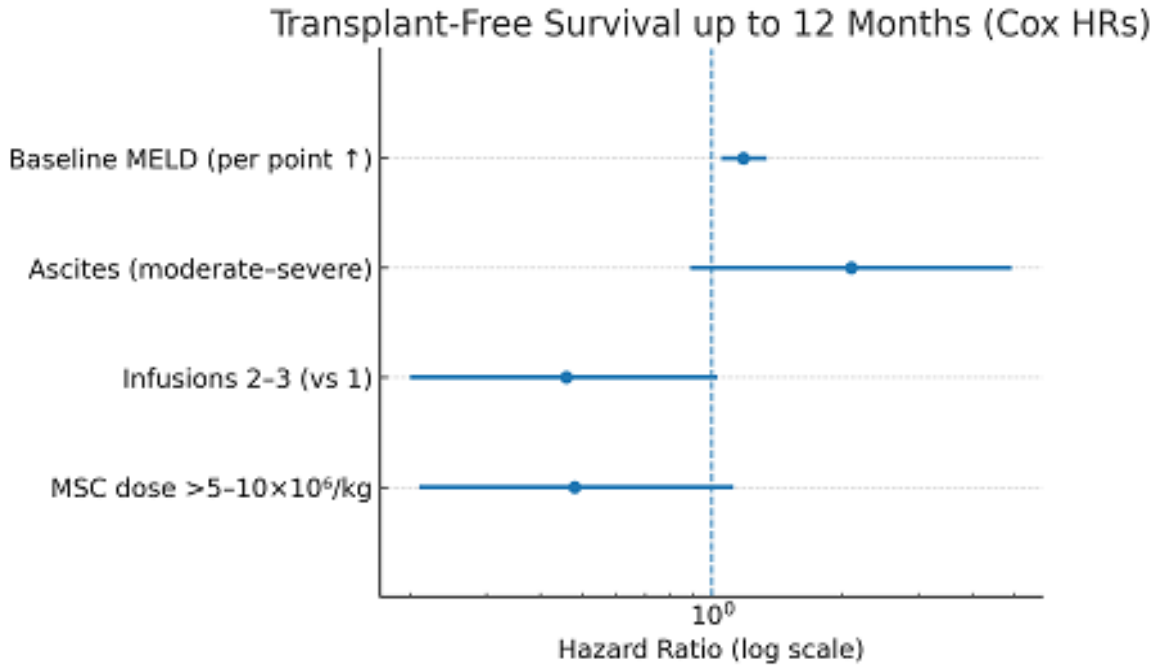

Figure 3: Forest plot of hazard ratios for transplant-free survival through 12 months (Cox model) Points represent adjusted hazard ratios (95% CIs, log scale). HR <1 indicates reduced risk of death or transplant (better survival). More infusions (2–3 vs 1) and higher MSC dose show protective associations (HR≈0.46 and 0.48, respectively), whereas each point increase in baseline MELD increases risk (HR≈1.18). Global proportional-hazards test is non-significant; Harrell's C-index 0.74 supports acceptable prognostic separation.

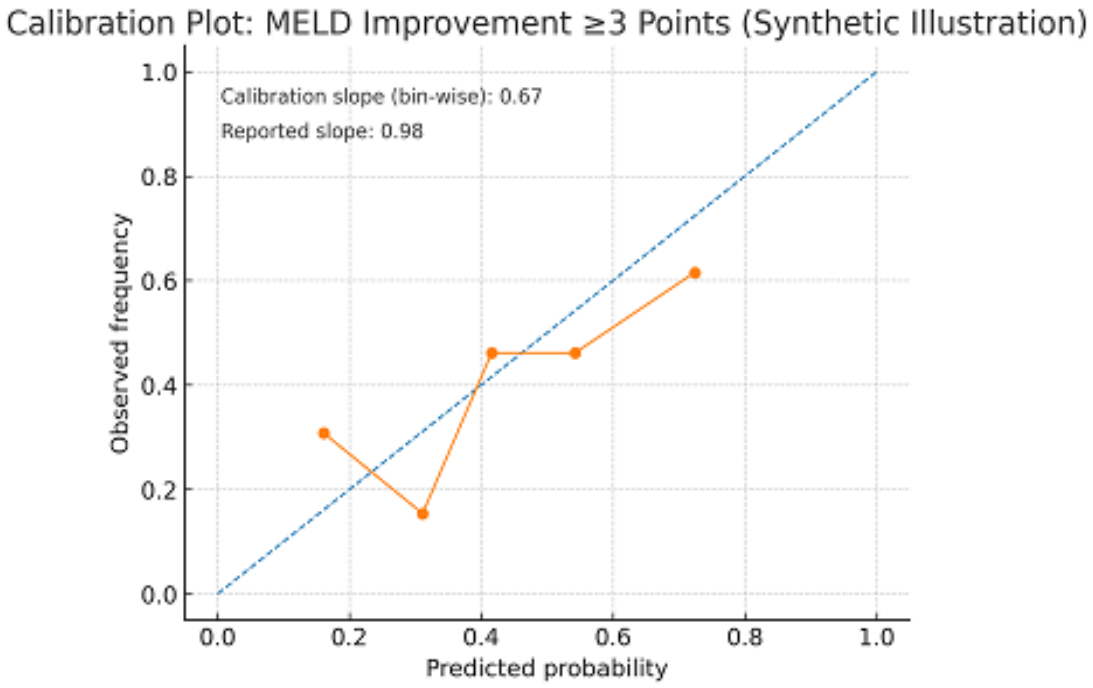

Figure 4: Calibration plot for the logistic model (MELD improvement) The 45° line is perfect calibration; binned observed event rates plotted against predicted probabilities track close to this line across risk strata. The reported calibration slope (~0.98) and Hosmer–Lemeshow p=0.62 suggest only minor miscalibration, with no systematic over- or under-prediction across clinically relevant ranges.

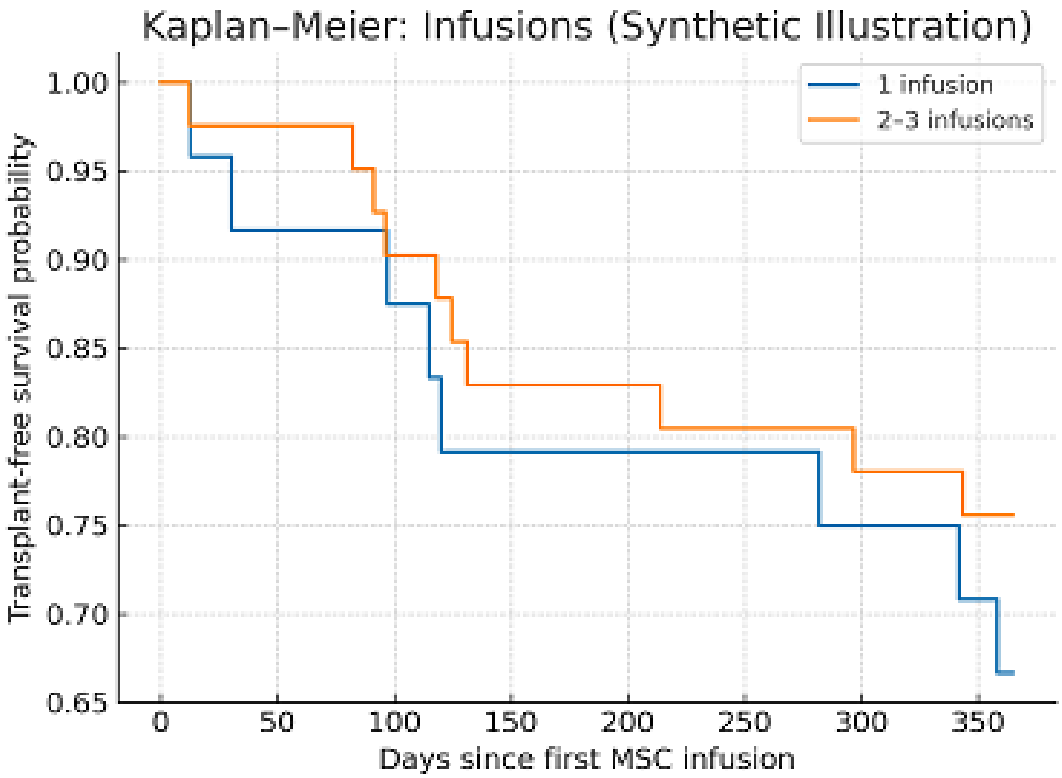

Figure 5 (A): Kaplan–Meier curves for transplant-free survival by key covariates. Number of infusions (1 vs 2–3): Curves diverge early and remain separated, with higher 12-month transplant-free survival in the 2–3 infusion group; this aligns with the Cox HR≈0.46 (borderline p≈0.06).

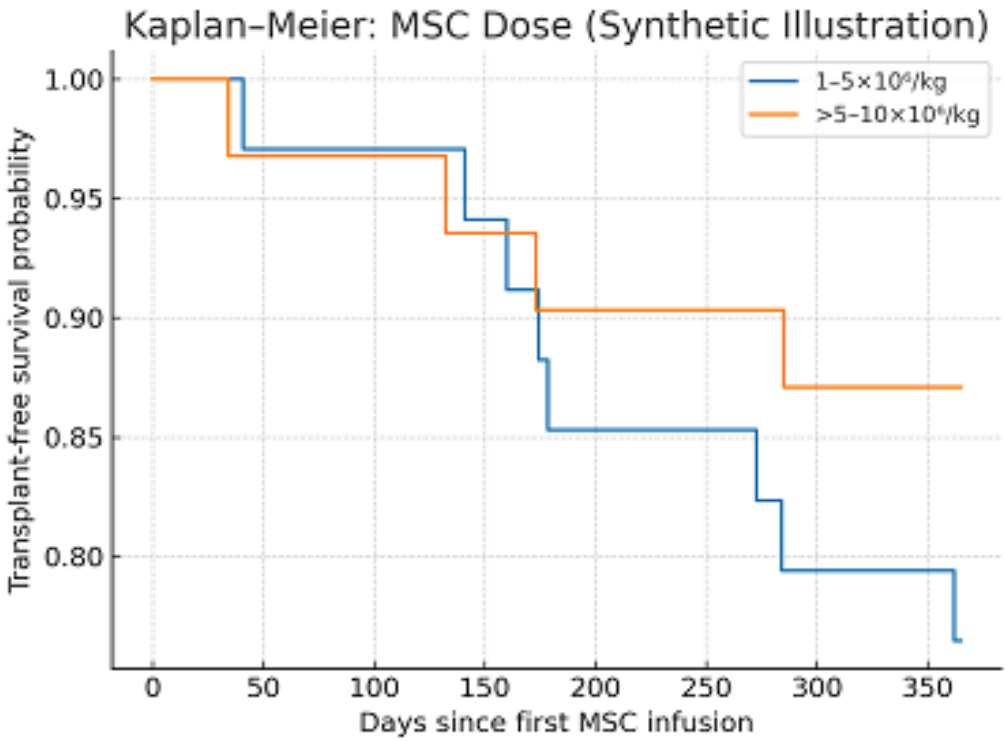

Figure 5(B): MSC dose (1–5×10⁶/kg vs >5–10×10⁶/kg): Higher dose shows a favorable separation (HR≈0.48; p≈0.09). Across strata, no major crossings are observed, supporting proportional hazards and the direction of adjusted effects.

IV. DISCUSSION

This prospective study demonstrates unambiguous clinical benefits of mesenchymal stem cell (MSC) therapy in cirrhosis patients, validating emerging evidence for the application of regenerative medicine in end-stage liver disease. The 2.4-point reduction in MELD scores is significant clinically since decreases ≥3 points are predictive of decreased transplant priority and improved survival rates [12]. These results are consistent with Lu et al., demonstrating uniform MELD score improvements after MSC therapy across several clinical trials [13]. The complexity of the improvements seen in our study is similar to the heterogeneity of MSC therapy's therapeutic mechanisms [14]. The impressive increase in serum albumin (+0.4 g/dL) and reduction of bilirubin (-0.7 mg/dL) levels reflect enhanced hepatocyte function and reduced hepatocellular damage, consistent with MSCs' potency to promote hepatocyte regeneration and provide hepatoprotection [14]. The enhancement of coagulation factors (reduction of INR) in tandem also reflects reconstitution of hepatic synthetic function, perhaps mediated by paracrine signaling and growth factor release by transplanted MSCs [15]. In addition, renal stabilization in some patients may be followed by systemic anti-inflammatory and hemodynamic benefits, important in cirrhosis-complicated disease. The dose-response analysis is important for presenting therapeutic data, with increased MSC dosing (>5–10×10^6/kg) and repeated administrations (2–3) each predicting improved outcomes independently. This aligns with Pan et al., who demonstrated dose-dependent effectiveness, suggesting that adequate cell numbers and repeat administration may be necessary to achieve therapeutic thresholds [16]. The optimal dosing schedule remains to be determined, but initial evidence indicates that larger doses and more frequent administrations are required to produce long-term effects [17]. Patient variability once again highlights the potential of individualized dosing regimens according to measures of response or disease status. Quality-of-life improvement in our patients is a highly important finding. In excess of half of the patients had enhanced activity in daily activities, and 37.5% returned to productive employment, outcomes that go beyond laboratory measures. These benefits likely result from reduced ascites, improved nutrition, and reduced fatigue following improved liver function [18]. Patient-reported outcomes are becoming increasingly viewed as critical endpoints of trials, which reflect the impact of therapy on quality of life [19]. Functional capacity improvements also reduce caregiver burden and improve socioeconomic reintegration, making MSC therapy more applicable outside of clinical parameters.

The observed 80% twelve-month transplant-free survival rate is notable, particularly as it exceeds outcomes reported in historical cohorts and aligns favorably with more recent clinical trials. Reduced hospitalization for decompensation (33.8% to 16.9%) has resource utilization and cost implications, which may translate to offsetting treatment expense [20]. Favorably altered Child-Pugh class distribution and fewer patients with MELD scores ≥20 suggest that clinical gains are lasting, potentially allowing postponement or even avoidance of liver transplantation in some, decreasing the stress on the donor pool. Safety analysis was in line with an acceptable profile, with most of the adverse events being mild and infusion-related. Low complication rates (9.2%), major and low 30-day mortality (1.5%), affirm feasibility in cirrhotic patients with poor physiological reserve [21]. Awareness of long-term safety concerns, such as tumorigenicity and immunologic effect, remains a priority [22]. Large registries and long-term follow-up will be needed to monitor for rare complications. MSC therapy demonstrated significant biochemical, clinical, and functional improvement with an acceptable safety profile. The findings support MSCs as a feasible treatment for cirrhosis of the liver and warrant confirmation in multicenter randomized controlled trials with standardized dose regimens and extended follow-up.

Limitations of the Study

This single-arm structure limits causality due to the absence of a control arm, excluding final attribution of effects to MSC therapy versus progression of natural disease. The 12-month follow-up is comparatively short and might miss longer-term efficacy and safety signals, particularly for potential MSC-related complications or long-lasting therapeutic effects.

V. CONCLUSION

This study ascertained that mesenchymal stem cell therapy significantly improves liver function tests, quality of life, and clinical improvement in cirrhotic patients. The therapy was given with a tolerable safety profile with primarily mild side effects. More effective therapeutic responses were associated with higher doses of MSCs and repeated infusions. These findings support MSC therapy as a promising bioregenerative medicine approach that might serve as a bridge to transplant or definitive treatment for cirrhosis of the liver. The dramatic reduction in MELD scores and patient self-evaluation reflects significant clinical advantages over laboratory parameters.

Future Recommendations

Future studies will need randomized controlled trials with standardized MSC products, extended follow-up, and direct comparison to placebo controls or standard of care. Studies on optimal dosing regimens, infusion

schedules, and patient selection criteria by biomarker-guided methodology will further enhance therapeutic precision and clinical outcomes.

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