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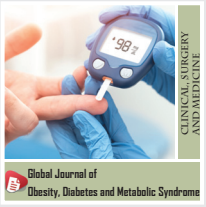

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Research Article

Ultrasound-Guided Targeted Infusion of Autologous Bone Marrow-Derived Platelet-Rich Plasma (BMPRP) for the Treatment of Liver Cirrhosis Complicated with Type 2 Diabetes Mellitus

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Keywords: Liver cirrhosis; Type 2 diabetes mellitus; Bone marrow-derived platelet-rich plasma; Ultrasound guidance; Targeted infusion; Regenerative medicine; Cell therapy

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Abstract

Background and Aim: Liver cirrhosis and type 2 diabetes mellitus (T2DM) mutually reinforce each other, creating a vicious cycle that accelerates disease progression. This study aimed to evaluate the efficacy and safety of ultrasound-guided targeted infusion of autologous bone marrow-derived platelet-rich plasma (BMPRP) in patients with cirrhosis complicated by T2DM.

Methods: In this multicenter retrospective cohort study, 50 patients from three medical centers between January 2023 and January 2024 were enrolled. The BMPRP group (n=30) received ultrasound-guided BMPRP infusion into the liver and pancreas in addition to conventional therapy, while the control group (n=20) received conventional hepatoprotective and hypoglycemic treatment only. Liver function (PT, ALB, TBIL, ascites volume) and glycemic parameters (FPG, HbA1c, insulin dosage, C-peptide) were compared at baseline and at 1, 3, 6, and 12 months after treatment. Longitudinal data were analyzed with linear mixed-effects models (LMMs) including fixed effects of group, time, and the group × time interaction, a patient-level random intercept, and adjustment for each outcome's baseline value and age; between-group comparisons at the four post-baseline visits were adjusted for multiplicity using the Holm–Bonferroni procedure.

Results: Baseline characteristics were comparable between the two groups; given the small sample size, baseline values of each outcome were additionally included as covariates in the adjusted analyses. At 12 months, the BMPRP group showed significant improvements: PT was markedly shortened (15.17±1.12 vs. 18.37±1.59 s, P<0.001), ALB increased (39.37±3.16 vs. 32.57±4.38 g/L, P<0.001), TBIL decreased (18.50±5.45 vs. 31.80±9.42 μmol/L, P<0.001), and ascites resolved completely in 60% of patients (volume decreased from 1200.0±1323.5 to 233.3±583.3 mL, P<0.001). Glycemic control improved significantly: FPG decreased to 6.23±1.03 mmol/L (P<0.001), HbA1c to 6.22±0.70% (P<0.001), insulin dosage was reduced (7.60±9.06 vs. 23.93±18.93 U/d, P<0.001), and C-peptide increased (1.58±0.38 vs. 1.20±0.61 ng/mL, P<0.001). No significant improvement was observed in the control group. Adjusted LMM analyses confirmed significant group × time interactions for all eight outcomes (all $P \leq 1.5 \times 10^{-6}$); after Holm–Bonferroni adjustment, the BMPRP group was significantly superior to the control group for every outcome at months 6 and 12 (all adjusted P<0.001). BMPRP was well tolerated, with no treatment-related serious adverse events.

Conclusion: In this exploratory, non-randomized retrospective cohort study, ultrasound-guided dual-target (hepatic and pancreatic) BMPRP infusion was associated with sustained improvements in liver function and glycemic control, and with reduced insulin requirements, over 12 months in patients with cirrhosis complicated by T2DM, without treatment-related serious adverse events. These findings are hypothesis-generating and suggest that this dual-organ regenerative strategy is feasible; confirmation of its efficacy and safety requires adequately powered randomized controlled trials.

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Introduction

Decompensated liver cirrhosis represents the common terminal pathological stage of chronic liver disease progression, often accompanied by portal hypertension, hepatic decompensation, and various complications. The prevalence of type 2 diabetes mellitus (T2DM) among patients with cirrhosis ranges from 20% to 70%, and their coexistence creates a vicious cycle that significantly increases the risk of hepatocellular carcinoma and mortality [1,2]. The underlying mechanisms involve complex interactions among insulin resistance, lipotoxicity, chronic inflammation, and mitochondrial dysfunction [3-6]. Epidemiological studies indicate that the prevalence of non-alcoholic fatty liver disease (NAFLD) reaches 65% in patients with T2DM, and metabolic dysfunction-associated steatotic liver disease now accounts for 26% of cirrhosis etiologies worldwide [7,8].

Current standard treatments (hepatoprotective agents, hypoglycemic drugs, and complication management) are unable to reverse liver fibrosis or restore islet function. In recent years, mesenchymal stem cell (MSC) therapy has shown promising prospects in regenerative medicine. A 2023 meta-analysis by Suk et al. [28][9] confirmed that MSC therapy significantly improves liver function and survival in patients with cirrhosis. However, conventional intravenous infusion is limited by first-pass pulmonary entrapment and low homing efficiency to target organs. A 2024 review noted that the shared inflammatory pathways between diabetes and cirrhosis provide a theoretical basis for combined dual-organ therapy [27][10].

Our team has conducted research on autologous bone marrow cell therapy for cirrhosis since 2009 and initiated ultrasound-guided targeted organ infusion in 2019. In 2024, Zhang et al. [29][11] further validated the superiority of local infusion through targeted stem cell delivery research. The present study employed dual-route (hepatic and pancreatic) infusion of bone marrow-derived platelet-rich plasma to simultaneously repair hepatic and pancreatic function, with 12-month follow-up to verify long-term efficacy and safety.

Given the retrospective, non-randomized design, this study is positioned from the outset as an exploratory, hypothesis-generating investigation; the statistical analysis plan, interpretation of results, and wording of conclusions have been adjusted accordingly.

Materials and methods

Study design

This multicenter retrospective cohort study enrolled patients with cirrhosis complicated by T2DM who attended Zhonghong Ruikang (Zhejiang) Health Management Center, Zigong Hospital Affiliated to Southwest Medical University, and Zhengzhou Renji Hospital between January 2023 and January 2024. The study protocol was approved by the ethics committees of all participating centers, and written informed consent was obtained from all patients.

Inclusion criteria: (1) diagnosis of liver cirrhosis (imaging, laboratory, or pathological evidence); (2) diagnosis of T2DM (American Diabetes Association 2022 criteria); (3) age 18–75 years; (4) complete clinical data with follow-up ≥12 months.

Exclusion criteria: (1) concomitant hepatocellular carcinoma or other malignancies; (2) severe infection or active bleeding; (3) history of liver transplantation or stem cell therapy; (4) pregnancy or lactation.

Grouping and treatment allocation

Patients were divided into two groups according to the treatment they received:

BMPRP group (n=30): received ultrasound-guided dual-target (hepatic and pancreatic) BMPRP infusion in addition to conventional therapy.

Control group (n=20): received conventional hepatoprotective therapy (compound glycyrrhizin, reduced glutathione, etc.), diuretics, albumin supplementation, and insulin/oral hypoglycemic agents, without cell therapy.

Treatment allocation was not randomized but was based on routine clinical decision-making. At each participating center, patients with persistent hepatic decompensation (e.g., recurrent ascites, hypoalbuminemia, or prolonged prothrombin time) and/or inadequate glycemic control despite at least 3 months of optimized conventional therapy were informed that autologous BMPRP infusion was available as an adjunctive treatment option. Patients who provided written informed consent for cell therapy and met the procedural safety criteria described in Section 2.4 received BMPRP in addition to conventional therapy; patients who declined cell therapy (mainly because of concerns about the invasive puncture procedure or its cost) or who did not meet the procedural safety criteria continued conventional therapy alone and constituted the control group.

We acknowledge that this allocation process may introduce selection bias and confounding by indication. To mitigate these risks, we report baseline characteristics in detail (Table 1), report the per-center enrollment distribution (Table 2), and adjust for prespecified baseline covariates in the longitudinal mixed-effects models (Section 2.6); residual confounding is addressed in the Limitations section.

BMPRP Preparation and characterization

1. Bone marrow aspiration: Under local anesthesia, 80 mL of bone marrow blood was aspirated from the anterior superior iliac spine using four dedicated 20-mL syringes (each prefilled with 4 mL of heparinized saline).

2. Cell separation: Density-gradient centrifugation was performed. After sealing the syringe tips, centrifugation sedimented the erythrocytes, and the upper plasma layer and interface layer (containing mononuclear cells, platelets, and stem cells) were collected to obtain 10 mL of concentrated bone marrow cell suspension (viability ≥95%).

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Table 1: Baseline characteristics of the study participants.

Characteristic	BMPRP group (n=30)	Control group (n=20)	t/χ^2	P value
Age (years)	50.4±11.2	48.6±10.5	0.58	0.564
Male	18 (60.0)	13 (65.0)	0.13	0.719
Etiology of cirrhosis			0.09	0.957
Hepatitis B	20 (66.7)	13 (65.0)		
Alcoholic	7 (23.3)	5 (25.0)		
Other	3 (10.0)	2 (10.0)		
Child-Pugh class			0.15	0.928
Class A	8 (26.7)	6 (30.0)		
Class B	16 (53.3)	10 (50.0)		
Class C	6 (20.0)	4 (20.0)		
Diabetes duration (years)	6.8±3.5	7.2±4.1	-0.37	0.715
PT (s)	18.37±1.59	17.90±1.71	0.98	0.331
ALB (g/L)	32.57±4.38	33.55±3.62	-0.83	0.41
TBIL (μmol/L)	31.80±9.42	27.15±7.18	1.82	0.075
Ascites volume (mL)	1200.0±1323.5	1175.0±1248.9	0.07	0.947
FPG (mmol/L)	8.24±1.46	8.32±1.24	-0.2	0.841
HbA1c (%)	8.25±1.16	7.75±1.13	1.52	0.136
Insulin dosage (U/d)	23.93±18.93	22.30±17.84	0.31	0.757
C-peptide (ng/mL)	1.20±0.61	1.56±0.64	-2.01	0.05

Note: Continuous variables are expressed as $\bar{x}$±s and categorical variables as n(%). Baseline values for TBIL, HbA1c, insulin dosage, and ascites volume were recalculated from the patient-level raw dataset and supersede the values in the original submission.

Table 2: Enrollment distribution of the treatment and control groups across the three centers.

Center	BMPRP group (n=30)	Control group (n=20)
Zhonghong Ruikang (Zhejiang) Health Management Center	16	4
Zigong Hospital Affiliated to Southwest Medical University	8	9
Zhengzhou Renji Hospital	6	7

Note: The Zhonghong Ruikang (Zhejiang) center enrolled predominantly BMPRP-treated patients, whereas the other two centers enrolled predominantly conventionally treated patients; every center enrolled participants in both groups.

3. Product characterization: The final 10-mL concentrate is a heterogeneous autologous product comprising plasma, concentrated platelets, mononuclear cells, and hematopoietic progenitor/stem cells; the operational term "bone marrow-derived platelet-rich plasma (BMPRP)" is therefore retained from clinical practice while explicitly acknowledging that it is not a purified platelet fraction. Flow-cytometric CD34+ quantification was not routinely performed for each preparation in this study (addressed as a limitation); the cellular composition is characterized by reference to a prior study using the identical preparation protocol [31][12], in which 80–100 mL of bone marrow typically yields 10 mL of concentrate containing approximately $2–6×10^8$ nucleated cells, including $1–5×10^6$ large immature (progenitor) cells.

Ultrasound-guided targeted infusion procedure

Pre-procedural assessment: Patients fasted for at least 6 hours before the procedure. Because the target population consists of cirrhotic patients who may have coagulopathy and portal hypertension, coagulation function was rechecked within 24 hours before each infusion, requiring a platelet count ≥$50×10^9$/L and prothrombin activity ≥40%; patients not meeting these thresholds received platelet transfusion or fresh frozen plasma correction before the procedure. Abdominal ultrasound with color Doppler was used to plan the puncture route and to exclude portal vein thrombosis and perihepatic vascular abnormalities.

Hepatic infusion: Under local anesthesia (1% lidocaine) and real-time ultrasound with color Doppler guidance to avoid intercostal and intrahepatic vessels, a fine puncture needle (a size-7 lumbar puncture needle, consistent with our team's previous report [31][12]) was advanced percutaneously through the right intercostal approach into the hepatic parenchyma adjacent to a portal venous branch, and 5 mL of BMPRP was slowly injected at approximately 1 mL/min.

Pancreatic infusion: Via an epigastric approach, with careful Doppler-guided avoidance of the main pancreatic duct, gastroduodenal artery, and peripancreatic vessels, the needle tip was placed within the pancreatic body/tail parenchyma, and 5 mL of BMPRP was slowly infused. During each injection, real-time monitoring showed transient hyperechogenicity reflecting distribution of the cell suspension, consistent with previous reports [31][12].

Post-procedural management: After needle withdrawal, the puncture site was compressed, color Doppler was used to confirm the absence of active bleeding along the needle track, and patients were observed for puncture-site bleeding and abdominal symptoms.

Reinfusion: The remaining bone marrow plasma and erythrocytes were reinfused via a peripheral vein.

Treatment course: Infusion was repeated at months 1 and 3 after the initial treatment, for a total of three sessions.

Outcome measures

Assessments were performed at baseline (before treatment) and at 1, 3, 6, and 12 months after treatment.

Primary endpoints — liver function: prothrombin time (PT, s), albumin (ALB, g/L), total bilirubin (TBIL, μmol/L); ascites volume: measured by abdominal ultrasound (maximum fluid depth) and calculated using the ellipsoid formula (mL).

Secondary endpoints — glycemic control: fasting plasma glucose (FPG, mmol/L), glycated hemoglobin (HbA1c, %); islet function: fasting C-peptide (ng/mL), daily insulin dosage (U/d).

Safety endpoints: adverse events, procedure-related complications, and death.

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Statistical analysis

Statistical analyses were performed with Python 3.12 (statsmodels 0.14, linear mixed-effects models) and SPSS 26.0 (IBM Corp., Armonk, NY, USA; descriptive and baseline analyses). Continuous variables are expressed as mean ± standard deviation ($\bar{x}\pm s$), and categorical variables as frequencies (percentages).

Baseline comparisons. Between-group comparisons of continuous variables used the independent-samples t-test (equal variances) or Welch's corrected t-test (unequal variances); categorical variables were compared using the chi-square test or Fisher's exact test. Because a non-significant baseline test does not establish group equivalence in small samples, baseline comparisons are interpreted descriptively, and clinically relevant baseline covariates are instead handled by the adjusted longitudinal models described below.

Longitudinal analysis (primary analysis). To accommodate repeated observations, unequal group sizes, and missing data, longitudinal outcomes were analyzed with linear mixed-effects models (LMMs) rather than repeated-measures ANOVA. For each outcome (PT, ALB, TBIL, ascites volume, FPG, HbA1c, insulin dosage, and C-peptide), a separate LMM was fitted with fixed effects of treatment group, time (categorical: baseline, 1, 3, 6, and 12 months), and their interaction, and a patient-level random intercept to account for within-subject correlation. Models were adjusted for the baseline value of the outcome and age as fixed-effect covariates. Patient-level Child-Pugh class, diabetes duration, and center identifiers were not available in the analysis dataset and therefore could not be included; this is stated transparently in the text and addressed as a limitation, with center effects assumed small relative to patient-level random effects. The group × time interaction for each outcome was tested by a likelihood-ratio test (4 degrees of freedom) comparing the full model with a model excluding the interaction. Adjusted between-group differences at each follow-up visit were estimated from the interaction coefficients and are reported with 95% confidence intervals; the four per-visit comparisons for each outcome were adjusted for multiplicity using the Holm–Bonferroni procedure.

Handling of missing data. The outcome dataset was essentially complete: of 2,400 data points, only one insulin value at month 6 in the BMPRP group was missing (99.96% completeness). The two deaths in the control group during follow-up both occurred after completion of the 12-month outcome assessment, so outcome data were available for all patients in both groups at every follow-up visit; no outcome data were missing as a result of death, and no imputation was required. A sensitivity analysis re-fitting all models after excluding the patient with the missing value yielded unchanged directions, magnitudes, and statistical significance of all group × time interactions.

Secondary (descriptive) analyses. Within-group comparisons of each time point against baseline were additionally performed using paired-samples t-tests (normally distributed data) or Wilcoxon signed-rank tests (non-normally distributed data) for descriptive purposes. A two-sided $P<0.05$ was considered statistically significant. Effect sizes (Cohen's d) were calculated for outcomes showing significant between-group differences: 0.2–0.5 small, 0.5–0.8 medium, >0.8 large.

Results

Baseline characteristics

The two groups showed no statistically significant differences in age, sex, cirrhosis etiology, Child-Pugh class, diabetes duration, or baseline laboratory parameters ($P>0.05$), and were comparable (Table 1). However, given the small sample size, these non-significant tests do not demonstrate equivalence — baseline C-peptide, for example, was borderline lower in the BMPRP group ($P=0.05$). The baseline value of each outcome and age were therefore included as covariates in the adjusted longitudinal analyses. The per-center enrollment distribution of the treatment and control groups is shown in Table 2.

Changes in liver function

Within-group comparisons: Liver function improved progressively in the BMPRP group: PT shortened significantly from month 3 (16.30±1.34 s, $P<0.05$), reaching 15.17±1.12 s at month 12 ($P<0.001$); ALB increased significantly from month 6 (36.97±3.36 g/L, $P<0.01$), reaching 39.37±3.16 g/L at month 12 ($P<0.001$); TBIL decreased significantly from month 3 (24.60±7.73 μmol/L, $P<0.05$), reaching 18.50±5.45 μmol/L at month 12 ($P<0.001$). No significant improvement over time was observed in the control group.

Between-group comparisons (adjusted analyses): LMM analyses showed highly significant group × time interactions for PT (likelihood-ratio $\chi^2(4)=59.2$, $P=4.3\times10^{-12}$), ALB ($\chi^2(4)=81.8$, $P=7.2\times10^{-17}$), and TBIL ($\chi^2(4)=144.0$, $P=3.9\times10^{-30}$), confirming divergent longitudinal trajectories between groups. After Holm–Bonferroni adjustment, the BMPRP group was significantly superior to the control group for PT from month 1, for ALB from month 6, and for TBIL from month 1 (Table 3); adjusted between-group differences at month 12 were −2.95 s (95% CI −3.72 to −2.18) for PT, +8.65 g/L (95% CI 6.73 to 10.57) for ALB, and −17.70 μmol/L (95% CI −20.53 to −14.87) for TBIL (all adjusted $P<0.001$) (Table 4).

Changes in ascites volume

Ascites volume in the BMPRP group decreased from 1200.0±1323.5 mL at baseline to 233.3±583.3 mL at month 12 ($P<0.001$), with complete resolution in 18 patients (60.0%). Ascites volume showed an increasing trend in the control group (1175.0→1775.0 mL). The group × time interaction for ascites volume was significant ($\chi^2(4)=69.8$, $P=2.6\times10^{-14}$); Holm-adjusted between-group differences were significant from month 1, reaching −1567 mL (95% CI −1964 to −1170) at month 12 (Tables 3 and 5).

Glycemic control and islet function

Glycemic parameters: In the BMPRP group, FPG decreased significantly from month 3 (6.87±0.91 mmol/L, $P<0.01$),

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Table 3: Adjusted between-group differences from the linear mixed-effects models (BMPRP − control).

Outcome	Month 1	Month 3	Month 6	Month 12
PT (s)	−1.07 (−1.84, −0.29) P=0.007	−1.72 (−2.49, −0.94) P<0.001	−2.42 (−3.19, −1.64) P<0.001	−2.95 (−3.72, −2.18) P<0.001
ALB (g/L)	+1.55 (−0.37, 3.47) P=0.153	+1.73 (−0.18, 3.65) P=0.153	+5.15 (3.23, 7.07) P<0.001	+8.65 (6.73, 10.57) P<0.001
TBIL (μmol/L)	−3.70 (−6.53, −0.87) P=0.010	−10.05 (−12.88, −7.22) P<0.001	−14.83 (−17.66, −12.00) P<0.001	−17.70 (−20.53, −14.87) P<0.001
Ascites (mL)	−400 (−797, −3) P=0.048	−1075 (−1472, −678) P<0.001	−1325 (−1722, −928) P<0.001	−1567 (−1964, −1170) P<0.001
FPG (mmol/L)	−0.21 (−0.74, 0.33) P=0.451	−0.57 (−1.10, −0.04) P=0.073	−1.24 (−1.78, −0.71) P<0.001	−1.61 (−2.14, −1.07) P<0.001
HbA1c (%)	−0.49 (−0.91, −0.06) P=0.024	−1.10 (−1.52, −0.68) P<0.001	−1.51 (−1.94, −1.09) P<0.001	−1.88 (−2.30, −1.46) P<0.001
Insulin (U/d)	−3.00 (−8.09, 2.09) P=0.248	−9.20 (−14.29, −4.11) P<0.001	−19.17 (−24.28, −14.06) P<0.001	−21.93 (−27.02, −16.84) P<0.001
C-peptide (ng/mL)	+0.26 (0.01, 0.51) P=0.040	+0.35 (0.10, 0.60) P=0.012	+0.57 (0.32, 0.82) P<0.001	+0.68 (0.43, 0.93) P<0.001

Note: Values are adjusted mean differences (BMPRP group − control group) at each follow-up visit with 95% confidence intervals in parentheses, derived from linear mixed-effects models adjusted for the baseline value of the outcome and age, with a patient-level random intercept. P values are Holm–Bonferroni adjusted across the four follow-up visits within each outcome. The group × time interaction was significant for every outcome (likelihood-ratio tests, all $P \leq 1.5\times10^{-6}$).

Table 4: Dynamic changes in liver function parameters (x̄±s).

Parameter	Group	Baseline	Month 1	Month 3	Month 6	Month 12
PT (s)	BMPRP	18.37±1.59	17.00±1.23	16.30±1.34	15.50±1.11	15.17±1.12
	Control	17.90±1.71	17.60±1.90	17.55±2.11	17.45±1.32	17.65±1.50
ALB (g/L)	BMPRP	32.57±4.38	34.07±3.58	34.70±3.44	36.97±3.36	39.37±3.16
	Control	33.55±3.62	33.50±3.65	33.95±3.12	32.80±2.73	31.70±2.20
TBIL (μmol/L)	BMPRP	31.80±9.42	28.10±9.14	24.60±7.73	20.27±5.83	18.50±5.45
	Control	27.15±7.18	27.15±7.65	30.00±8.23	30.45±7.66	31.55±7.19

Note: Unadjusted means ± standard deviations calculated from the patient-level raw dataset; n=30 (BMPRP) and n=20 (control) at every time point except as noted in Table 8. Adjusted between-group statistics are presented in Table 3.

reaching 6.23±1.03 mmol/L at month 12 (P<0.001); HbA1c decreased progressively to 6.22±0.70% at month 12 (P<0.001). The group × time interactions were significant for FPG ($\chi^2(4)=44.9$, $P=4.1\times10^{-9}$) and HbA1c ($\chi^2(4)=80.9$, $P=1.1\times10^{-16}$); after Holm adjustment, the BMPRP group was significantly superior to the control group for FPG from month 6 and for HbA1c from month 1 (Tables 3,6,7).

Insulin dosage and C-peptide: Daily insulin dosage decreased markedly in the BMPRP group (from 23.93±18.93 to 7.60±9.06 U/d, P<0.001), and C-peptide at month 12 was significantly higher than baseline (1.58±0.38 vs. 1.20±0.61 ng/mL, P<0.001); C-peptide showed a declining trend and insulin requirements an increasing trend in the control group. The group × time interactions were significant for insulin dosage ($\chi^2(4)=87.9$, $P=3.6\times10^{-18}$) and C-peptide ($\chi^2(4)=32.5$, $P=1.5\times10^{-6}$); after Holm adjustment, insulin dosage was significantly lower in the BMPRP group from month 3, and C-peptide was significantly higher at every follow-up visit (Tables 3,8,9).

Safety assessment and follow-up completeness

All patients in the BMPRP group completed the three cell infusions. Four patients (13.3%) developed peripuncture ecchymosis at the bone marrow aspiration site, which resolved spontaneously within 2 weeks. Four patients (13.3%) experienced gastrointestinal bleeding (related to cirrhotic portal hypertension), which was controlled with endoscopic ligation and symptomatic treatment; no deaths occurred in the BMPRP group. Four patients (20.0%) in the control group experienced gastrointestinal bleeding, two of whom died of post-hemorrhagic liver failure. No treatment-related serious adverse events, hepatic artery embolism, portal vein

Table 5: Dynamic changes in ascites volume (mL, x̄±s).

Time point	BMPRP group	Control group	Unadjusted P value
Baseline	1200.0±1323.5	1175.0±1248.9	0.947
Month 1	550.0±661.1	925.0±1091.5	0.232
Month 3	250.0±504.3	1300.0±1341.6	0.001
Month 6	200.0±501.7	1500.0±1317.9	<0.001
Month 12	233.3±583.3	1775.0±1601.6	<0.001

Table 6: Dynamic changes in fasting plasma glucose (mmol/L, x̄±s).

Group	Baseline	Month 1	Month 3	Month 6	Month 12
BMPRP	8.24±1.46	7.46±1.19	6.87±0.91	6.55±0.88	6.23±1.03
Control	8.32±1.24	7.74±1.42	7.51±1.39	7.87±1.38	7.91±1.27

Table 7: Dynamic changes in glycated hemoglobin (%, x̄±s).

Group	Baseline	Month 1	Month 3	Month 6	Month 12
BMPRP	8.25±1.16	7.72±1.06	7.07±0.67	6.60±0.58	6.22±0.70
Control	7.75±1.13	7.71±0.87	7.67±0.70	7.62±0.76	7.60±0.70

Table 8: Dynamic changes in daily insulin dosage (U/d, x̄±s).

Group	Baseline	Month 1	Month 3	Month 6	Month 12
BMPRP	23.93±18.93	20.93±16.61	13.93±12.70	9.45±9.74*	7.60±9.06
Control	22.30±17.84	22.30±17.94	21.50±16.02	26.40±15.32	27.90±15.89

*n=29 at month 6 in the BMPRP group (one missing value); all other cells n=30 (BMPRP) or n=20 (control).

Table 9: Dynamic changes in C-peptide levels (ng/mL, x̄±s).

Group	Baseline	Month 1	Month 3	Month 6	Month 12
BMPRP	1.20±0.61	1.46±0.47	1.52±0.48	1.53±0.46	1.58±0.38
Control	1.56±0.64	1.56±0.51	1.52±0.46	1.31±0.41	1.26±0.45

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thrombosis, or pancreatitis occurred in the BMPRP group. Both deaths in the control group occurred after completion of the 12-month outcome assessment; consequently, outcome data were available for all patients in both groups at every follow-up visit, including month 12, no outcome data were missing as a result of death, and no imputation was required. Overall completeness of the outcome dataset was 99.96% (one missing insulin value among 2,400 data points). The number of patients contributing data at each follow-up visit is shown in Table 10. With only two deaths, these data cannot support any conclusion regarding a mortality benefit of BMPRP. Likewise, the absence of treatment-related serious adverse events among 30 patients over 12 months, while reassuring, is insufficient to detect infrequent or delayed adverse events; the safety of this therapy should be regarded as preliminary rather than definitive (Table 10).

Table 10: Number of patients contributing outcome data at each follow-up visit.

Time point	BMPRP group (n=30)	Control group (n=20)	Remarks
Baseline	30	20	—
Month 1	30	20	—
Month 3	30	20	—
Month 6	29–30	20	one insulin value missing
Month 12	30	20	both control-group deaths occurred after the month-12 assessment

Note: In the analysis dataset, outcome data were complete for all patients in both groups at every follow-up visit (except one insulin value at month 6 in the BMPRP group); the two control-group deaths occurred after completion of the 12-month outcome assessment and therefore caused no missing outcome data.

Discussion

This multicenter retrospective cohort study suggests that ultrasound-guided dual-target (hepatic and pancreatic) BMPRP infusion can significantly improve liver function and glycemic control in patients with cirrhosis complicated by T2DM, with efficacy sustained for at least 12 months and a preliminarily favorable safety profile; these results remained robust in linear mixed-effects models accounting for repeated measures, baseline covariates, and multiple comparisons, but given the exploratory, non-randomized design they should be interpreted as hypothesis-generating.

Mechanisms of dual-organ repair

The pathophysiology of cirrhosis complicated by T2DM involves hepatogenous diabetes mechanisms: reduced hepatic insulin inactivation due to declining liver function, portosystemic shunting causing hyperinsulinemia, and peripheral insulin resistance [3-5]. In this study, BMPRP treatment simultaneously improved hepatic synthetic function (increased ALB, shortened PT) and glucose metabolism (reduced insulin dosage, increased C-peptide), suggesting synergistic dual-organ repair.

Hepatic repair mechanisms: BMPRP may promote hepatocyte regeneration and inhibit hepatic stellate cell activation and fibrosis through paracrine effects [19,20][13,14]. A 2023 systematic review and meta-analysis of 13 randomized controlled trials by Suk et al. [28][9] confirmed that MSC therapy significantly reduces Child-Pugh and MELD scores and improves survival in patients with cirrhosis, providing high-level evidence supporting our findings. The progressive improvements in ALB and PT in this study suggest restoration of hepatic synthetic and metabolic function; however, these laboratory changes do not directly demonstrate recovery of functional hepatocyte mass — improvements in ALB and PT may also reflect reduced hepatocellular injury, improved microcirculation, or paracrine support, and no histological or imaging evidence of hepatocyte regeneration was obtained in this study.

Islet function improvement mechanisms: Direct intrapancreatic infusion under ultrasound guidance may increase cell engraftment rates. The increase in C-peptide accompanied by a marked reduction in insulin dosage is consistent with improved β-cell secretory function and/or improved peripheral insulin sensitivity secondary to improved liver function; however, changes in C-peptide and insulin requirements do not establish pancreatic β-cell regeneration, and the relative contributions of these mechanisms cannot be distinguished with the available data. A 2024 Japanese study with 33-month follow-up confirmed that autologous bone marrow mononuclear cell therapy for T2DM sustains C-peptide improvement and reduces complications [17][15], consistent with the immunomodulatory and anti-inflammatory effects of MSCs and their capacity to improve the pancreatic microenvironment [21-23][16-18].

Advantages of targeted infusion technology

Compared with conventional peripheral intravenous infusion, ultrasound-guided percutaneous dual-target (hepatic and pancreatic) infusion offers significant advantages: (1) avoidance of first-pass pulmonary entrapment, increasing target-organ cell concentration; (2) real-time ultrasound guidance ensuring precise positioning and reducing vascular injury; (3) a dedicated syringe centrifugation system enabling "bedside" injection with cell viability >95% and reduced contamination risk. The 2024 study by Zhang et al. [29][11] on ultrasound-guided targeted MSC delivery further confirmed the superiority of local infusion in improving cell survival and therapeutic efficiency. The three-infusion protocol (months 0, 1, and 3) adopted in this study is consistent with the cumulative-effect pattern of multiple stem cell infusions. Because this invasive procedure is performed in cirrhotic patients who may have coagulopathy and portal hypertension, the procedural safeguards described in Section 2.4 — including pre-procedural coagulation assessment and correction, continuous Doppler-guided fine-needle technique, slow injection, and post-procedural verification of needle-track hemostasis — are integral to the safety outcomes reported here [31][12].

Clinical significance

This study fills an evidence gap in dual-organ regenerative therapy for cirrhosis complicated by T2DM. Notably, 60%

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of patients in the BMPRP group achieved complete ascites resolution, and insulin dosage decreased markedly (from 23.9±18.9 to 7.6±9.1 U/d), with some patients discontinuing insulin entirely — findings of considerable significance for quality of life and healthcare burden. Although gastrointestinal bleeding — an expected complication of cirrhotic portal hypertension — occurred in both groups, and no deaths occurred in the BMPRP group whereas two control patients died of post-hemorrhagic liver failure, the number of events is far too small to support any conclusion regarding a mortality benefit; this observation is reported for completeness and is hypothesis-generating only.

Limitations and future perspectives

This study has the following limitations: (1) the retrospective design with non-randomized grouping is subject to selection bias and confounding by indication — although treatment allocation was based on routine clinical decision-making and the mixed-effects models adjusted for the available baseline covariates (age and the baseline value of each outcome), patient-level Child-Pugh class, diabetes duration, and center identifiers were unavailable in the analysis dataset and could not be modeled; residual and unmeasured confounding therefore cannot be excluded, and non-significant baseline comparisons in small samples do not establish equivalence; (2) the sample size was small (n=50) with unequal group sizes, limiting statistical power; (3) cell tracing and subpopulation analyses were lacking, so the mechanistic discussion remains superficial ; the biologic product is a heterogeneous concentrate of plasma, platelets, mononuclear cells, and progenitor cells, and flow-cytometric CD34+ quantification was not routinely performed on each preparation, so mechanistic interpretations remain speculative; (4) follow-up was limited to 12 months, and long-term efficacy and safety require further observation ; (5) two control-group patients died during follow-up (both after completion of the 12-month outcome assessment, causing no missing outcome data), but the number of deaths is too small to permit mortality conclusions, and the effect of the treatment on survival cannot be evaluated in this study; (6) the efficacy endpoints are laboratory and imaging surrogate measures that cannot directly demonstrate hepatocyte or β-cell regeneration; (7) enrollment across three centers may have introduced center effects — treatment allocation was correlated with center (the Zhonghong Ruikang center contributed predominantly treated patients, 16/20, whereas the other two centers contributed predominantly controls, 8/17 and 6/13), and center effects could not be modeled with the available data, so residual center-level confounding cannot be excluded; (8) multiple comparisons across outcomes and time points — although per-visit comparisons were Holm–Bonferroni adjusted and the principal conclusions rest on omnibus group × time interactions, some risk of type I error remains. The absence of treatment-related serious adverse events, while reassuring, is insufficient to definitively establish overall safety. Future studies should include large-scale, prospective randomized controlled trials exploring optimal infusion dosage, frequency, and cell type (e.g., the correlation between CD34+ cell proportion and efficacy), with longer follow-up, centrally adjudicated adverse events, and mechanistic substudies incorporating cell tracing and clamp-based assessments of β-cell function[19-31].

Conclusion

In this exploratory, multicenter, retrospective cohort study, ultrasound-guided dual-target (hepatic and pancreatic) autologous BMPRP infusion was associated with significant and sustained improvements over 12 months in liver function (coagulation, albumin synthesis, bilirubin metabolism, and ascites resolution) and glycemic control (FPG, HbA1c, insulin dosage, and C-peptide levels) in patients with cirrhosis complicated by T2DM; adjusted linear mixed-effects models confirmed significant group × time interactions for every outcome, and no treatment-related serious adverse events were observed. Given the non-randomized design, small sample size, reliance on surrogate endpoints, and the small number of deaths during follow-up, these results should be regarded as hypothesis-generating: they suggest that dual-organ targeted BMPRP infusion is a feasible and potentially effective regenerative treatment option for cirrhosis complicated by diabetes, but definitive conclusions regarding efficacy and safety await confirmation in adequately powered randomized controlled trials.

Declarations

Ethics approval and consent to participate: This study was approved by the ethics committees of all participating hospitals, and written informed consent was obtained from all patients.

Author contributions

Qin Zhang: study design, data collection, statistical analysis, and manuscript writing.

Xiong Gao and Yuanhuai Chen: clinical study implementation and data collection.

Qiqiang Dong: clinical study implementation and technical support.

Baochi Liu: study conception, technical guidance, and manuscript review and revision.

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