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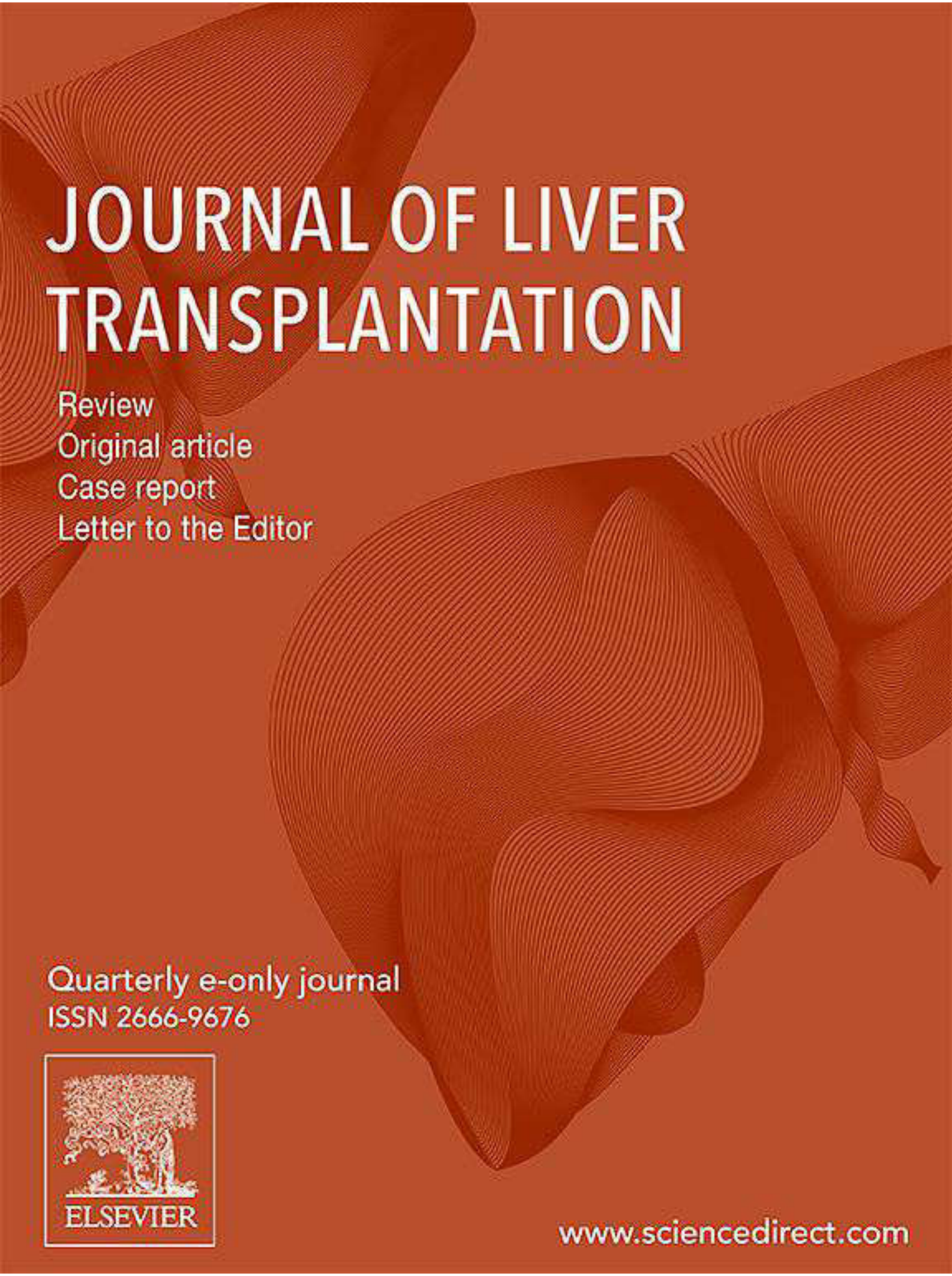
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Autologous liver cells mini liver implant for liver cirrhosis treatment: A phase II single center controlled trial

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ABSTRACT

Background: Liver cirrhosis represents a major healthcare burden, with its prevalence continuing to rise. While orthotopic liver transplantation (OLT) remains to be the only treatment, persistent shortage of donor organ contributes to significant waitlist mortality. Hepatocyte transplantation offers a regenerative approach as a bridging therapy to OLT. However, transplantation through portal vein infusion often ends with poor cell engraftment and allogeneic rejection. Herein, we designed a mini liver implant, composed of a 3-dimensional biodegradable poly-L-lactic acid matrix carrying autologous hepatocyte and islets.
Methods: A phase II clinical trial was conducted in patients with liver cirrhosis to receive either a mini liver implant or standard treatment (control group). Liver stiffness and steatosis were measured by FibroScan® at baseline, 6-, and 12-months after implantation. Child-Pugh score, MELD (Model for End-stage Liver Disease) score, serum albumin, and other biochemical parameters were assessed at baseline, 2-, 4-, 6-, and 12-months.
Results: The implant group demonstrated a progressive reduction in liver stiffness from 19.23 kPa at baseline to 15.33 kPa at 12 months (20.28 % decrease), although not statistically significant. The control group showed worsen liver stiffness from 25.92 kPa to 62.22 kPa (140.05 % increase). Other hepatic parameters, including steatosis, albumin, and liver enzymes, showed no significant differences between groups. The implant was well tolerated with only mild adverse events reported. Overall survival was comparable between both groups.
Conclusions: While larger studies are required to confirm efficacy, autologous mini liver implantation shows promise as a regenerative therapy that could delay or complement liver transplantation.

1. Introduction

Orthotopic liver transplantation (OLT) remains the definitive treatment for terminal liver diseases such as liver cirrhosis. Patients in the initial stages of cirrhosis often remain asymptomatic, but over time, decompensation occurs, marked by ascites, esophageal variceal bleeding, and hepatic encephalopathy. Once decompensated, morbidity and mortality rates increase dramatically, often leading to fatal outcomes [1,2]. With the rising global prevalence of liver cirrhosis, the demand for OLT has surged. In 2022, approximately 36,000 OLT procedures were performed worldwide, representing a 25 % increase from 2015 [1,3]. Despite this growth, the demand for transplantable livers continues to outpace supply, leaving many patients to die on waiting lists or become too ill to receive a transplant.

Hepatocyte transplantation has emerged as an alternative therapy to replace damaged cells and restore liver function. Over three decades of

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research demonstrate its clinical safety, but challenges remain [4,5]. These include insufficient engraftment, allogeneic rejection, and disrupted hepatocyte functions following isolation processes, which are primarily related to hepatocyte infusion (commonly into the portal vein) [6]. Co-culturing hepatocytes with pancreatic islets has shown promise in improving cell viability and liver function [7–9].

Unlike most terminally differentiated cells, hepatocytes possess remarkable regenerative capabilities. Yimlamai *et al.* has revealed that hepatocytes can exhibit stem cell-like properties [10], while Yanger's work demonstrates that new hepatocytes primarily arise from pre-existing differentiated ones through self-duplication rather than from stem cell differentiation [11]. This intrinsic regenerative capacity allows hepatocytes to restore liver function following acute damage. However, aging or extensive damage, as seen in cirrhosis, impairs this regenerative function, affecting the efficacy of autologous transplantation [4,12].

The isolation process presents additional challenges, as the loss of cell-to-cell and cell-to-matrix contacts disrupts normal hepatocyte functions [6]. To address these limitations, co-culture of hepatocytes with pancreatic islets exerts beneficial effect in enhancing hepatocyte survival, through the secretion of hepatotrophic factors, *e.g.* insulin and microRNAs derived from extracellular vesicles. This co-culture approach promotes hepatocyte implantation efficacy through multiple mechanisms, including improved cell viability, albumin secretion, ammonia metabolism, and other hepatic functions. These improvements stem not only from islet-secreted factors but also from cellular interactions between islets and hepatocytes [7–9].

Previously, we conducted a successful phase I clinical trial in patients with longstanding liver cirrhosis (ClinicalTrials.gov identifier: NCT01335568). Our approach utilized a mini liver construct comprising autologous hepatocytes and islet cells co-seeded onto a 3D collagen-coated PLLA scaffold [13,14]. As spatial orientation significantly influences hepatocyte differentiation and function, 3D scaffolding was utilized to promote effective transplantation [6,8]. Moreover, this 3D mini liver construct was implanted into small bowel mesentery, enabling mass cell delivery and improved cell engraftment. Our phase I clinical results demonstrated general safety, feasibility, and suggested improved liver function [14].

This phase II clinical trial rigorously evaluates the efficacy of the mini liver implant in cirrhosis patients, comparing outcomes against best practice treatments. Additionally, we seek to determine the duration of therapeutic effects conferred by the mini liver implant, addressing a critical gap in our understanding of this novel therapeutic approach.

2. Methods

The protocol has been described in detail by Baer *et al.* during the phase I study (NCT01335568) [13]. Current study followed the improved protocol (9th version study protocol) to replace the type I template used in the phase I clinical trial with a refined matrix type II that guarantees higher attachment rates of the cells to the template.

2.1. Study design and participant criteria

The Mini Liver Implant study was a prospective, non-randomized, open label phase II clinical study conducted in accordance with the Declaration of Helsinki, approved by The Ministry of Health of the Republic of Indonesia (No. LB.02.01/KE.071/2018 and LB.02.01/2/KE.064/2019). Written informed consent was obtained from all patients prior to participation. Patient screening, recruitment, and basic examination were conducted in Prof. Ali Sulaiman Liver Clinic (Jakarta, Indonesia); those eligible for the study were later appointed to Gading Pluit Hospital (Jakarta, Indonesia) to enroll the treatment. In this phase II study, the inclusion criteria were slightly modified from the phase I study by recruiting only patients with earlier stages of liver cirrhosis; indicated by Child-Pugh score of 6 – 10 and MELD (Model for End-Stage Liver Disease) score of less than or equal to 15. Confirmed patients were grouped into the treatment group receiving the mini liver implant and control group receiving best practice treatment (hepatoprotectant, antiviral, vitamins).

2.2. Mini liver implant: novel autologous hepatocyte-based regenerative template

The regenerative template employed an engineered three-dimensional poly-L-lactic acid (PLLA) scaffold with controlled porosity (355–425 μm pore diameter with >90 % porosity), optimized for hepatic tissue architecture. The scaffold underwent a specialized surface modification process incorporating a nanoscale bovine collagen coating, creating a hydrocolloid interface. This surface was further enhanced through plasma treatment to optimize hydrophilicity, facilitating cellular adhesion and interaction. Real sterilization was achieved by a proprietary low temperature sterilization process using vaporized H_2O_2.

The cellular component was derived through subsegmental hepatic and pancreatic biopsy, yielding a comprehensive population of autologous liver cells, including both parenchymal and non-parenchymal populations. These cells underwent specialized laboratory processing to maintain their phenotypic stability and functional capacity. The processed cells were then seeded onto the modified scaffolds.

This bioengineered construct, incorporating up to 300 million viable cells (hepatocytes co-seeded with islet cells), serves as a functional template for hepatic regeneration when reimplanted. This construct offers key advantages displayed in Table 1. The mini liver constructs were then implanted into the small bowel mesentery of each patient by forming a cavity to accommodate the placement of mini liver implant within a well-vascularized substratum (Fig. 1).

2.3. Outcomes and assessments

The co-primary outcomes were evaluated by assessing the changes of FibroScan® examination (stiffness and steatosis) and serum albumin level at 6 months and 1 year from the baseline. Secondary outcomes included the scoring of Child-Pugh, MELD, and Quality of Life (QoL) assessment through EQ-5D (European Quality of Life 5 Dimensions) questionnaires, as well as blood measurement of aspartate aminotransferase (AST), alanine transaminase (ALT), gamma glutamyltransferase (GGT), lactate dehydrogenase (LDH), cholinesterase (CHE), ammonia, bilirubin (total, direct, and indirect), international normalized rate (INR), prothrombin time (PT), and alfa fetoprotein (AFP), which were carried during every follow-up. Safety and adverse events were assessed, documented, and managed from the beginning until the completion of the study (or withdrawal).

2.4. Statistical analysis

Categorical variables are presented with its frequencies and

Table 1
Key advantages of the Mini Liver template.

Biomaterial design	Cellular Components	Safety Profile
• Optimized PLLA scaffold architecture	• Complete autologous cell population	• No immunological complications
• Controlled porosity for cellular integration	• Preserved hepatic cellular diversity	• Preserved cellular phenotype
• Nanoscale collagen surface modification	• Maintained functional capacity	• Controlled degradation kinetics
• Enhanced hydrophilicity through plasma treatment	• Significant therapeutic cell mass	• Minimal risk of rejection
• Low temperature sterilization		

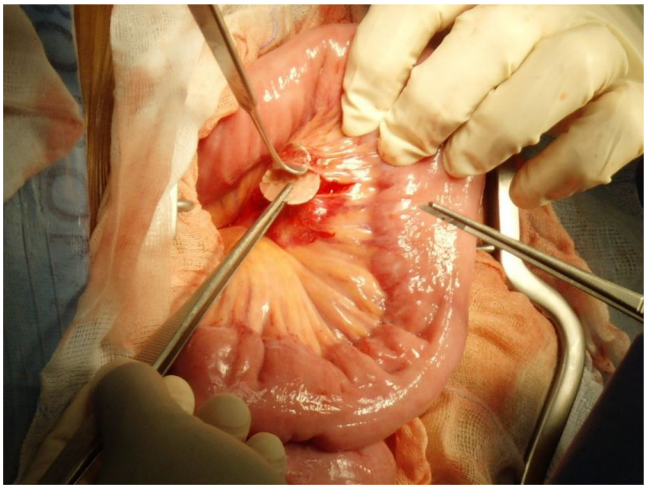

Fig. 1. Representative image of mini liver implant placement in the small bowel mesentery.

proportions, while continuous variables are summarized with their means and standard deviations or medians and their minimum to maximum values. Repeated measure statistics were carried out to ascertain whether the cell implants affected patient's liver stiffness and steatosis. Mauchly's test of sphericity was used to determine which statistic association results to be inferred. Mean differences in liver stiffness and steatosis are reported with their corresponding 95 % confidence intervals. All statistical analysis were performed using IBM SPSS Statistics 25th Version.

3. Results

3.1. Study population and baseline characteristics

A total of 23 participants were included in this study to receive either best practice treatment ($n = 11$) or the mini liver implant ($n = 12$) (Fig. 2). During the study period, one participant receiving mini liver implant died before the first follow-up and two more participants died from each group after the third follow-up. This makes ten participants left from each group to be succesfully observed until the last follow-up, that is one year following treatment. The baseline characteristics of all enrolled participants were shown in Table 2.

3.2. Cell processing and implantation

Mini liver group consisted of 12 patients, of which underwent the first surgery to obtain subsegmental hepatic and pancreatic tissue. Cell isolation from all patients resulted a mean hepatocyte number of 252.75 ± 153.54 × 10^6 with viability of 80.73 ± 10.39 %. Meanwhile, pancreatic islet yield averaged 1.73 ± 1.48 × 10^6, with 71.67 ± 15.97 % viability. From the mixture of isolated hepatocytes and islet cells, each patient received the final implants containing an average of 185.62 ± 110.63 × 10^6 cells, distributed across 26 ± 4 matrices. The adherence of cells seeded on matrix implant achieved a mean rate of 74.0 ± 12.6 % (Supplementary Table 1). Following the implantation procedure, follow up assessments were conducted on each patient at designated time points.

Table 2
Baseline demographic and clinical information of participants.

Characteristics	Control	Implant
n	11	12
Sex		
Male	6	11
Female	5	1
Age (years) mean ± SD	50.27 ± 8.89	47.50 ± 8.24
EQ-5D score, mean ± SD	75.00 ± 6.71	73.85 ± 13.10
MELD score, mean ± SD	11.64 ± 2.20	12.77 ± 1.59
≤9 (n/total number)	3/11	0/12
10–15 (n/total number)	8/11	12/12
Child Pugh score, mean ± SD	6.27 ± 1.42	6.23 ± 1.17
Blood parameters, mean ± SD		
Aspartate aminotransferase (U/L)	41.18 ± 13.11	49.15 ± 20.76
Alanine aminotransferase (U/L)	29.82 ± 9.69	33.08 ± 18.03
Gamma-glutamyltransferase (U/L)	38.73 ± 25.06	31.62 ± 19.69
Albumin (g/dL)	3.58 ± 0.72	3.51 ± 0.48
Ammonia (μmol/L)	74.55 ± 30.24	59.46 ± 31.09
LDH (U/L)	217.09 ± 63.88	211.23 ± 39.75
CHE (U/L)	4029.45 ± 1470.96	4034.08 ± 963.77
Total bilirubin (mg/dL)	1.89 ± 0.97	1.91 ± 0.78
INR	1.29 ± 0.12	1.29 ± 0.13
Glucose (mg/dL)	129.00 ± 42.19	117.00 ± 32.53
Prothrombin time	13.38 ± 1.19	13.30 ± 1.35
Alfa fetoprotein	22.09 ± 58.37	21.66 ± 59.13

3.3. Effects of mini liver implant on liver stiffness and steatosis

Liver stiffness measurement by FibroScan® revealed a marked improvement in the mini liver implant group over the course of time (Fig. 3a). Mean liver stiffness in the implant group decreased from 19.23 kPa (12.00–26.45) at baseline to 17.20 kPa (7.40–27.00) at 6 months, and further declined to 15.33 kPa (−29.61–60.26) at 12 months follow-up, although the change was not statistically significant within or between groups. Conversely, the control group showed an increasing trend

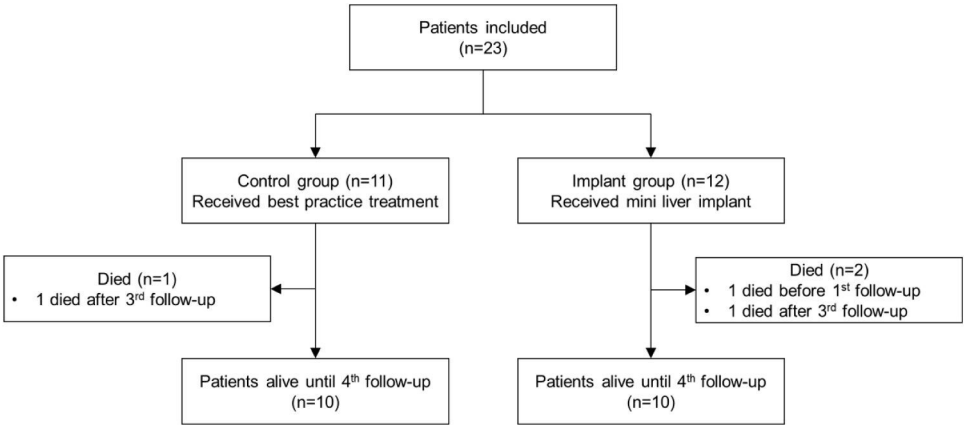

Fig. 2. Study participants flow chart.

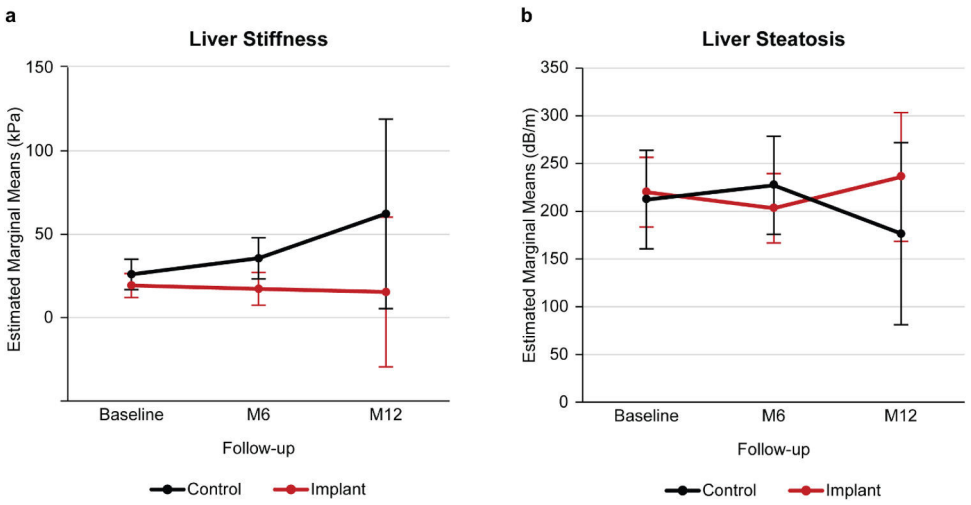

Fig. 3. Changes in liver stiffness and steatosis assessment as measured through FibroScan® analysis. Observed estimated marginal mean changes of a) stiffness (in kPa) and b) Controlled Attenuation Parameter (CAP) value estimating liver steatosis (in dB/m) in control and implant group (error bars: 95 % CI). M6: 6 months follow-up; M12: 12 months follow-up.

from baseline (25.92 kPa [16.78–35.06]) to 6 months (35.54 kPa [23.15–47.93]), reaching the highest value at 12 months (62.22 kPa [5.38–119.06]), also without statistical significance.

Hepatic steatosis, however, as estimated by CAP (Controlled Attenuation Parameter) values, showed different patterns (Fig. 3b). In the implant group, the mean steatosis was slightly decreased from 220 dB/m (183.46–256.54) at baseline to 203.13 dB/m (166.88–239.37) after 6 months of implantation. However, after 12 months, the CAP value increased to 236 dB/m (168.53–303.47). On a contrary, mean CAP values in control group increased from 212.25 dB/m (160.57–263.93) to 227.25 dB/m (175.99–278.51) after 6 months, and decreased to 176.58 dB/m (81.16–272.00) after 12 months. These results were unaccompanied with any statistical power, indicating that both groups had no clear effect in reducing fatty liver buildup.

3.4. *Effects of mini liver implant on liver function parameters*

Median value of serum albumin levels remained relatively stable in both groups throughout the study (implant group 3.48–3.75 g/dL *vs.* control group 3.50–3.80 g/dL), with no significant differences between each timepoint and group (Fig. 4). The range of albumin levels observed, however, was still in the normal range of 3.50–5.50 g/dL.

Additionally, several blood markers of liver injury were also assessed: AST, ALT, GGT, LDH, CHE, ammonia, bilirubin, INR, PT, and AFP. Both groups showed relatively stable blood markers, with no significant changes throughout the study (Supplementary Fig. 1). In overall, mini liver implant showed no significant effect in terms of overall liver function, compared to control group.

3.5. *Effects of mini liver implant on liver disease severity and quality-of-life*

As presented in Fig. 5a, both groups maintained stable Child-Pugh scores throughout the study period, that is 5.0 to 6.0, which falls into grade A and interpreted as having mild cirrhosis [15]. Similarly, MELD scores showed minimal variation in both groups, with median scores ranging from 10 to 13, indicating a MELD class 2 with 90-day mortality risk of 6 % (Fig. 5b) [16]. No significant differences were seen between groups ($p > 0.05$ for all comparisons). These results showed that mini liver implant had no significant effect in alleviating disease severity and patient prognosis.

To assess the effect of mini liver implant to health-related quality-of-life, EQ-5D tool was utilized across the follow-up duration. The implant group had improved quality-of-life, from 80 points at baseline to 88

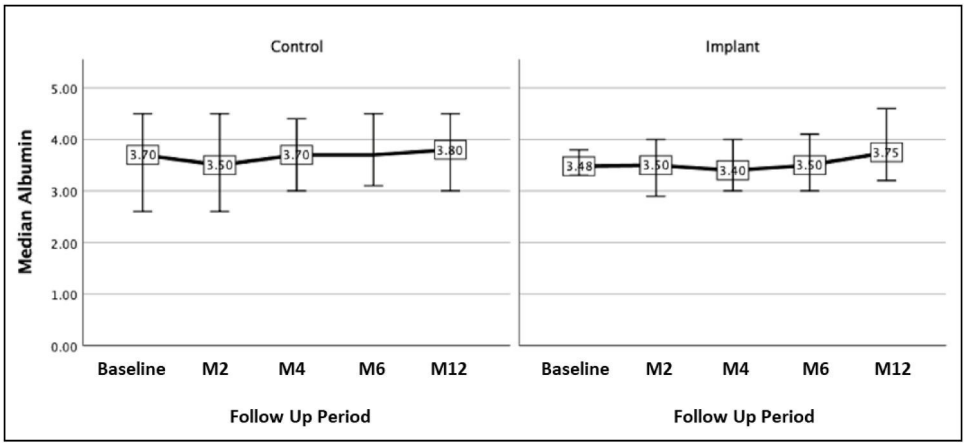

Fig. 4. Effect of mini liver implant on albumin level of patients with liver cirrhosis. Median values of total albumin (g/dL) in control and implant group were displayed over designated follow-up periods (error bars: 95 % CI). Normal albumin level: 3.5 – 5.5 g/dL. M2: 2 months follow-up; M4: 4 months follow-up; M6: 6 months follow-up; M12: 12 months follow-up.

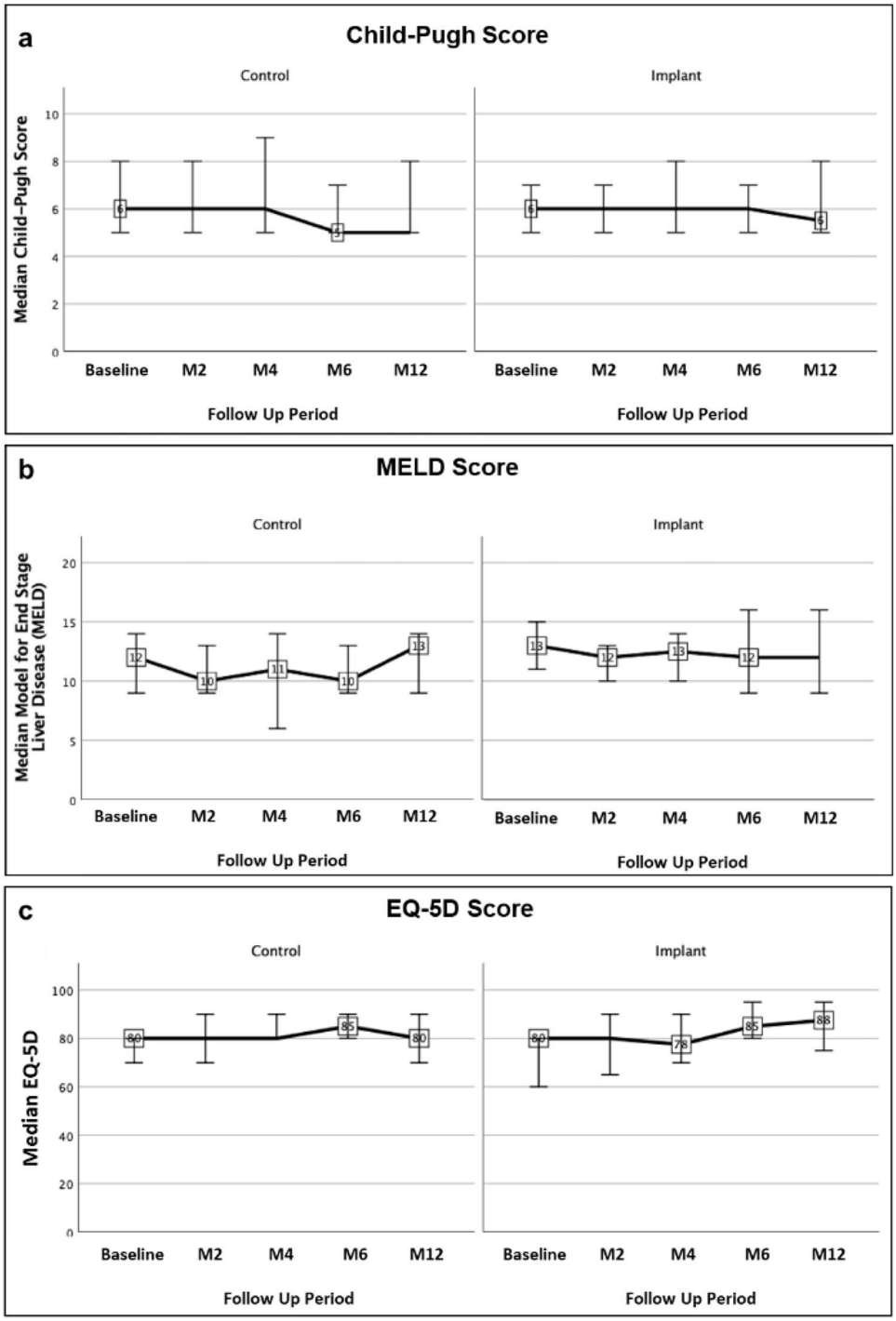

Fig. 5. Median changes of Child-Pugh, Model of End-stage Liver Disease (MELD), and European Quality-of-Life 5 Dimensions (EQ-5D) scores in control and implant group. Observed median changes of a) Child-Pugh score, b) MELD score, and c) EQ-5D questionnaires in control and implant group over designated timepoints (error bars: 95 % CI). M2: 2 months follow-up; M4: 4 months follow-up; M6: 6 months follow-up; M12: 12 months follow-up.

points at 12 months following implantation. In contrast, no improvement was seen in control group, as the median EQ-5D value was 80 points at both baseline and 12 months follow-up (Fig. 5c). Although not statistically significant, these results demonstrated better quality-of-life outcome in mini liver implant group.

3.6. Adverse effects and safety of mini liver implant

The mini liver implant was well tolerated by all participants. Reported symptoms, including ascites, pruritus, jaundice, and limb edema, were mild and occurred in both the implant and control groups, which were all related to natural disease progression. One patient in the implant group, however, experienced pain in the surgery site and nausea, which were resolved after hospitalization. During the study period, three participants died following the treatment. One from control group died after the 6-month follow-up. Two participants from the implant group died before 2-month follow-up and after 6-month follow-up. Mortality events were due to the disease progression and regarded as unrelated to the implant or intervention.

4. Discussion

The global rise in patients with liver disorders represents a significant healthcare challenge, as OLT remains the only effective treatment for those with end-stage liver disease. Recent studies have shifted focus toward stem-cell based therapies, owing to their ease of expansion [17]. However, despite safety report in several clinical studies, the use of stem cells still carries a higher risk of tumorigenicity due to uncontrolled differentiation. In the context of liver cirrhosis, stem cells are likely to be chemoattracted to the tumor microenvironment, with paradoxical roles in either suppressing or promoting the development of hepatocellular carcinoma [18–20]. Hence, more studies are still underway to prove its safety.

Autologous hepatocyte transplantation is one of the earliest approaches explored, but persistent challenges related to scalability and efficacy remain. In this study, a mini liver implant was fabricated to overcome major drawbacks related to OLT, essentially donor scarcity and high cost, with less tumorigenicity risk. Utilization of autologous hepatocyte/islet cells prevents the risk of host rejection and further need of lifelong immunosuppressants [21]. To address the issues in obtaining viable hepatocytes, islet cells were co-seeded into a 3D matrix made of a collagen-coated PLLA polymer. These islet cells stimulate hepatocyte survival and proliferation when implanted into an ectopic site [22]. Each matrix could hold more than ten million cell suspension, crucial for delivering bulk hepatocytes. As a result, each patient received a total of 185 million hepatocyte/islet mixture, implanted within 26 matrices in average. This construct was transplanted into the small bowel mesentery, which provides a well-vascularized space for oxygen and nutrient uptake, as well as waste elimination while the cell regeneration takes place. Other routes, such as intrasplenic, portal venous, and intraperitoneal injections, are posed with risks of emboli and portal hypertension when involving bulk cells transplantation [22].

This phase II clinical trial demonstrated a progressive reduction of liver stiffness in the implant group (20.28 % decrease over 12 months) when contrasted with the control group's (140.05 % increase in stiffness). Align with this result, quality-of-life assessment revealed a marked improvement, exclusively in the implant group. Although without significant statistical differences, this divergent trend between groups suggests a potential beneficial effect on fibrosis progression that warrants further investigation. The mechanism underlying this improvement appears to be multifaceted.

Transplantation of hepatocytes into extrahepatic site of small bowel mesentery could promote survival rate of hepatectomized rats. Although the viability of cells deteriorated at the transplant site, these transplanted cells exerted paracrine activity through the secretion of hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1), and other chemokines, leading to its protective effect for the remaining liver. These factors could be absorbed through the mesenteric microvessels into the portal vein [23]. Additionally, our *in vivo* study utilizing mini liver implant in cirrhosis-induced rats demonstrated that mini liver implants system was able to preserve cell viability after four months following implantation [24]. Kneser *et al.* also found that implantation of porous 3D polyvinyl-alcohol matrices containing hepatocyte/islet cells could be metabolically functional after 12 months of implantation [25]. These findings indicated that implantation of mini liver into the mesentery may continue to function for an extended amount of time. All of which suggested the possible mechanisms on how our mini liver implant works.

To maintain tissue homeostasis, hepatocytes possess remarkable capacity to enlarge, proliferate, and generate new hepatocytes. Miyaoka *et al.* found that hepatic cells in normal liver tissue consist of ~30 % binuclear hepatocytes. These binuclear hepatocytes undergo reductive division, in which each cell divides into two cells with single nucleus [26,27]. These findings suggest that our liver cell matrix implant might not only consisted of end-differentiated hepatocytes but also of binuclear hepatocytes, supporting sustained regenerative capacity.

While a clear trend was observed in terms of liver stiffness and quality-of-life, other parameters showed no distinct tendencies in both groups. Hepatic steatosis appeared to be slightly increased in implant group by 7.27 % after 12 months of implantation, while mean CAP values in control group decreased by 16.81 %. Serum albumin, as one of the indicators of hepatic synthetic function, remained relatively stable in both groups throughout the study period. Identically, other blood biochemical markers showed no significant differences. The overall survival was also comparable in both group with no statistical differences. These findings suggest that mini liver implant did not exert a meaningful impact on patient severity and prognosis.

The limited efficacy of the mini liver implant in reducing hepatic steatosis and other blood parameters may be attributed to two main limitations: insufficient number of transplanted cells and the small sample size of this study. The hypothetical target for hepatocyte transplantation is estimated to be approximately 5–10 % of the total liver cell mass. Considering that the average adult liver contains roughly 2.8×10^{11} hepatocytes, the ideal transplant dose would range from 1.4 to 2.8×10^{10} cells [28]. The mean number of transplanted hepatocytes in the present study was approximately 2.53×10^{8} cells, which is nearly 100-fold lower than the proposed therapeutic threshold. This substantial discrepancy, coupled with the limited number of subjects involved, might influence the overall statistical outcomes observed in this study. During the subject recruitment process, financial challenges and rapid deterioration of patients' medical conditions hindered the inclusion process. Likely, most registered trials delivering hepatocyte transplantation (*e.g.* NCT00282542, NCT01345565, NCT01345578, NCT01465100) ended with study withdrawal or termination, due to limited funding, donor cell availability, or technical challenges [29].

While the trend outcomes are favorable, they should be viewed in light of the study's inherent limitations. Current study reported patients' status until 12 months follow-up, which might be relatively short to further evaluate long-term safety and efficacy of the mini liver implant. The study was initially designed with a 24-month follow-up period. However, the COVID-19 pandemic severely disrupted patient recruitment, while financial constraints further limited cohort expansion. The prolonged study duration, combined with the already modest sample size, resulted in significant patient attrition at extended timepoints, primarily due to relocation. Despite professional efforts to trace and re-contact these participants, follow-up data beyond 12 months could not be obtained in sufficient numbers to permit meaningful statistical analysis. Moreover, although FibroScan® could assess the liver stiffness and steatosis status, other direct parameters are still missing to estimate liver fibrosis and regeneration. Liver biopsies were not performed in the current study due to the invasive nature of the procedure and the heightened bleeding risk in patients with advanced cirrhosis and potential coagulopathy. Histological confirmation of fibrosis regression therefore remains pending for future studies, which may employ emerging non-invasive imaging modalities, such as magnetic resonance elastography as alternatives to tissue sampling. Hence, future study should report the safety and efficacy of mini liver implant in a longer follow-up period, that is up to 5 years.

Other validated parameters should be included as well, such as enhanced liver fibrosis (ELF) test, PRO—C3, and C3M screening. ELF test comprises of hyaluronic acid (HA), tissue inhibitor of metalloproteinase 1 (TIMP1), and amino-terminal propeptide of type III procollagen (PIIINP) serum detection, which is a clinically validated immunoassay to monitor fibrosis progression. Meanwhile, PRO—C3 and C3M are serum biomarkers which correlate to the formation and degradation of type III collagen, respectively. PRO—C3, particularly, measures active fibrosis and presents an important predictor of clinical outcomes in patients with advanced liver disease [30]. Addition of these parameters will better portray the effect of mini liver implant on fibrosis status of each patient.

Post-implant surveillance will include FibroScan® assessments at 6-month intervals to monitor liver stiffness and steatosis progression. This

will be complemented by abdominal ultrasonography to evaluate implant site integrity, detect potential mesenteric complications, and assess portal venous hemodynamics. Serial liver function panels, including albumin, bilirubin, and liver enzymes, as well as metabolic parameters, will be monitored to detect any delayed effects on hepatic function. Although it is possible to label and track the implanted cells within the mini liver implant, we avoided such method due to possible risks of the labeling effect on cell viability and efficacy [31].

Moving forward, new strategies will be essential to generate larger numbers of functional hepatocytes. The development of bioreactor systems capable of expanding hepatocytes to 1.5 billion cells or more would fundamentally transform the clinical applicability of this approach. Furthermore, utilizing stem cells derived products, such as secretome or exosomes, is of interest to boost hepatocyte function and survival. Our early *in vivo* study demonstrated the potential of secretome supplementation in supporting mini liver implant function, with comparable outcomes to islet cells co-culture [24]. This refined protocol would minimize surgical risk while maintaining the regenerative benefits observed in the current study. Although validation in larger cohorts is needed, our mini liver implant may represent a promising step towards regenerative therapies that could delay, or even complement, the need for liver transplantation.

5. Conclusion

This phase II trial offers the first clinical evidence supporting the potential of autologous mini liver implantation to alleviate liver stiffness in cirrhosis. Although other hepatic parameters remained largely unchanged and statistical significance was not achieved, patients receiving mini liver implant also had a marked quality-of-life improvement. These findings highlight the promise of cell-based liver support systems as a bridge or even alternative to transplantation. With further refinement hepatocytes amplification strategies, larger patient cohorts, and longer follow-up, mini liver implant holds the potential as a bridging therapy to advanced liver disease.

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Human and animal rights

This study was conducted in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving human, and was approved by The Ministry of Health of the Republic of Indonesia (No. LB.02.01/KE.071/2018 and LB.02.01/2/KE.064/2019). No animal studies were conducted as part of this research.

Informed consent and patient details

Written informed consent was obtained from all individual participants included in the study after explanation of the purpose, procedures, risks, and benefits of participation. This article does not contain any personal information that could lead to their identification.

CRediT authorship contribution statement

Hans Ulrich Baer: Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **Andri Sanityoso Sulaiman:** Supervision, Methodology, Investigation. **Nunuk Tri Wahyuni:** Validation, Supervision, Project administration, Formal analysis. **Barlian Sutedja:** Supervision, Methodology, Investigation. **Peter Ian Limas:** Project administration, Methodology, Investigation. **Olivia Marcelina:** Writing – original draft, Project administration, Investigation. **Jennifer Lheman:** Writing – review & editing, Project administration, Investigation. **Nuraeni:** Writing – review & editing, Project administration, Investigation. **Clement Drew:** Validation, Formal analysis, Data curation. **Siufui Hendrawan:** Writing – original draft, Supervision, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hans Ulrich Baer has an interest in acquiring intellectual properties in tissue engineering. Other authors declare no potential conflict of interest.

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N/A

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.liver.2025.100314.

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