Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Donor-Specific Whole Blood From Brain-Dead Organ Donors in Liver Transplantation: A Randomized Controlled Trial

Sara Farifteh
Shiraz University of Medical Sciences
Mohammad Eslamian
Isfahan University of Medical Sciences
Mohammad Shahdadian
Isfahan University of Medical Sciences
Hamed Nikoupour
Shiraz University of Medical Sciences
Alireza Salah
High Institute for Education and Research in Transfusion Medicine
Fatemeh Khalili
Shiraz University of Medical Sciences
Mehran Jafari
Shiraz University of Medical Sciences
Mohammad Alikhani
Shiraz University of Medical Sciences
Sahar Sohrabi Nazari
Shiraz University of Medical Sciences
Mohammad Mahdi Lashkarizadeh
Shiraz University of Medical Sciences
Alireza Shamsaeefar
shamsaeefar@yahoo.com
Shiraz University of Medical Sciences
Saman Nikeghbalian
Shiraz University of Medical Sciences

Research Article

Keywords: Liver Transplantation, Blood Transfusion, Brain Death, Tissue Donors, Blood Donors, Randomized Controlled Trial

Posted Date: November 26th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11265064/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Donor-Specific Whole Blood From Brain-Dead Organ Donors in Liver Transplantation: A Randomized Controlled Trial

Sara Farifteh[1], Mohammad Eslamian[2], Mohammad Shahdadian[3], Hamed Nikoupour[1], Alireza Salah[4], Fatemeh Khalili[1], Mehran Jafari[1], Mohammad Alikhani[1], Sahar Sohrabi Nazari[1], Mohammad Mahdi Lashkarizadeh[1], Alireza Shamsaeefar[1], Saman Nikeghbalian[1]

Affiliation:

1. Shiraz Transplant Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
2. Department of Surgery, Isfahan University of Medical Sciences, Isfahan, Iran
3. Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4. High Institute for Education and Research in Transfusion Medicine, Tehran, Iran

Corresponding Author:

Alireza Shamsaeefar

Tel: +989177111566

Email: shamsaeefar@yahoo.com

Funding Statement

This study received no external funding.

Conflict of Interest

The authors declare no conflicts of interest related to this work.

Clinical Trial Registration

Registered at Iranian Registry of Clinical Trials (IRCT) under ID IRCT20211008052699N2

Ethics Approval

Approved by the Shiraz University of Medical Sciences Ethics Committee (Ref. IR.SUMS.REC.1401.543)

Donor-Specific Whole Blood From Brain-Dead Organ Donors in Liver Transplantation: A Randomized Controlled Trial

Abstract:

Background: Blood loss during liver transplantation (LT) can require substantial transfusion support and place pressure on blood-bank resources. Donor-specific whole blood collected from the same brain-dead organ donor may reduce exposure to unrelated donors, but its safety and clinical effects in LT remain uncertain.

Methods: In this double-blind, single-center randomized controlled trial, 61 first-time LT recipients were assigned to donor-specific whole blood (intervention, n = 30) or standard component therapy with packed red blood cells with or without fresh-frozen plasma (control, n = 31). Outcomes included intraoperative blood loss, transfusion requirements, postoperative blood-culture positivity, acute cellular rejection, graft complications, and 90-day follow-up.

Results: All 61 randomized recipients were included in the primary analysis. Positive postoperative blood cultures occurred in 1/30 (3.3%) intervention recipients and 9/31 (29.0%) control recipients ($p = 0.012$); all positive cultures were obtained within 14 days. Primary non-function occurred in 2/30 and 1/31 recipients, respectively. Acute cellular rejection was observed in 0/26 versus 6/29 evaluable recipients at 1 month (Fisher exact $p = 0.024$) and in 3/25 versus 1/28 at 3 months ($p = 0.33$); these secondary comparisons were exploratory. Mortality did not differ significantly. By 3 months, 25/30 and 28/31 recipients remained evaluable for longitudinal nonmortality outcomes because of death or loss to follow-up.

Conclusion: Donor-specific whole-blood transfusion was feasible in this selected cohort of transfused LT recipients. The lower observed early blood-culture positivity is hypothesis-generating rather than evidence of a donor-specific causal effect because the intervention also differed from control care in blood-product composition and storage characteristics, and the trial was small. Larger studies that include recipients with higher transfusion requirements and detailed microbiologic data are needed.

Trial registration: Iranian Registry of Clinical Trials (IRCT), IRCT20211008052699N2. Retrospectively registered on 23 July 2023.

Key words: “Liver Transplantation”, “Blood Transfusion”, “Brain Death”, “Tissue Donors”, “Blood Donors”, “Randomized Controlled Trial”

Introduction

Liver transplantation (LT) is a complex and lifesaving procedure for the treatment of end-stage liver disease or acute liver failure (1). It is often associated with substantial blood loss, requiring the utilization of blood products intraoperatively as well as postoperatively (2). Blood transfusion, especially red blood cells (RBCs), is in high demand during liver transplantation, which poses challenges in the context of blood bank shortages (3). In contrast, packed red blood cell (PRBC) and fresh-frozen plasma (FFP)transfusion have been consistently associated with increased morbidity and mortality both intraoperatively and postoperatively, likely reflecting the severity of intraoperative blood loss and coagulopathy rather than a direct causal effect (4). Indeed, Several clinical studies have shown that reducing PRBC and blood products transfusions during LT can decrease mortality and morbidity besides the incidence of acute cellular rejection (5).

One of the options is donor-specific blood transfusion (DST), which means transfusion of blood from organ donor directly into organ recipients. Although this strategy has been investigated in other types of transplantation, such as kidney transplants, with promising findings, its use in liver transplantation has not received the same attention (6). However, there is renewing interest in whether DST could ameliorate blood supply issues during liver transplantation. Several early reports in the field of kidney transplantation indicate that the practice of DST may lead to modulate immune responses and improve graft survival; however, the importance of this practice has diminished in recent years given advances in immunosuppressive therapy (6,7).

Few Recent studies have highlighted the potential of donor-specific red blood cell transfusions as a strategy to address blood supply shortages in liver transplantation (8,9).

Moreover, in case of ABO-compatible organ, additional risk to transfuse foreign antigens and antibodies is also reduced by transfusion from the same donor which may overall decrease the chance of graft rejection. However, little is known about the safety, feasibility, and potential impact of donor blood in liver transplantation. Key questions about whether donor-specific transfusions might affect liver function, post-transplant infection rates, and other complications remain unanswered.

Due to the continuing global scarcity of blood products and the necessity for innovative approaches to maximize liver transplantation results, the present study was performed to evaluate the effects of using whole blood from brain-dead donors in liver transplantation at the Abu Ali Sina Organ Transplant Center. The results of this trial will help us better understand the impact of donor-specific transfusion on graft survival, immune response, and perioperative measures, all of which could potentially change clinical practice during periods of blood supply shortage.

Donor-derived blood has been explored in transplantation, most commonly in kidney transplantation and, in LT, primarily through observational designs or donor RBCs alone. Randomized evidence in LT remains limited. Our trial therefore evaluated donor-specific whole blood collected by sterile venous cannulation and compared this strategy with standard component therapy. Because the intervention differs from standard care in both donor source and blood-product composition, the trial was designed primarily to assess feasibility and short-term safety, with other clinical outcomes considered exploratory.

Methods:

Study design:

This study was a single center, double-blind, randomized controlled trial (RCT) performed at the Abu Ali Sina Organ Transplant Center from January to December 2023. It was designed to assess the effect of using whole blood from brain-dead liver donors during liver transplantation on

recipient outcomes. This trial was approved by the Shiraz University of Medical Sciences Ethics Committee under reference number "IR. SUMS. REC. 1401. 543", and informed consent from liver transplant candidates and also the families of the donor for donation after brain death (DBD) was obtained.

This randomized controlled trial is reported in accordance with the CONSORT reporting guidelines.

Participant selection:

Inclusion Criteria for Brain-Dead Donors:

- Stable hemodynamic (heart rate <100 bpm, systolic blood pressure >100 mmHg).
- No high-dose inotropes needed. (High dose is considered as Dopamine >10 µg/kg/min, Dobutamine >20 µg/kg/min, Epinephrine >0.1 µg/kg/min, Norepinephrine >0.5 µg/kg/min)
- Donation after brain death (DBD)
- Hemoglobin level >11 g/dL.
- Age between 18 and 60 years.
- Blood group (ABO, RH) compatibility between donor and recipient.
- low risk for CMV virus infection (recipient(R)+, donor(D)- or R-, D- or R+, D+)
- HBsAg, HBsAb, HCVAb, and HIV ELISA negative
- Covid 19 PCR: negative
- Blood culture: negative
- Donors who required massive transfusion support prior to organ procurement were not eligible for inclusion in the study.

- Informed consent from relatives
- Donate only liver and kidneys

Eligibility criteria for liver transplant recipients:

- Blood compatibility testing between donor and recipient.
- Liver transplantation from a brain-dead donor.
- Stable vital signs at the time of surgery.
- Whole organ transplant
- Hb>7 before transplant
- No need for inotropes prior to transplantation.
- No history of hepatic vein thrombosis (Budd-Chiari syndrome) or complete portal vein thrombosis or other Hyper coagulopathy conditions.
- Age between 15 and 75 years.
- First-time liver transplantation

The randomized cohort comprised LT recipients who required intraoperative red-cell transfusion; recipients managed without transfusion were outside the target population of this transfusion trial.

Exclusion Criteria:

- Insufficient donor whole-blood collection to support the assigned transfusion strategy.
- Complete portal vein thrombosis.
- Use of veno-venous bypass during transplantation.

No participant was excluded from analysis after randomization because of subsequent transfusion requirements. Clinically indicated additional blood-bank components could be administered after the assigned transfusion strategy and were recorded as outcomes; such treatment did not remove the recipient from the randomized group.

Randomization and Blinding:

This study was double-blind. Neither the person who received the organ nor the person who collected information during and after the transplant knew the type of product that was transfused.

The team responsible for organ retrieval and blood collection was a different one from the team performing the liver transplantation, which allowed the liver transplant team to be oblivious of the nature of the transfused blood. Furthermore, patients undergoing transplantation were not told the type of blood transfused after written informed consent. The data collector in the post transplantation ward was also unaware of the type of blood was transfused.

Patients were computer-randomized into two groups by an independent programmer using the randomization.com platform. All 61 randomized recipients remained in their assigned groups for the primary analysis.

Data Collection:

During Surgery:

Blood loss, urine output, blood gas analyses, transfusion volume, number of transfused FFP and platelet units, and any intraoperative complications such as reperfusion syndrome (a sudden ≥30 % drop in mean arterial pressure from the anhepatic baseline that lasts at least one minute within the first five minutes after graft reperfusion during liver transplantation) or transfusion-related adverse events were recorded by a trained anesthesiology expert.

No additional pro-coagulant agents (e.g., antifibrinolytics, cryoprecipitate, or factor concentrates) were administered in either group.

Postoperative Data:

Postoperative complications, including bleeding, need for packed cell (P.C.) transfusion, infection, and primary non-function, as well as liver function tests, graft survival, ICU stay, and other clinical outcomes, were documented using a predefined checklist by a blinded clinician.

Intervention Process – Blood Collection from Brain-Dead Donors:

Following confirmation of donor eligibility, a 10 mL blood sample was collected into a K3-EDTA tube prior to any surgical incision. The sample was labeled with the donor's code and date of birth, then sent to the hospital's central blood bank for cross-matching with the recipient's blood.

An anesthesiologist then inserted a radial arterial line for continuous blood pressure monitoring. Next, an 8-French double-lumen catheter was placed via the right jugular vein. Procurement surgery commenced, and after organ attachments were released, major vessels including the aorta, SMV, and IVC were carefully identified, isolated and controlled.

A blood collection bag was connected to a 16-gauge connector on the catheter, and blood flow was directed into it. Each bag was filled with approximately 450 mL of blood in under 5 minutes. A second and third bag was filled in the same manner. Blood bags were automatically shaken using a heamoshaker. Three units of whole blood (approximately 1350 mL total) were collected from each eligible donor.

The anesthesiologist continuously monitored the donor's MAP, holding blood collection if MAP dropped below 60 mmHg; such donors were excluded. After completing blood collection, Heparin (300 units/kg) was administered, and 5 minutes later, aortic cross-clamping was performed. Standard multi-organ retrieval followed.

After collection, the blood bags were kept at 22°C for two hours to allow bacterial phagocytosis, per manufacturer guidelines. The blood was then filtered through a leukocyte depletion filter and

mixed with SAGM (saline, adenine, glucose, mannitol) at a ratio of 100 mL SAGM per 450 mL of whole blood. Processed blood was stored at 4°C for potential use during transplantation.

Blood collected from the brain-dead donor was transfused to recipients assigned to the intervention when transfusion was judged clinically necessary by the anesthesiologist during LT. Control recipients received standard blood-bank component therapy. Additional postoperative blood-bank components were administered when clinically required and were recorded without excluding recipients from their randomized group.

During surgery, the control group received packed red-cell units of approximately 330 mL each, whereas the intervention group received donor-specific whole-blood units of approximately 450 mL each. Because these products differ in cellular and plasma composition, unit counts and FFP use are not composition-equivalent measures and were interpreted descriptively.

Outcome Measures:

Primary outcomes comprised post-transplant liver biochemistry (AST, ALT, ALP, total bilirubin, and INR); primary non-function of the graft; postoperative blood-culture positivity and clinically diagnosed sepsis; portal-vein thrombosis; hepatic-artery thrombosis; and biopsy-confirmed acute cellular rejection. Acute rejection was defined as an elevation of liver enzymes to more than three times the upper limit of normal that triggered liver biopsy; specimens were assessed by an expert pathologist and classified according to the Rejection Activity Index (10). Organism-level microbiologic classification and source attribution were not analyzed as prespecified study outcomes.

Secondary outcomes included all-cause postoperative mortality, quantified intra-operative blood loss, total peri-operative red-cell transfusion volume, and the volume of fresh-frozen plasma and platelet products administered during surgery or in the immediate postoperative period.

Statistical Analysis:

Statistical analyses were conducted with the IBM SPSS Statistics software (version 26). Baseline characteristics and outcomes were presented with descriptive statistics (mean ± standard deviation or median with interquartile range). Between-group comparisons were conducted with:

- **Parametric tests:** independent t-tests of normally distributed continuous data.
- **Tests for Assumption Violations**: Wilcoxon signed-rank test (paired sample) or Mann-Whitney U test (independent samples).
- **For categorical variables**: Chi-square tests or Fisher's exact tests.

Sample size was calculated using G*Power with 80% power and a two-sided alpha of 0.05 based on expected differences in postoperative outcomes, yielding a target sample of approximately 60 participants. All randomized recipients contributed to the primary analysis. Follow-up analyses at 1 and 3 months used the available denominators shown in the CONSORT diagram; reduced denominators reflect death or loss to follow-up.

Results

A total of 61 liver transplant recipients were randomized: 30 to donor-specific whole blood and 31 to standard component therapy (Figure 1). All randomized recipients received the assigned intraoperative transfusion strategy and were retained in the primary analysis. No intervention recipient required intraoperative rescue beyond the available donor-specific whole-blood supply. Recipient age, sex, BMI, liver-disease etiology, MELD score, and blood group were broadly similar, although preoperative hemoglobin was lower in the intervention group (9.99 vs 11.01 g/dL, $p = 0.04$; Table 1).

These small-sample baseline imbalances were considered when interpreting exploratory between-group outcome differences.

Donor Characteristics

Donor age, sex, and BMI did not differ significantly between groups (Table 3). However, donor ICU stay (4.23 vs 3.84 days, p = 0.004) and donor hemoglobin (13.46 vs 11.86 g/dL, p = 0.002) differed between groups. These imbalances are relevant in a small randomized trial and limit causal interpretation of secondary outcomes.

Liver macrosteatosis, assessed as a percentage by an expert pathologist, showed that macrosteatosis was evident in 11 donors 10–30%, and 19 donors 5–10%. The remaining 31 donors had less than 5% (nonspecific) macrosteatosis.

Intraoperative Outcomes

Graft type, cold ischemia time (CIT), and warm ischemia time (WIT) were similar between groups (Table 2). Estimated intraoperative blood loss was lower in the intervention group (1289 [SD 641] mL) than in the control group (2074 [SD 1633] mL; p = 0.03). Because the assigned products differed in composition and the intervention itself included plasma within whole blood, this comparison is exploratory and cannot isolate an effect of donor specificity.

The mean number of assigned intraoperative blood-product units was 2.53 (approximately 1,140 mL of donor-specific whole blood) in the intervention group and 2.71 (approximately 894 mL of PRBCs) in the control group (p = 0.52). FFP was administered only in the control group, averaging 0.97 units, whereas none was administered separately in the intervention arm. Because whole blood itself contains plasma, the between-group difference in separate FFP use should not

be interpreted as an independent transfusion-sparing effect. Reperfusion syndrome occurred in 10/30 and 11/31 recipients, respectively ($p = 0.86$).

Postoperative Outcomes

At day 7 and month 1, the measured liver biochemistry values did not differ significantly between groups (Table 4). At month 3, AST was higher in the intervention group (25.76 vs 18.68 U/L, $p = 0.034$) and ALP was also higher (319.08 vs 187.86 U/L, $p = 0.002$), whereas ALT and total bilirubin did not differ significantly. These later comparisons are based on reduced follow-up denominators and should be interpreted cautiously.

Acute cellular rejection was observed in 0/26 evaluable intervention recipients and 6/29 controls at 1 month (Fisher exact $p = 0.024$), and in 3/25 and 1/28, respectively, at 3 months ($p = 0.33$). The 1-month difference is an exploratory secondary finding and should not be interpreted as confirmatory because of the small sample, multiple outcome comparisons, and reduced follow-up denominators. By 3 months, 25/30 intervention recipients and 28/31 controls remained evaluable for longitudinal nonmortality outcomes because of death or loss to follow-up. These changing denominators limit precision and may introduce attrition bias in later comparisons.

Postoperative Complications

Postoperative bleeding, additional PRBC transfusion, and CMV positivity did not differ significantly between groups (Table 5). Positive postoperative blood cultures occurred in 1/30 (3.3%) intervention recipients and 9/31 (29.0%) controls ($p = 0.012$); all positive cultures were obtained within the first 14 postoperative days. The 29% rate therefore occurred in the control group, not the intervention group. Because organism-level results and infection-source

attribution were not analyzed, the present study cannot determine whether the control-arm excess reflected a specific pathogen, source, or cluster.

Mortality did not differ significantly between groups. Primary non-function occurred in 2/30 (6.7%) intervention recipients and 1/31 (3.2%) controls; hepatic-artery thrombosis occurred in 1 and 2 recipients, respectively. The small number of events precludes a reliable between-group safety comparison. The intervention recipient who died with clinically diagnosed sepsis had negative postoperative blood cultures, underscoring that blood-culture positivity and sepsis were not interchangeable outcomes. Detailed postoperative complications are shown in Table 5.

Discussion

This randomized, double-blind trial evaluated donor-specific whole blood from brain-dead organ donors as an alternative transfusion strategy during LT. In the selected cohort studied, the strategy was feasible, all randomized recipients remained in the primary analysis, and there was no consistent rejection pattern across follow-up and no clear excess of vascular complications or mortality. The observed reduction in early postoperative blood-culture positivity should, however, be interpreted as an exploratory signal rather than proof of a protective effect.

A central limitation is that the randomized intervention changed more than donor source. Intervention recipients received donor-specific whole blood, whereas controls received standard component therapy with PRBCs with or without FFP. The groups therefore differed simultaneously in donor exposure, blood-product composition, and storage characteristics. Prior LT work has shown that whole blood and component therapy can differ in donor exposures while providing effective replacement therapy (11). Consequently, neither the lower estimated

blood loss nor the difference in blood-culture positivity can be attributed specifically to donor specificity. The difference in separate FFP use is particularly structural because plasma was already present in the intervention product.

The present findings should also be interpreted in the context of previous studies examining whole blood and donor-derived blood during liver transplantation. In a prospective randomized study of 33 liver transplant recipients, Laine et al. compared whole blood with conventional RBC and FFP component therapy and found that whole blood provided similarly effective replacement of blood loss while significantly reducing the number of donor exposures (11). Importantly, coagulation profiles and the overall volume of blood replacement were largely comparable between groups. These findings are relevant to our trial because they demonstrate that whole blood itself may alter transfusion characteristics independently of whether the blood originates from the organ donor. Therefore, the lower estimated blood loss and absence of separate FFP administration observed in our intervention group cannot be attributed solely to donor specificity.

More recent studies have specifically investigated the use of organ-donor blood during liver transplantation. Shaylor et al., in a propensity-matched retrospective cohort of 350 deceased-donor liver transplant recipients, found that recipients receiving donor blood were less likely to require additional intraoperative banked PRBC transfusion and received fewer PRBC units, without significant differences in the assessed postoperative outcomes (13). Similarly, Tang et al., in a larger retrospective cohort of 992 liver transplant recipients, reported lower use of banked RBCs among recipients who received donor blood (8). Although graft survival was higher in the donor-blood group in unadjusted analyses, donor-blood transfusion was not an

independent predictor of graft survival, and no significant differences in patient survival or rejection were demonstrated. These observations support the feasibility and potential blood-conservation value of donor-derived blood but do not establish an independent beneficial effect on graft or patient outcomes.

Lv et al. subsequently evaluated donor-specific RBC transfusion in a prospective, nonrandomized study performed during the COVID-19 blood shortage (9). Among 26 recipients receiving donor-specific RBCs and 37 controls, donor-specific transfusion reduced the requirement for third-party banked RBCs and was not associated with transfusion-related complications. However, postoperative infection rates were similar between groups (23.1% vs. 18.9%, P=0.688). This differs from the lower rate of culture-proven bacteremia observed in our intervention group. Accordingly, our infection finding should not be interpreted as confirmation of an established protective effect of donor-specific transfusion. Differences in blood-product composition, storage duration, recipient characteristics, perioperative exposures, microbiological definitions, and local infection epidemiology may all contribute to the different findings across studies.

Taken together, the available literature consistently suggests that donor-derived blood can be collected and used during liver transplantation and may reduce exposure to third-party blood-bank products. This concept is also aligned with contemporary patient blood-management strategies, which emphasize minimizing unnecessary allogeneic transfusion and donor exposure during liver transplantation (12). However, the existing studies differ substantially in design, blood-processing techniques, transfused products, and outcome definitions. Our study extends this literature by providing randomized evidence using donor-specific whole blood, but because

the intervention differs from standard care in both donor source and product composition, the present trial cannot determine which component of the strategy accounts for the observed differences.

The concern regarding exclusion according to transfusion requirement also requires qualification. No recipient was removed from the randomized analysis after assignment because additional transfusion was subsequently required, and postoperative PRBC transfusions were recorded in both groups (6/30 vs 13/31). Nevertheless, no intervention recipient required intraoperative rescue beyond the available three donor-specific whole-blood units. The trial therefore provides little information about recipients with very high-volume bleeding or massive transfusion needs; such patients may have a less favorable perioperative risk profile than the cohort represented here. Generalization to those patients should be avoided.

Positive postoperative blood cultures occurred in 1/30 intervention recipients and 9/31 controls, and all positive cultures were obtained within 14 days. The 29% figure was therefore observed in the control arm. For context, a 596-recipient study of living-donor LT reported 9.7% bacteremia within 1 month, although infection rates vary substantially with recipient population, surveillance practices, definitions, and local epidemiology (16). The relatively high control-arm rate in our small single-center sample may reflect local epidemiology, perioperative exposures, baseline imbalance, or chance. Because organism-level identification and source attribution were not analyzed, we cannot determine whether a particular organism, catheter, biliary source, abdominal source, or institutional cluster explains the difference.

The study also does not establish a mechanism for the bacteremia difference. Randomization did not manipulate immunosuppressive therapy, and cumulative immunosuppressive exposure or

immune phenotypes were not evaluated as mechanistic endpoints. Reduced exposure to unrelated blood donors, the shorter storage time of donor-derived blood, and the different composition of whole blood are plausible explanations, but they are inseparable in the present design. The association should therefore not be interpreted as evidence that donor-specific transfusion directly improves host immunity or reduces infection risk.

Primary non-function is an important safety observation. PNF occurred in 2/30 intervention recipients (6.7%) and 1/31 controls (3.2%), for an overall rate of 3/61 (4.9%). In a large SRTR analysis of adult deceased-donor LT, PNF occurred in 5.81% of recipients (15). Thus, the two events in the intervention arm warrant explicit attention but, with only three events overall, the trial cannot distinguish a treatment-related signal from random variation. Donor age, graft type, CIT, and WIT were broadly similar, but donor ICU stay and donor hemoglobin differed between groups, and early allograft dysfunction was not prospectively defined; these limitations prevent a mechanistic explanation for the PNF events.

Follow-up completeness also limits the later outcomes. At 1 month, 26/30 intervention recipients and 29/31 controls were evaluable for rejection assessment; by 3 months the corresponding denominators were 25/30 and 28/31. The CONSORT diagram combines death and loss to follow-up, so the exact contribution of nonfatal loss cannot be separated from the information presented here. Differential nonavailability may bias comparisons of rejection and liver biochemistry, and these later results should be viewed as descriptive and exploratory rather than definitive.

Several additional limitations deserve emphasis. The sample was small and single-center, and randomization did not eliminate all baseline imbalance: recipient preoperative hemoglobin differed, as did donor ICU stay and donor hemoglobin. Recipient ICU duration was not

prospectively recorded as a predefined study variable, limiting assessment of an important infection-related exposure. Early allograft dysfunction was not prospectively defined, viscoelastic coagulation testing was not used, and the intervention blood was fresher than typical stored blood-bank components; storage age itself may influence perioperative outcomes (14). These factors restrict mechanistic interpretation and external validity.

The findings nevertheless support the operational feasibility of collecting, processing, and transfusing donor-specific whole blood in a carefully selected LT setting. Future multicenter trials should retain all randomized recipients regardless of rescue transfusion, prespecify an intention-to-treat analysis, include patients with higher transfusion requirements, use a comparator that can better separate donor specificity from whole-blood composition when feasible, record storage age and immunosuppressive exposure, and collect organism-level microbiology with source attribution. PNF and other early graft-failure outcomes should be prespecified safety endpoints with standardized definitions.

In summary, donor-specific whole blood was feasible in this selected trial population, but the study is not designed to establish that donor specificity caused the observed differences in blood loss or bacteremia. The infection finding is hypothesis-generating, the PNF events require continued safety surveillance, and the 1- and 3-month outcomes are limited by small numbers and incomplete follow-up.

Conclusion

Donor-specific whole-blood transfusion was feasible in this selected cohort of transfused liver-transplant recipients. Because the intervention differed from standard care in donor source,

blood-product composition, and storage characteristics, the observed differences in blood loss and early blood-culture positivity cannot be attributed specifically to donor specificity. Larger multicenter trials with broader transfusion requirements, complete follow-up, standardized graft-failure definitions, and detailed microbiologic assessment are required before clinical benefit can be concluded.

Declarations

Abbreviations

- Iranian Registry of Clinical Trials (IRCT)
- liver transplantation (LT)
- red blood cells (RBCs)
- packed red blood cell (PRBC)
- fresh-frozen plasma (FFP)
- donor-specific blood transfusion (DST)
- randomized controlled trial (RCT)
- donation after brain death (DBD)
- recipient(R)
- donor(D)
- packed cell (P.C.)
- cold ischemia time (CIT)
- warm ischemia time (WIT)
- cytomegalovirus (CMV)
- primary non-function (PNF)
- hepatic artery thrombosis (HAT)
- standard deviation (SD)
- Aspartate Aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Alkaline Phosphatase (ALP)
- International Normalized Ratio (INR)
- Intensive Care Unit (ICU)
- Body Mass Index (BMI)
- Autoimmune Hepatitis (AIH)
- Primary Biliary Cholangitis (PBC)
- Acute Liver Failure (ALF)

- Primary Sclerosing Cholangitis (PSC)
- Non-Alcoholic Fatty Liver Disease (NAFLD)
- Hepatitis B Virus (HBV)
- Hepatitis C Virus (HCV)
- Hepatocellular Carcinoma (HCC)
- Model for End-Stage Liver Disease (MELD)

AI was used to check the grammar and spelling of the current article.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (approval number: IR.SUMS.REC.1401.543). Written informed consent was obtained from liver transplant candidates and from the families of brain-dead organ donors, as described in the study protocol. All procedures involving human participants, human data, and human biological materials were conducted in accordance with the Declaration of Helsinki and applicable institutional and national guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to applicable ethical and institutional requirements.

Competing interests

The authors declare that they have no competing interests.

Funding

This study received no external funding.

Authors' contributions

SF, ME, MS, HN, AS, FK, MJ, MA, SSN, MML, ASH, and SN contributed to the conduct of the study, including implementation of the study protocol, patient recruitment and/or clinical data acquisition. MS performed the data analysis and drafted the initial manuscript. SF, ME, and ASH contributed substantially to the interpretation of the findings and critically revised and edited the manuscript for important intellectual content. HN, AS, FK, MJ, MA, SSN, MML, and SN reviewed the manuscript critically for important intellectual content and contributed to the interpretation of the study findings. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work, including the accuracy and integrity of the study.

References

1. Neuberger J. Follow-up of liver transplant recipients. Best Pract Res Clin Gastroenterol. 2020;46–47:101682.
2. Silva MA, Muralidharan V, Mirza DF. The management of coagulopathy and blood loss in liver surgery. Semin Hematol. 2004 Jan;41(1 Suppl 1):132–9.
3. Ramos E, Dalmau A, Sabate A, Lama C, Llado L, Figueras J, et al. Intraoperative red blood cell transfusion in liver transplantation: influence on patient outcome, prediction of requirements, and measures to reduce them. Liver Transpl. 2003 Dec;9(12):1320–7.
4. Masior Ł, Grąt M, Grąt K, Krasnodębski M, Wronka KM, Stypułkowski J, et al. Importance of Intraoperative Transfusions of Packed Red Blood Cells and Fresh Frozen Plasma in Liver

Transplantation for Hepatocellular Cancer. Ann Transplant. 2020 Oct 9;25:e923665-1-e923665-7.

5. Palomo Sanchez JC, Jimenez C, Moreno Gonzalez E, Garcia I, Palma F, Loinaz C, et al. Effects of intraoperative blood transfusion on postoperative complications and survival after orthotopic liver transplantation. Hepatogastroenterology. 1998;45(22):1026–33.

6. Donor-specific transfusion and donor bone marrow infusion in renal transplantation tolerance: A review of efficacy and mechanisms. American Journal of Kidney Diseases. 1995 Nov 1;26(5):701–15.

7. Barber WH. Donor-specific transfusions in renal transplantation. Clin Transplant. 1994 Apr;8(2 Pt 2):204–6.

8. Gt T, R S, V H, G P, Rm J, G S, et al. The use of organ donor blood in liver transplantation. Clinical transplantation [Internet]. 2021 Sep [cited 2024 Nov 13];35(9). Available from: https://pubmed.ncbi.nlm.nih.gov/34236114/

9. T L, X X, J S, Y T, L J, J Y, et al. Use of donor-specific red blood cell transfusions for patients undergoing liver transplantation during the COVID-19 pandemic. Hepatobiliary surgery and nutrition [Internet]. 2021 Aug [cited 2024 Nov 16];10(4). Available from: https://pubmed.ncbi.nlm.nih.gov/34430527/

10. Acute T cell mediated rejection [Internet]. [cited 2025 Jun 6]. Available from: https://www.pathologyoutlines.com/topic/liveracutetcellmediatedrejection.html

11. Laine E, Steadman R, Calhoun L, Blackall D, Levin P, Braunfeld M, et al. Comparison of RBCs and FFP with whole blood during liver transplant surgery. Transfusion. 2003 Mar;43(3):322–7.

12. Pérez-Calatayud AA, Hofmann A, Pérez-Ferrer A, Escorza-Molina C, Torres-Pérez B, Zaccarias-Ezzat JR, et al. Patient Blood Management in Liver Transplant-A Concise Review. Biomedicines. 2023 Apr 4;11(4):1093.

13. Shaylor R, Desmond F, Lee DK, Koshy AN, Hui V, Tang GT, et al. The Impact of Intraoperative Donor Blood on Packed Red Blood Cell Transfusion During Deceased Donor Liver Transplantation: A Retrospective Cohort Study. Transplantation. 2021 Jul 1;105(7):1556–63.

14. Kim Y, Amini N, Gani F, Wagner D, Johnson DJ, Scott A, et al. Age of Transfused Blood Impacts Perioperative Outcomes Among Patients Who Undergo Major Gastrointestinal Surgery. Ann Surg. 2017 Jan;265(1):103–10.

15. Johnson SR, Alexopoulos S, Curry M, Hanto DW. Primary nonfunction (PNF) in the MELD Era: An SRTR database analysis. Am J Transplant. 2007;7(4):1003–1009. doi:10.1111/j.1600-6143.2006.01702.x.

16. Park J, Kim BW, Choi HJ, Hong SH, Park CS, Choi JH, et al. Risk stratification for early bacteremia after living donor liver transplantation: a retrospective observational cohort study. BMC Surg. 2020;20:2. doi:10.1186/s12893-019-0658-6.

Tables and Figures:

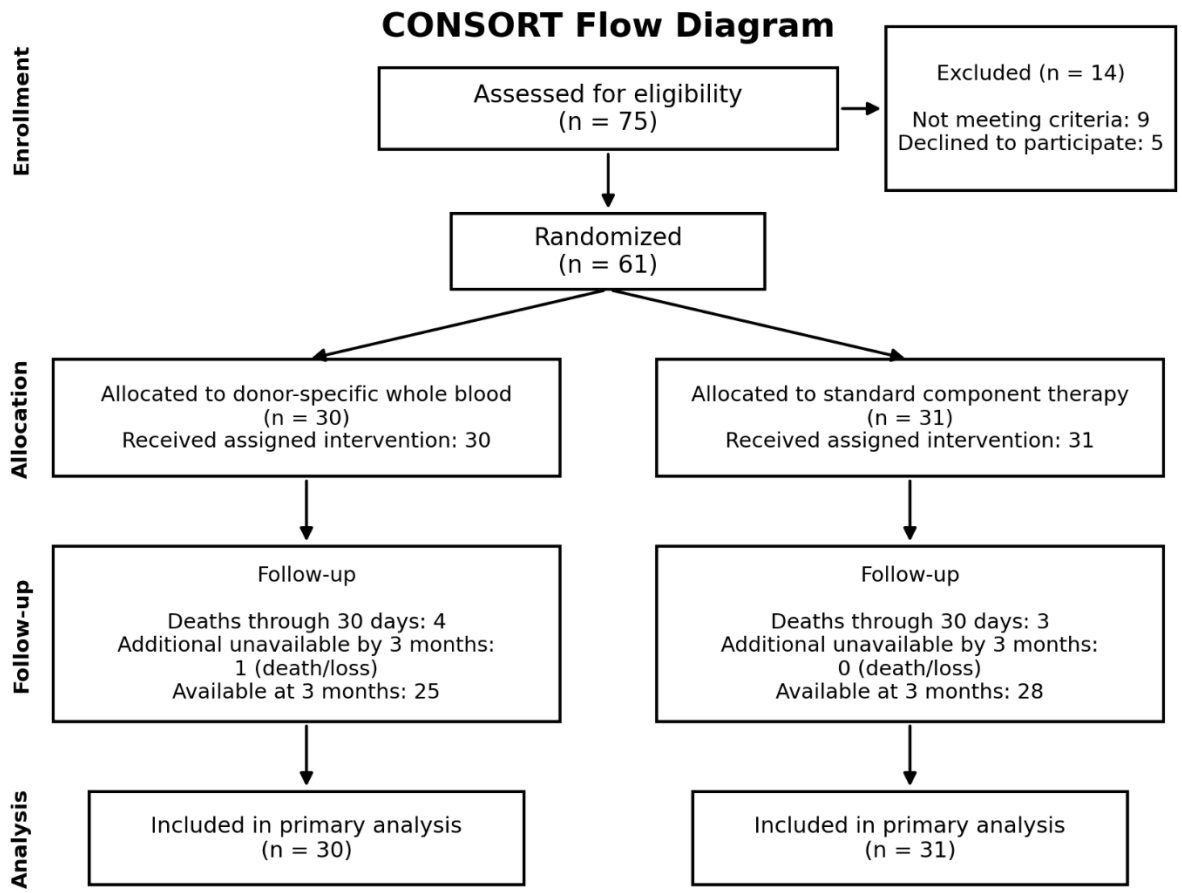


Figure 1: CONSORT diagram. Of 75 liver-transplant candidates screened, 14 were excluded and 61 were randomized (30 to donor-specific whole blood and 31 to standard component therapy). All randomized recipients received the assigned intraoperative strategy and were included in the primary analysis. For longitudinal nonmortality outcomes, 26 vs 29 recipients were evaluable at 1 month and 25 vs 28 at 3 months because of death or loss to follow-up.

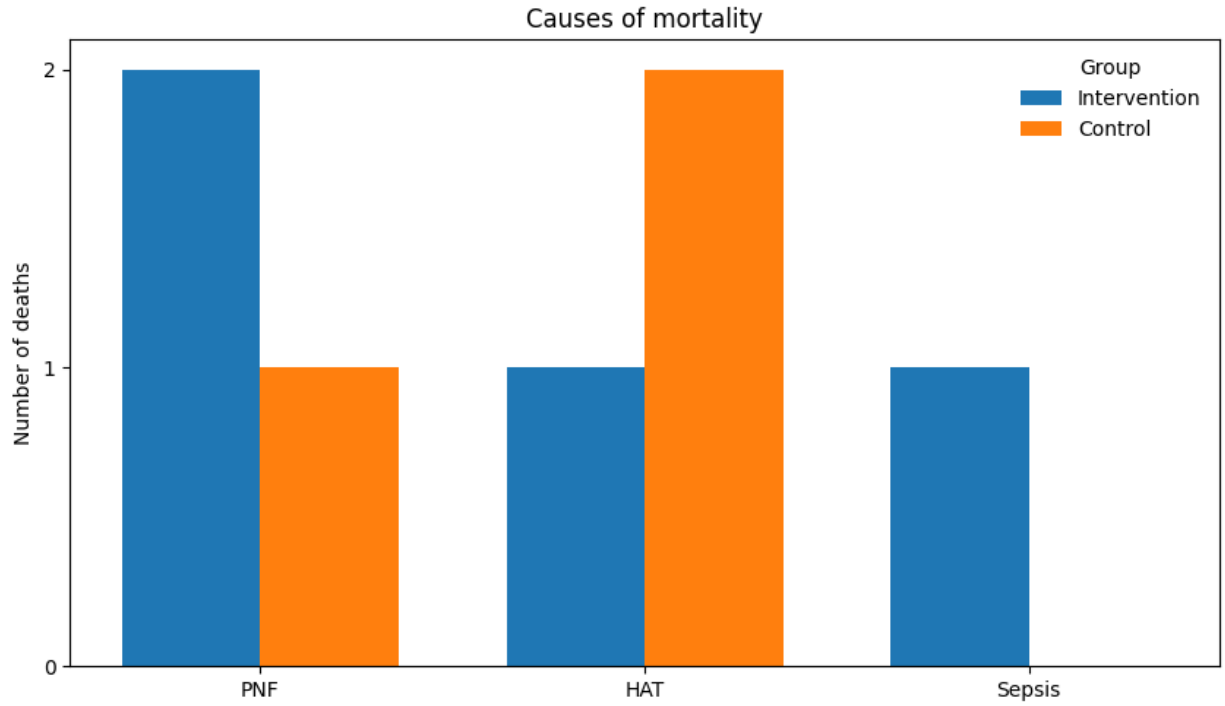


Figure 2: Mortality causes

Variable		Intervention group (n=30)	Control group (n=31)	p Value
Age years mean (SD)		45.23(16.61)	44.81(14.29)	0.91
Sex (male)		14/30	20/31	0.16
BMI mean (SD)		24(2.96)	24.75(3.9)	0.51
cause of liver disease	AIH	4	3	0.21
	Budchiarry syndrome	2	1	
	Cryptogenic	2	0	
	Hyperoxaluria	1	0	
	PBC	2	0	
	ALF	0	1	

	PSC	5	10	
	NAFLD	5	8	
	Wilson's disease	2	1	
	HBV	4	1	
	HCV	1	4	
	Alcoholic liver cirrhosis	0	2	
	HCC	1	0	
	Hemochromatosis	1	0	
MELD score means (SD)		22.83(5.98)	21.29(5.19)	0.28
Preoperative hemoglobin		9.99(1.84)	11.01(1.96)	0.04
Blood group	A	9	8	0.55
	B	10	8	
	AB	1	4	
	O	10	11	

Table 1: Baseline demographic data and causes of liver disease in liver transplant recipients. Age is in years and BMI in kg/m². AIH: autoimmune hepatitis; PBC: primary biliary cholangitis. Values are shown as mean (SD) or counts.

Variable		Intervention group (n=30)	Control group (n=31)	p Value
Graft type	whole	29	30	
	split	1	1	
CIT (cold ischemic time)		171.33(60.26)	172.71(96.87)	0.53
WIT (warm ischemic time)		40.83(8.15)	37.61(9.49)	0.22
Intraoperative blood loss (ml)		1289(641)	2074(1633)	0.03
Intraoperative assigned blood product (units)		2.53(1) [1,140 mL]	2.71(2.38) [894 mL]	0.52
Intraoperative FFP infusion (units)		0	0.97(1.8) [242.5mL]	0.003

Table 2: Intraoperative variables and transfusion exposure in liver transplant recipients. CIT: cold ischemic time; WIT: warm ischemic time. Blood loss is in milliliters (mL); ischemic times are in minutes. Assigned blood-product volumes are shown in mL, using approximately 450 mL per donor-specific whole-blood unit and 330 mL per PRBC unit; one FFP unit was approximately 250 mL. Because whole blood and PRBC/FFP are not composition-equivalent products, unit counts and separate FFP use should not be interpreted as equivalent biologic exposure. Values are shown as mean (SD) or counts.

Variable		Intervention group (n=30)	Control group (n=31)	p Value
Age years mean (SD)		42.50(11.31)	46.58(16.11)	0.25
Sex (male)		20/30	18/31	0.49
BMI mean (SD)		23.46(3.41)	24.59(2.45)	0.5
ICU stay (days)		4.23(1.19)	3.84(4.15)	0.004
AST		50.6(41.19)	104.68(133.15)	0.32
ALT		43.5(27.47)	76.1(98.57)	0.22
Total Bilirubin		1.04(0.53)	0.89(0.71)	0.86
INR		1.38(0.27)	1.46(1.06)	0.267
Hemoglobin		13.46(1.28)	11.86(2.44)	0.002
Creatinine		1.33(0.82)	1.21(0.52)	0.96
Liver pathology	5-10%	5	14	0.11
	10-30%	4	7	
	5%> (nonspecific change)	21	10	

Table 3: Demographic and clinical characteristics of organ donors on the day of liver procurement. Age is reported in years; BMI: Body Mass Index (kg/m²); ICU: Intensive Care Unit; AST: Aspartate Aminotransferase (U/L); ALT: Alanine Aminotransferase (U/L); INR: International Normalized Ratio. Data are presented as mean (standard deviation) or count. Donor ICU stay and hemoglobin differed between randomized groups and are treated as baseline imbalances in interpretation.

	Variable	Intervention group	Control group	p Value
Day 7	AST	76.75(63.167)	73.7(67.21)	0.85
	ALT	137.04(151.77)	167.37(121.02)	0.15
	ALP	414.39(219.52)	444.97(292.7)	0.69
	Total Bilirubin	2.19(1.19)	3.28(2.69)	0.18
First month	AST	30.23(18.58)	28.43(25.53)	0.26
	ALT	35.96(25.08)	33.9(38.63)	0.37
	ALP	281.85(176.18)	397.33(486.55)	0.79
	Total Bilirubin	1.05(0.49)	1.76(2.09)	0.19
Third month	AST	25.76(11.84)	18.68(7.31)	0.034
	ALT	29.88(17.59)	23.64(14.42)	0.097
	ALP	319.08(255.22)	187.86(91.57)	0.002
	Total Bilirubin	1.17(1.4)	0.97(0.65)	0.971

Table 4: Postoperative liver function tests at day 7, first month, and third month after liver transplantation. AST: Aspartate Aminotransferase (U/L); ALT: Alanine Aminotransferase (U/L); ALP: Alkaline Phosphatase (U/L); Total Bilirubin (mg/dL). Data are presented as mean (standard deviation). Month 1 and month 3 comparisons reflect the available follow-up denominators shown in Figure 1.

variable		Intervention group	Control group	p Value
Positive post operative blood culture		1	9	0.012
Positive post-transplant CMV		1	5	0.195
Post operative bleeding		4	3	0.707
Postoperative need for additional PRBC transfusion		6	13	0.064
PNF		2	1	0.549
HAT		1	2	
Sepsis		1	0	
Mortality	0-7 days	2	1	0.822
	7-30 days	2	2	

Table 5: Postoperative complications following liver transplantation. PRBC: Packed Red Blood Cells; CMV: Cytomegalovirus; PNF: Primary Non-Function; HAT: Hepatic Artery Thrombosis. Values represent the number of cases in each group. Additional postoperative PRBC transfusion did not result in exclusion from the randomized analysis. Comparisons were made using Fisher's exact or chi-square tests where appropriate.