Safe use of Liver Grafts from Syphilis-Positive Donors in Liver Transplantation and Review of the Literature

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Research

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Abstract

Background: The growing disparity between organ availability and the number of candidates for organ transplantation has urged the use of marginal grafts including grafts from syphilis-positive donors. However, few knowledges could be acknowledged about this due to the rare data from case reports. Therefor we evaluate our data and summarize our experience of the management of liver grafts from syphilis-positive donors.

Methods: From January 2015 to December 2019, 22 adult patients received liver transplantation from syphilis-positive donors while 873 patients got liver transplantation from syphilis-negative donors at our center. Given the imbalance in several baseline variables, propensity score matching was used. The outcomes were compared including complications, hospital stay, recovery of liver function and survival of the two groups and the management of the recipients was reviewed.

Results: There were no differences in complications and hospital stay of the recipients after transplantation. And it showed similar trends in the liver function recovery. Patient and graft survivals were comparable to that of syphilis-negative grafts. And benzathine penicillin is effective to protect the recipients from syphilis.

Conclusions: The use of liver grafts from syphilis-positive donors does not to increase the morbidity and mortality of the recipients. Also, the prophylactic theory of benzathine penicillin is helpful.

Introduction

To date there is no better therapeutic options for patients with end-stage liver disease except for liver transplantation. Nevertheless, the shortage of liver donors does not match the increasing demand for liver grafts, which has led to broadening of acceptance criteria for potential organ donor candidates, in other words, utilizing marginal grafts regardless of the risk of transmission of infection.

Syphilis, caused by Treponema pallidum, has a worldwide distribution. The risk of syphilis in organ donors should not be neglected, and Gibel et al estimate it to be about 0.15%. Unfortunately, the prevalence of syphilis in organ donors should have increased with the substantially growing incidence of syphilis over the past decades.

Although syphilis is mainly transmitted by sexual contract and is infrequent in other ways, it theoretically has the transmission possibility via organ transplantation. In fact, there are two reports documented describing this phenomenon, one after kidney transplantation and the other after liver transplantation. Serologic testing of organ donors for syphilis is recommended but evidence of donor syphilis infection is not considered a contraindication for using organs if prophylactic antibiotics are administered to the recipient. However, no cohort study of liver grafts from syphilis-positive donors in liver transplantation has been reported, as the possibility of syphilitic hepatitis after liver transplantation that may result in poor prognosis.

Hence, we report our promising results on the clinical outcome of liver transplantation using syphilis-positive liver grafts within our mono-center experience. In addition, we performed the useful prophylactic theory of penicillin.

Materials And Methods

From January 2015 to December 2019, 22 adult patients had liver transplantation from syphilis-positive donors at our center while 873 patients underwent liver grafts from syphilis-negative donors. Given the imbalance in several baseline variables, 1:4 propensity score matching was used. Here we reviewed the outcomes of these 22 recipients and took those 88 patients as control in this study. Before transplantation all patients received syphilis-positive liver grafts were notified of potential poor prognosis and the possibility of infection.

Syphilis-positive Donors

Age, sex, and serum features of the syphilis-positive donors are listed in Table 1. The median age is 48 years (range: 22–68). Most donors are male.
### Table 1
Main demographic and serovirological features of syphilis-positive donors.

| Case ID | Sex | Age | Syphilis IgG EIA | TPPA | RPR (titer) |
|---------|-----|-----|-----------------|------|-------------|
| 1#      | M   | 58  | +               | NT   | -           |
| 2#      | F   | 43  | +               |      | -           |
| 3#      | M   | 46  | +               | NT   | +(1:2)      |
| 4#      | M   | 22  | +               | NT   | +(1:2)      |
| 5#      | M   | 62  | +               | NT   | +(1:2)      |
| 6#      | M   | 59  | +               | NT   | -           |
| 7#      | M   | 50  | +               | NT   | -           |
| 8#      | M   | 58  | +               | +    | -           |
| 9#      | M   | 33  | +               | NT   | +(1:1)      |
| 10#     | M   | 48  | +               | NT   | +(1:32)     |
| 11#     | M   | 44  | +               | NT   | -           |
| 12#     | F   | 48  | +               | NT   | -           |
| 13#     | M   | 46  | +               | NT   | -           |
| 14#     | M   | 55  | +               | NT   | +(1:1)      |
| 15#     | M   | 39  | +               | NT   | -           |
| 16#     | M   | 39  | +               | NT   | -           |
| 17#     | M   | 48  | +               | NT   | +(1:1)      |
| 18#     | F   | 61  | +               | NT   | -           |
| 19#     | M   | 43  | +               | NT   | -           |
| 20#     | M   | 61  | +               | NT   | -           |
| 21#     | M   | 68  | +               | NT   | +(1:2)      |
| 22#     | M   | 48  | +               | NT   | -           |

*+ = detected; − = not detected; NT = not tested; EIA = Enzyme Immunoassay; TPPA = Treponema Pallidum Particle Agglutination; RPR = Rapid Plasma Reagin.*

### Prophylactic therapy

Prophylactic antibiotics were given to all recipients of syphilis-positive grafts from the first post-transplant day. Usually we gave them single dose 2.4 MU of benzathine penicillin intramuscularly. Another 2-weekly doses 2.4 MU of intramuscular benzathine penicillin would be given to recipients if they had positive serology results of syphilis at day 5 after transplantation.

### Follow-up after transplantation

After transplantation all patients were monitored intensively until they were stable. The evaluation included clinical symptoms, biochemical tests and image surveillance. Serology test for syphilis was monitored at day 5, then month 1, 3, 6 and 12. The evaluation of follow-up after discharge mainly concentrated on liver function, complications, and survival. Computed tomography was conducted every half a year while ultrasound monthly.

### Propensity score matching

The R language 3.5.1 was used to match the patients as 1:4 pairing through the propensity score matching (PSM). The matching variables included gender, age, BMI of donors and recipients, making the baseline data of these two groups comparable.

### Statistics
The statistical software SPSS 25.0 (SPSS, Inc., Chicago, IL) was used to analyze the data. The mean value and standard deviation of the data were then presented. Statistical analysis methods included Chi-square test, Student’s t test and Kaplan-Meier method with log-rank test. It was considered statistically significant when P < 0.05.

**Results**

**Syphilis-positive grafts did not result in poor prognosis**

From January 2015 to December 2019, 22 adult patients had liver transplantations from syphilis-positive donors (positive group) at our center while 88 patients received liver grafts from syphilis-negative donors (negative group) after 1:4 propensity score matching. There were 16 males and 6 females in the positive group while 64 males and 24 females in the negative group. There were no significant differences between two groups on sex, age (47.6 vs. 47.0 p = 0.8), body mass index (BMI) (23.3 vs. 23.6 p = 0.76), calculated Model for End-Stage Liver Disease (MELD) score (23.5 vs. 23.5 p = 0.82), Child-Pugh score (10 vs. 10 p = 0.88), total operation time (309.5 vs. 317.5 min p = 0.75), and cold ischemia time (608.1 vs. 536.4 min p = 0.09). At transplantation 4 patients in the positive group (18.2%) were diagnosed with tumor while the negative group had 23.9% (Table 2).

Table 2
General characteristics of liver transplant recipients who received syphilis-positive liver grafts (positive group) and syphilis-negative liver grafts (negative group) and donors correspondingly.

|                          | Positive group | Negative group | P value |
|--------------------------|----------------|----------------|---------|
| **Recipients**            |                |                |         |
| Age (year)               | 47.6 ± 7.3     | 47.0 ± 10.7    | 0.80    |
| Gender (M/F)             | 16/6           | 64/24          | 1.00    |
| BMI                      | 23.3 ± 3.3     | 23.6 ± 3.4     | 0.76    |
| Indication for LT        |                |                | 0.79    |
| Cirrhosis                | 9 (40.9%)      | 26 (29.5%)     |         |
| Acute liver failure      | 9 (40.9%)      | 30 (34.1%)     |         |
| HCC                      | 4 (18.2%)      | 21 (23.9%)     |         |
| Graft Failure            | 0              | 5 (5.7%)       |         |
| PSC/PBC                  | 0              | 4 (4.5%)       |         |
| Other                    | 0              | 2 (2.3%)       |         |
| MELD                     | 23.5 (14.5–29.0) | 23.5 (11.0–29.8) | 0.82 |
| CHILD                    | 10 (9–11)      | 10 (7–12)      | 0.88    |
| CIT                      | 608.1 ± 195.9  | 536.4 ± 169.6  | 0.09    |
| Hepatitis B virus-related liver disease | 17 (77.3%) | 70 (79.5%) | 1.00 |
| **Donors**               |                |                |         |
| Age                      | 49.1 ± 10.7    | 47.9 ± 12.6    | 0.69    |
| Gender                   | 19/3           | 81/7           | 0.68    |
| BMI                      | 22.8 ± 1.7     | 23.5 ± 3.1     | 0.16    |
| WTI                      | 10.1 ± 5.0     | 8.1 ± 6.9      | 0.13    |
| HBV                      | 1 (4.5%)       | 15 (17.0%)     | 0.25    |

BMI = Body Mass Index; MELD = Model for End-Stage Liver Disease.
Post-transplantation results showed there were no differences between these two groups concerning hospital stay (21 vs. 21 day, \( p = 0.90 \)) and post-transplant complications, such as primary non-function (4.5% vs. 3.4%, \( P = 1.00 \)), biliary complications (13.6% vs. 15.9%, \( P = 1.00 \)) and renal failure (4.5% vs. 12.5%, \( P = 0.49 \)) (Table 3). As for the liver function recovery after liver transplantation, no significant differences were observed in these two groups. The trends of the mean value of serum liver function markers, for example alanine transaminase, aspartate aminotransferase, international normalized ratio and total bilirubin were similar in both groups after liver transplantation (Fig. 1). No syphilis hepatitis was observed in any patient. What was more, there were no differences between these two groups in patient and graft survival (Fig. 2). All these results above demonstrated that syphilis-positive grafts did not result in poor prognosis or increase the morbidity and mortality.

Table 3
Surgical characteristics in recipients between the two groups.

|                         | Positive group (n = 22) | Negative group (n = 88) | P value |
|-------------------------|------------------------|-------------------------|---------|
| Operative time (mins)   | 309.5 (279.5–356.0)    | 317.5 (285.7–365.7)     | 0.75    |
| Blood loss (ml)         | 1000.0 (900–1625)      | 1000 (725–1500)         | 0.44    |
| Use of blood products   |                        |                         |         |
| RBC (units)             | 5.5 (3.0–7.6)          | 5.0 (3.1–8.0)           | 0.72    |
| Hospital stay (days)    | 21 (17–26)             | 21 (17–25)              | 0.90    |
| Overall complication    |                        |                         |         |
| Primary nonfunction     | 1 (4.5%)               | 3 (3.4%)                | 1.00    |
| Biliary complications   | 3 (13.6%)              | 14 (15.9%)              | 1.00    |
| Vascular complications  | 1 (4.5%)               | 6 (6.8%)                | 1.00    |
| Intra-abdominal hemorrhage | 2 (9.1%)           | 4 (4.5%)                | 0.75    |
| Acute rejection         | 4 (18.2%)              | 9 (10.2%)               | 0.51    |
| Renal failure           | 1 (4.5%)               | 11 (12.5%)              | 0.49    |

Prophylactic therapy of benzathine penicillin is effective

Prophylactic therapy for patients of syphilis-positive grafts was single dose 2.4 MU of intramuscular benzathine penicillin. Serology test for syphilis was monitored at day 5. With positive serology results of syphilis, recipients would get another 2-weekly dose 2.4 MU of benzathine penicillin intramuscularly. Details of serology test results of syphilis for recipient prior and post Liver transplantations are shown in Table 4. Only one of 22 patients (case 13) had positive enzyme immunoassay (EIA) and Treponema pallidum particle agglutination (TPPA) results at day 5 while at month 1 his TPPA results was negative and EIA remained positive. Case 10 had negative EIA at day 5 but had positive EIA and PRP (1:1) at month 1. Afterwards, his PRP became negative and EIA remained positive. Case 14 had weakly positive EIA and negative TPPA at month 1 only once. After reexamination, his EIA became negative. Case 4 and case 20 died from hepatocellular carcinoma recurrence 13 months and 1 month after liver transplantation. Case 4 died from severe sepsis 1 month after transplantation. Case 7 and case 18 died from multiple organ failure within 1 week after transplantation. The serology results of syphilis of these dead cases remained negative all the time until they died. Case 5 had acute rejection reaction after the surgery, so she had re-transplantation and recovered well, but her serology results of syphilis kept negative. Our results of long-term follow-up indicated that with the usage of benzathine penicillin most recipients would not be infected of syphilis. It seems benzathine penicillin is useful and effective.
Table 4
Serology test results of syphilis for recipients prior and post liver transplantation

| Case | Before transplantation | Day 5 | Month 1 | Month 3 | Month 6 | Month 12 |
|------|------------------------|-------|---------|---------|---------|---------|
| ID   | IgG-EIA | TP | RPR | IgG-EIA | TP | RPR | IgG-EIA | TP | RPR | IgG-EIA | TP | RPR | IgG-EIA | TP | RPR | IgG-EIA | TP | RPR |
| 1    | - | nt | nt | - | nt | nt | - | nt | nt | - | nt | nt | - | nt | nt |
| 2    | - | nt | nt | - | nt | nt | - | nt | nt | - | nt | nt | - | nt | nt |
| 3    | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 4    | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 5    | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 6    | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 7    | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 8    | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 9    | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 10   | - | nt | nt | - | nt | nt | + | nt | + | (1:1) | + | nt | - | + | nt | - |
| 11   | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 12   | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 13   | - | nt | nt | + | + | - | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 14   | - | nt | nt | - | nt | nt | ± | - | nt | nt | nt | nt | nt | nt | nt |
| 15   | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 16   | - | nt | nt | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt |
| 17   | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 18   | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 19   | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| 20   | - | nt | nt | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt |
| 21   | - | nt | nt | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt |
| 22   | - | nt | nt | - | nt | nt | - | nt | nt | nt | nt | nt | nt | nt | nt |

+ = detected; − = not detected; ± = equivocal; nt = not tested; EIA = Enzyme Immunoassay; TPPA = Treponema Pallidum Particle Agglutination; RPR = Rapid Plasma Reagin

Conclusions

The use of liver grafts from syphilis-positive donors does not increase the morbidity and mortality of the recipients which can relatively alleviate the shortage of donor liver. And the prophylactic theory of benzathine penicillin for recipients is helpful.

Discussion

During the last 2 decades, the growing disparity between organ availability and the number of candidates for organ transplantation has compelled the use of sub-optimal or marginal donors. Extensive donor test is recommended to prevent transmission of disease by transplantation. Traditionally, syphilis screening involves a nontreponemal anticardiolipin serological test (eg, Rapid Plasma Reagin [RPR] or Venereal Disease Research Laboratory [VDRL]). Subsequently positive results are confirmed by a specific treponemal test (eg, TPPA)\(^2\). Nowadays, it has the trend to use treponemal-specific EIA for syphilis screening and a nontreponemal test will be taken on
positive results\textsuperscript{13,14}. As we can see in Table 1, we would miss syphilis positivity if we tested our donors in the traditional way. However, the latter method also has its limitation with about 17\% of EIA results false-positives and discordant test results as reported\textsuperscript{14}. Hence, it is recommended that discordant results should be tested using the TPPA test\textsuperscript{15}. So, we use EIA as the initial screening method, and positive results will be confirmed by TPPA and RPR.

The EIA test was negative in all recipients before transplantation. One recipient (case 13) had positive EIA and TPPA at day 5 but his TPPA results was negative and EIA remained positive afterwards. An explanation of this phenomenon may be the passive transmission of antibodies from donor at transplantation or transmission of lymphocytes with the grafts, which has been described already in kidney transplantation\textsuperscript{16,17}. Case 10 had negative EIA at day 5 but had positive EIA and PRP (1:1) at month 1, it was considered that he was infected with syphilis in the past, but had been cured and was not infectious. Afterwards, his PRP became negative and EIA remained positive\textsuperscript{18}. With this recipient (case 10), we should be aware of the possibility of syphilitic hepatitis. It is uncommon in immunocompetent individuals\textsuperscript{10} while it has been depicted in immunocompromised patients, such as those infected with human immunodeficiency virus (HIV)\textsuperscript{19}. In syphilitic hepatitis, there would be a notable increase in alkaline phosphatase and a modest increase in aspartate aminotransferase, alanine transaminase and bilirubin along with clinical symptoms including rash and hepatomegaly\textsuperscript{10}. Case 14 had weakly positive EIA and negative TPPA at month 1 which was considered false positive. After reexamination, his EIA became negative.

Though positive EIA and TPPA results with negative RPR do not mean active syphilis, it is recommended that recipients of potentially infected organs should be treated with an appropriate course of benzathine penicillin\textsuperscript{20}. Fischer et al\textsuperscript{20} recommend 3-weekly doses 2.4 MU of intramuscular benzathine penicillin while UK guidelines\textsuperscript{21} recommend benzathine penicillin 2.4 MU as a single-dose intramuscular injection, or doxycycline 100 mg by mouth twice daily for 14 days, as alternative therapy. Gibel et al\textsuperscript{3} also recommend a single dose of 2.4 MU of benzathine penicillin. Ko et al\textsuperscript{22} and Marek al\textsuperscript{23} utilize 3-weekly doses 2.4 MU of intramuscular benzathine penicillin as the prophylactic therapy. Cortes et al\textsuperscript{9} consider two doses of intramuscular 2.4MU benzathine penicillin a week apart to be an appropriate regime for prophylaxis and treatment of early syphilis acquired via transplantation. In our case, we split the difference of the above. We recommend single dose 2.4 MU of intramuscular benzathine penicillin with or without another 2-weekly doses 2.4 MU of intramuscular benzathine penicillin according to the serology results of syphilis at day 5 after transplantation.

The follow-up duration of recipients with syphilis-positive liver grafts is unclear. There was no documents especially for this. Ko et al\textsuperscript{22} monitored their patients using Venereal Disease Research Laboratory (VDRL) and Treponema pallidum hemagglutination (TPHA) at 2, 4, 6, and 12 months after transplantation. Cortes et al\textsuperscript{9} monitored their patients at 1, 3, 6 and 12 months after transplant using TPPA, RPR and an immunoblot for IgM and IgG. Marek al\textsuperscript{23} monitored their patients similarly to Cortes et al\textsuperscript{9}.

Summariy, our cohort study illustrates that syphilis-positive liver grafts did not result in poor prognosis or increase the morbidity and mortality of the recipients after liver transplantation. Benzathine penicillin is effective to protect recipients from transmission of syphilis. Furthermore, we summarize and share our experience in the management of recipients with syphilis-positive liver grafts. With the increasing disparity between donors and recipients, it is vital to be aware that syphilis-positive liver grafts are safe for recipients as long as prophylactic antibiotics are administered to the recipients.

**Abbreviations**

BMI, Body Mass Index; EIA, Enzyme Immunoassay; MELD, Model for End-Stage Liver Disease; RPR, Rapid Plasma Reagin; TPPA, Treponema Pallidum Particle Agglutination.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University.

**Consent for publication**

Not applicable

**Availability of data and materials**
The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests

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**Authors’ contributions**

TL and XB conceived of the study, and participated in its design and coordination and helped to draft the manuscript. WZ and MZ participated in the design of the study and collected the data and built the datasets. XD and YS conceived of the study and performed the statistical analysis. LY and CQ performed the statistical analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

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