



Survival Rate of Liver Transplantation in Asia: A Systematic Review and Meta-Analysis

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Abstract

Background: Liver transplantation is one of the most effective treatments for acute liver failure, chronic liver cirrhosis, and hepatocellular carcinoma. This study was implemented to evaluate the survival rate of liver transplant in Asia.

Methods: Studies that investigated the survival rate of liver transplant were selected using a systematic search strategy in the following databases: Medline, Embase, Scopus, ProQuest, ISI Web of Science, and Cochrane to Nov 30th, 2020. Pooled survival rate and 95% confidence intervals were calculated using Der-Simonian and Laird method. Stata 16.0 (Stata Corp, College Station, TX, USA) was used for analysis.

Results: One, 2, 3, 5, and 10-year survival rates of liver transplant were estimated to be 85%, 80%, 75%, 73%, and 71%, respectively. The results of the univariate meta-regression for defining the sources of heterogeneity for one-Year survival rate (SR) showed significant effects of bias ($\beta_{\text{high risk/moderate risk}}=0.059$, 95% CI: 0.002, 0.115, $P\text{-Value}=0.04$) and follow up time ($\beta=-0.0002$, 95% CI: -0.0003, -0.00, $P\text{-Value}=0.02$) on heterogeneity.

Conclusion: The survival rate of liver transplant in Asia is comparable with the corresponding rate reported in the United States and Europe. This study provides a better view of the efficiency of medical cares, regarding liver transplantation. Medical care be enhanced to increase the survival of liver transplant patients.

Keywords: Liver transplantation; Survival analysis; Meta-analysis; Asia

Introduction

Liver Transplantation (LT) has been identified as one of the most effective treatments for acute

liver failure, chronic liver cirrhosis, and hepatocellular carcinoma (1, 2). Since then, liver trans-



plantation has evolved rapidly, and the survival rate is being improved significantly over the past 25 years (lately 96% and 71% for 1-year and 10-year survival respectively) (3). In 2016, a global estimate suggested that the United States and China had the first and second largest number of liver transplantation with 7496 and 3264 cases, respectively (1). In addition, an increasing trend in LTs has been reported from different countries (4).

As a global average, the one, 10, and 18-year survival rates of liver transplantation are reported to be between 83%-88%, 68%-72%, and 48%-55%, respectively (5). In addition, the 5-year survival rates of liver transplantation for Asian, Spanish, white, and black patients were 74%, 65%, 68%, and 57% respectively (6). Moreover, in 2020 years LT in Europe achieved respectable 1- and 5-year overall survival rates of 86% and 74% (7, 8). In the United States, years one- and 5-year graft survivals for LDLT recipients were 88.4% and 78.1%, respectively, compared with 92.5% and 80.7% in propensity-score matched DBD recipients ($P=0.005$), respectively. Older donor age, recipient diabetes and life support requirement were significantly associated with graft failure among LDLT recipients ($P<0.05$) (9). Various factors such as age, sex, ethnicity, surgical techniques, type of immunosuppressive drugs, and even the individual's economic and social status affect the survival rate of liver-transplanted patients (10, 11).

Liver transplantation has revolutionized the acute prognosis of liver failure via increasing the survival of patients by 20% to 80% in 1-year and 70% in 5-year survival of the patients (3). Understanding the survival rate of liver transplants in Asia can provide valuable information on the effectiveness of the treatment strategies and determinants of the transplantation outcome. We found no comprehensive study on liver transplantation's survival rate in Asian countries.

We aimed to do a systematic review and meta-analysis on the published studies to determine the survival rate and its general determinants of liver transplantation in Asia.

Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were followed for the current study (12).

Search strategy

Studies that investigated the survival rate of patients with liver transplant were identified using a defined search strategy in the following databases: Medline, Embase, Scopus, ProQuest, ISI Web of Science, and Cochrane to November 30th, 2020. Moreover, we reviewed the reference lists from retrieved articles to search for further relevant studies.

Eligibility criteria

Each identified study was independently reviewed by two reviewers (FM and RKH) to determine whether the study was eligible for being included in the meta-analysis. The inclusion criteria were as follow: 1) prospective design; 2) all studies conducted on the SR of liver transplantation patients in Asia; 3) only articles published in English were included, and 4) animal studies, reviews, comments, and editorials were excluded. This study was approved by the research Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1400.257).

Data extraction and quality assessment

From each included study, the following data were extracted: first author, publication year of the study, where the study was performed, characteristics of the study population, follow up time, patients' average age, the study sample size, and the study results.

The quality of the included studies were defined by Hoy's checklist (13). The studies were categorized as low, moderate, and high risk of bias if their scores were equal or more than 7, between 4 and 6, and less than 4 respectively.

Statistical analysis

For estimating the pooled survival rates, we used random-effects meta-analysis. Cochran Q test

was performed ($P < 0.001$, CI 95%) to evaluate the heterogeneity among the studies and the presence of heterogeneity was analyzed using inconsistency test ($I^2 > 50\%$) (Higgins and Thompson 2002). Subgroup analysis was performed based on country and risk of bias. We did meta-regression analyses to identify factors that modify the survival rate of the patients and contribute to heterogeneity between the studies' results (14). Publication bias was assessed by funnel plot and trim and fill analysis (15). The Stata 16.0 (Stata Corp, College Station, TX, USA) was used for analysis.

Results

Description of studies

The search identified 3046 studies. In total, 713 were duplicates, 2156 defined irrelevant after reading their titles and abstracts, and 60 articles were not original (i.e. letter, commentary, review) or did not meet the inclusion criteria. As such, 117 studies (16-127), recruiting 406,464 participants, were included in this meta-analysis (Fig. 1).

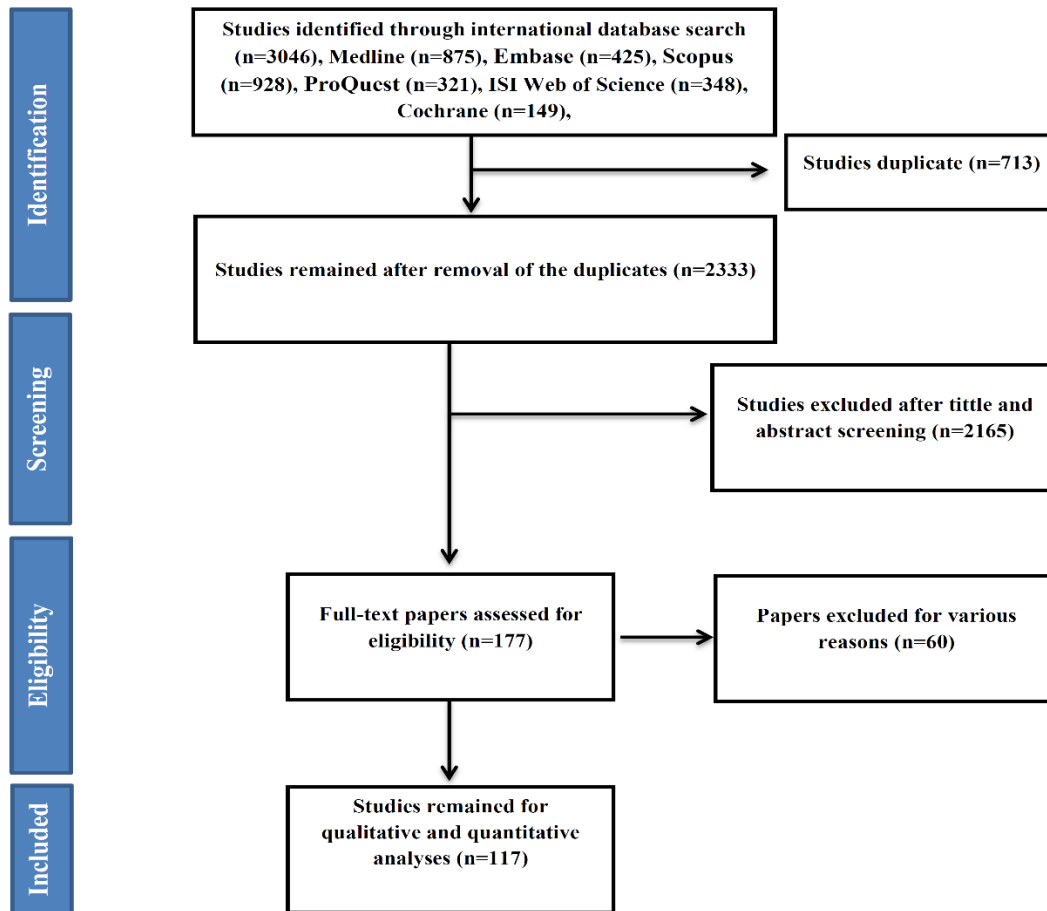


Fig. 1: Flow chart of the included eligible studies in systematic review

All studies were cohort. Of 117 studies included in this meta-analysis, 113, 22, 75, 88, and 16 reported one-year, two-year, three-year, five-year,

and ten-year survival rates, respectively. Of the included studies, 39 were from China, 30 from Japan, 14 from Iran and the remaining studies

(n=34) were from other countries in the Asia continent.

Assessment of the Risk of Bias

The risk of bias of the included studies, 10 were in the high risk of bias category, 85 studies in moderate risk and 22 studies were in the low risk of bias.

In this study one, 2, 3, 5, and 10-year survival rates (SR) of liver transplant were estimated to be 85%, 80%, 75%, 73%, and 71%, respectively (Fig. 2). Also, the result of test for group difference was not significant ($Q=Chi^2(2)=6.60$, $P\text{-Value}=0.16$ (Fig. 3). Survival rates of liver transplantation for different times according to countries and quality of studies are presented in Fig. 4.

Survival rate

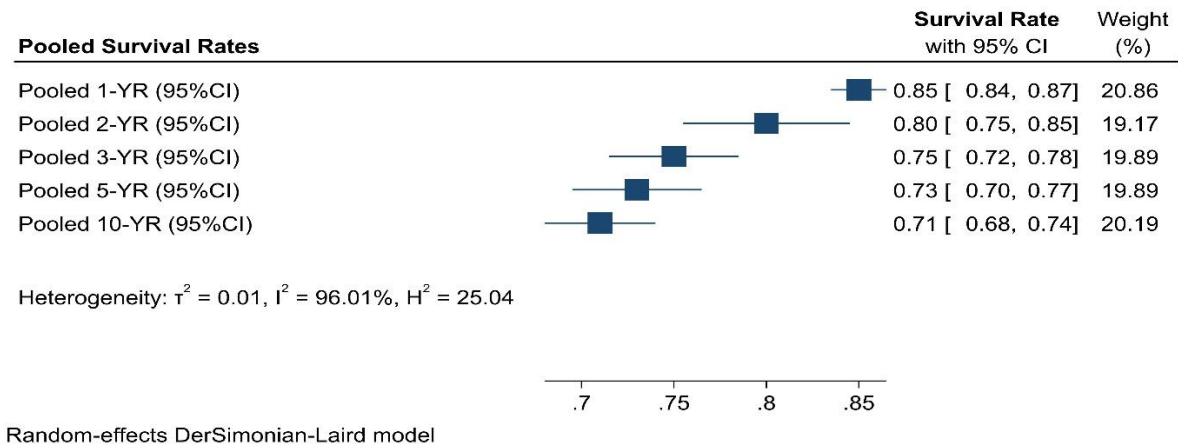


Fig. 2: Pooled survival rate of liver transplantation

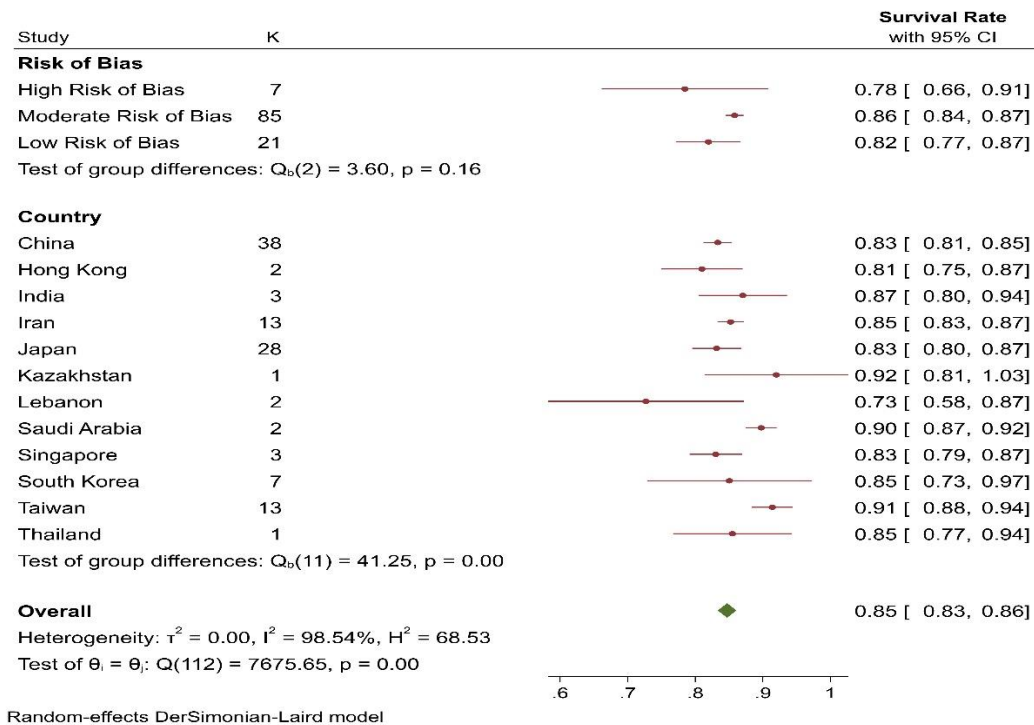


Fig. 3: One-year survival rate of liver transplantation

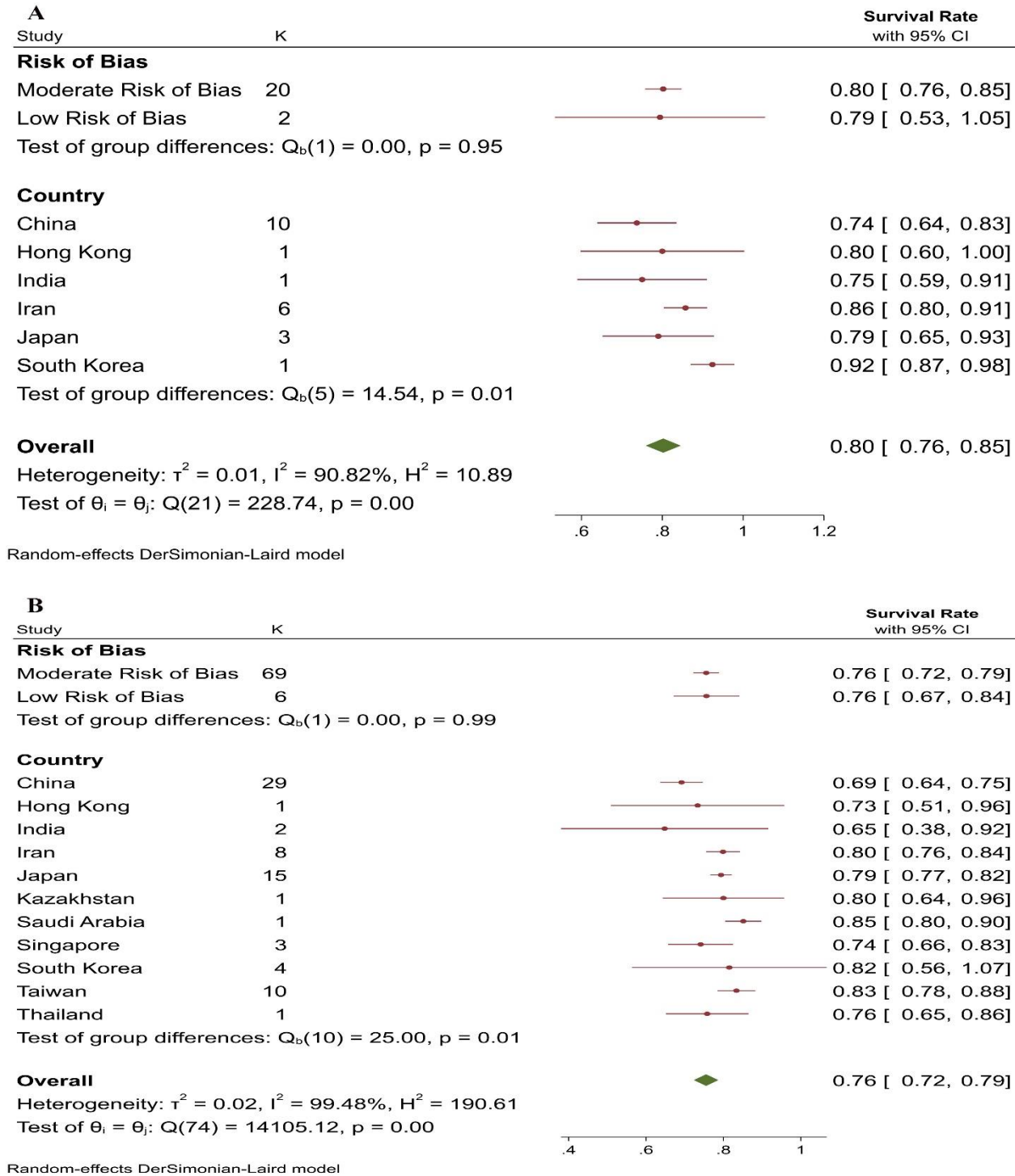


Fig. 4: A: 2-years survival rate of liver transplantation, B: 3-years survival rate of liver transplantation

Meta-regression analyses

The results of the univariate meta-regression for defining the sources of heterogeneity for one-Year SR showed significant effects of bias ($\beta_{\text{high risk/moderate risk}}=0.059$, $P\text{-Value}=0.04$) and follow up time ($\beta=-0.0002$, $P\text{-Value}=0.02$) on heteroge-

neity. The sources of heterogeneity for three-Year SR were time ($\beta_{2005-2010/\text{before } 2005}=-0.102$, $P\text{-Value}=0.03$) and the length of follow up time ($\beta=0.0014$, $P\text{-Value}=0.001$). None of the covariates had a significant effect on heterogeneity of five-Year SR (Table 1).

Table 1: Meta-regression results for one, three, and five-Year survival rates of liver transplant

| Variables | 1-YSR | | 3-YSR | | 5-YSR | |
|-----------------------|--------------------------------|---------|--------------------------------|---------|---------------------------------|---------|
| | β (95% CI) | P-value | β (95% CI) | P-value | β (95% CI) | P-value |
| Risk of bias | | | | | | |
| High risk of bias | Ref | | - | | Ref | |
| Moderate Risk of Bias | 0.059 (0.002, 0.115) | 0.04 | Ref | | -0.044 (-0.200, 0.111) | 0.56 |
| Low risk of bias | 0.015 (-0.048, 0.079) | 0.63 | -0.013 (-0.14, 0.12) | 0.84 | -0.063 (-0.240, 0.114) | 0.48 |
| Date of publication | | | | | | |
| Before 2005 | Ref | | Ref | | Ref | |
| 2005-2010 | 0.025 (-0.016, 0.066) | 0.23 | -0.102 (-0.19, -0.008) | 0.03 | -0.0073 (-0.126, 0.112) | 0.90 |
| After 2010 | 0.015 (-0.024, 0.055) | 0.44 | -0.054 (-0.14, 0.034) | 0.23 | 0.0103 (-0.102, 0.123) | 0.85 |
| Follow up time | -0.0002 (-0.0003, -0.00) | 0.02 | 0.0014 (0.0006, 0.002) | 0.001 | 0.0003 (-0.00007, 0.0008) | 0.10 |
| Year of publication | 0.0014 (-0.002, 0.004) | 0.40 | 0.0000 (-0.008, 0.008) | 0.99 | 0.0026 (-0.0071, 0.012) | 0.59 |
| Sample size | -1.24e-08 (-5.94e-07 5.69e-07) | 0.96 | -2.37e-07 (-1.44e-06 9.63e-07) | 0.69 | -1.78e-07 (-1.61e-06, 1.25e-06) | 0.80 |

Publication bias

When we plotted the one, three, and five-Year survival rate; there was no publication bias. Based on the Trim and fill method no study was identified to collaborate publication bias for any survival time.

Discussion

In this meta-analysis, the probability of progression from liver transplant to the transplant rejection in 1, 2, 3, 5, and 10 years was estimated to be 85%, 80%, 75%, 73%, and 71%, respectively. The liver transplantation survival rate in Asia is comparable with the corresponding rate reported from the USA and Europe.

Factors that can affect the survival of liver transplant include disease type, clinical features, and the age of the patients. In more details, the chance of survival of patients is strongly related to the type of disease. Patients with fulminant and chronic types of disease are considerably different with regard to the survival rate, as most deaths occur in the first six months after transplantation among patients with acute liver failure (128, 129). Age is another influential variable as the function of organs, such as the liver, reduces with age (1). However, there is no cut-point recommended for the age of recipients and donors for longer survival of liver transplantation.

In addition, it is essential to consider the cause of death following each transplant. The leading causes of death are secondary to recurrent prima-

ry liver disease, especially malignancy and cirrhosis due to hepatitis C virus (HCV) (130). Graft dysfunction, technical obstacles, and infection are among the other reasons for mortality following liver transplant (131).

The highest risk of mortality associated with hepatic transplantation is during the first year post-operation, especially the first three months (132). Men and patients older than 60 year had poorer outcomes than women and younger cases (133). However, the cause of transplantation and the epidemiology of liver disease are increasingly evolving and becoming more weighted by HCV, causing a lower survival rate, compared to many other diseases. In other words, patients with HCV are distinct from the cases of primary biliary cirrhosis or primary sclerosing cholangitis (PSC), a phenomenon that makes this issue even more complex (7, 128). Although the comparable survival rates in the USA, Europe, and Asia are due to the similarity in health care practices and the expertise of surgeons, a much wider view is needed to reach a defined conclusion.

Comparing the results of studies based on their publication year, we found that the publication time of the articles was one of the factors influencing the heterogeneity of the results suggesting survival is being improved with the time goes by Smits et al. reported the same pattern in the survival of patients. The authors also reported the age of donor and recipient and blood type compatibility as significant predictors of the transplant's survival (4, 134). According to the studies published in recent years, the transplant survival rates of European and American patients are catching up, and as observed in our study, the survival rate in Asia is becoming comparable. The improving patients' survival rate seems to continue over time if transplantations at various times are conducted among patients with more desirable clinical conditions (9, 128).

Therefore, factors related to the donor, recipient, perioperative, and postoperative phases of transplantation may influence the survival rate of the grafts (135). For example, the donor's characteristics that may result in poorer outcomes include older age, high body mass index, length of hospi-

talization, usage of vasopressors, and the presence of infection. Perioperative factors encompass cold and warm ischemia time, blood product requirements, and surgical difficulties are other factors that affect the survival of the graft (135, 136). Finally, postoperative factors are primary non-function, renal dysfunction, center experience, need for mechanical ventilation, and prolonged stay in an intensive care unit.

Strengths and Limitations

The risk of bias and the period of the study did significantly affect the survival rate of the patients. Moreover, we assessed follow-up time, year of publication, and sample size. We had few limitations in our meta-analysis. The studies on the subject did not report the characteristics of donors and recipients and the type of the selected surgical procedures, factors that can be effective in the survival of transplant. We observed statistical heterogeneity in our study.

Conclusion

Our results presented the survival rate of liver transplantation in Asia and revealed that the survival rate is comparable to that in the US and European countries. In addition, the 1 and 5-year survival rates reported in the Eastern Mediterranean countries were similar to the United States. We need further studies to define the determinants of survival of liver transplant patients. We need to consider these factors when comparing the survival of the patients. Further studies considering these factors in different subgroups are needed for estimating the survival of the grafts in different geographical locations. Medical care be enhanced to increase the survival of liver transplant patients.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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