

INPLASY PROTOCOL

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None declared.

INTRODUCTION

Review question / Objective: Iron overload conditions is a well-established risk factor for infection of pathogens. The possible association of iron overload with infectious complications and prognosis of patients receiving transplants are not well

Increased Serum Iron Levels and Infectious Complications after Liver Transplantation: A Systematic Review and Meta-Analysis

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Review question / Objective: Iron overload conditions is a well-established risk factor for infection of pathogens. The possible association of iron overload with infectious complications and prognosis of patients receiving transplants are not well understood. The purpose of this study is to investigate the effect of iron load on infective complications in patients after liver transplantation, and further observe the effect on their overall survival.

Condition being studied: Elevated serum iron levels have been associated with infectious outcomes in various patient populations but have never been studied after liver transplantation.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 November 2022 and was last updated on 02 February 2024 (registration number INPLASY2022110022).

understood. The purpose of this study is to investigate the effect of iron load on infective complications in patients after liver transplantation, and further observe the effect on their overall survival.

Condition being studied: Liver transplantation often represents a life-saving treatment for an increasing number

of patients with end-stage liver disease. With the improvements in surgical techniques, immunosuppression strategies, and post-LT management of complications, the recipient mortality has steadily declined after LT. The survival rates were 83% at 1 year, 71% at 5 years in western countries. However, the use of immunosuppressants increased risk of infections as an adverse effect resulting in severe morbidity. Globally, infection caused by including bacteria, fungus, viruses remain one of the leading causes of morbidity and mortality among transplant recipients. Knowledge of modifiable risk factors and potentially reversible causes is essential to develop targeted preventive strategies.

METHODS

Search strategy: We conducted a systematic review and meta-analysis of published studies as of September 2022 using PubMed, Embase, Web of Science and the Cochrane Library. Hazard ratio (HR) and 95% confidence interval (CI) were extracted to estimate the association of iron overload with infectious outcomes and overall survival (OS) after liver transplantation (LT), respectively.

Participant or population: Liver transplant patients.

Intervention: Data reported on the effect of iron overload markers on the prognosis in liver transplant patients.

Comparator: Patients with iron overload and patients with normal iron load/low iron burden.

Study designs to be included: Retrospective study.

Eligibility criteria: Studies were included in the systematic review if they met the following criteria: (1) A trial must have investigated the infection rate and mortality after liver transplantation; (2) Studies evaluated the predictive ability of one or more iron-related markers in blood or hepatic explants (serum ferritin, stainable

hepatic iron and hepatic iron index) for postoperative infection rate and mortality in liver transplant patients. (3) Definite infection was defined as laboratory isolation of an organism from a normally sterile site and together with symptoms of infection. (4) Possible infection was defined as case present with signs and symptoms of infection warranting empiric treatment of antibiotics but confirmatory evidence of positive microbiology lacking.

Information sources: PubMed, Embase, Web of Science and the CochraneLibrary.

Main outcome(s): The iron overload was strongly associated with increased infections after LT (HR 1.66, 95% CI 1.03-2.68). The increase in serum ferritin was associated with an increased risk of infection after LT (HR 1.44, 95% CI 1.09-1.91). Iron overload was a significant predictor of worse OS (HR 1.35, 95% CI 1.11-1.64). In addition, the high levels serum ferritin was statistically significantly associated with an increased risk of death (HR 1.34, 95% CI 1.10-1.64).

Quality assessment / Risk of bias analysis: We tested for publication bias by assessing funnel plots for symmetry. The publication bias funnel indicated that there is no substantial publication bias (Figure 4).

Strategy of data synthesis: The following data were recorded: study characteristics (study design, Study Period, location, sample size, measures of iron-load and outcome measures used), participant characteristics (number, etiology of liver disease and pretransplantation MELD score). Subsequently, we extracted the hazard ratio (HR) with 95% confidence interval (CI) associated with the iron-load and outcome (infection and death). When critical data were missing or unclear in published reports, we attempted to contact the trial authors. We resolved any disagreements in opinion through discussion.

Subgroup analysis: Subgroup analyses showed the increase in serum ferritin was independently associated with an

increased risk of infection after LT (HR 1.44, 95% CI 1.09-1.91; $p=0.01$), with no heterogeneity ($I^2=0\%$, $P=0.43$) (Figure1). To evaluate whether the serum ferritin could be evaluated as a non-invasive prognostic indicator on its own, we performed a subgroup analysis. The pooled results revealed that preoperative or postoperative high levels of serum ferritin was statistically significantly associated with an increased risk of death (HR 1.34, 95% CI 1.10-1.64; $p=0.004$), with low heterogeneity ($I^2=46\%$; $P=0.12$). Higher preoperative serum ferritin was also associated with poor survival (HR 1.54, 95% CI 1.06-2.25; $p=0.003$), with moderate heterogeneity ($I^2=53\%$; $P=0.09$).

Sensitivity analysis: We performed various sensitivity analyses and found largely consistent results across the board, supporting the robustness of the main findings.

Language restriction: No.

Country(ies) involved: China (West China Hospital of Sichuan University).

Keywords: Iron; Liver transplantation; Infection; prognosis; meta-analysis.

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