

REVIEW ARTICLE

The impact of perioperative red blood cell transfusions in patients undergoing liver resection: a systematic review

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Abstract

Background: Liver resection is associated with a high proportion of red blood cell transfusions. There is a proposed association between perioperative transfusions and increased risk of complications and tumor recurrence. This study reviews the evidence of this association in the literature.

Methods: The Medline, EMBASE, and Cochrane databases were searched for clinical trials or observational studies of patients undergoing liver resection that compared patients who did and did not receive a perioperative red blood cell transfusion. Outcomes were mortality, complications, and cancer survival.

Results: Twenty-two studies involving 6832 patients were included. All studies were retrospective, with no clinical trials. No studies were scored as low risk of bias. The overall proportion of patients transfused was 38.3%. After multivariate analysis, 1 of 5 studies demonstrated an association between transfusion and increased mortality; 5 of 6 demonstrated an association between transfusion and increased complications; and 10 of 18 demonstrated an association between transfusion and decreased cancer survival.

Conclusion: This review supports the evidence linking perioperative blood transfusions to negative outcomes. The most convincing association was with post-operative complications, some association with long-term cancer outcomes, and no convincing association with mortality. These findings support the initiation, and further study, of restrictive transfusion protocols.

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Introduction

Liver resection is commonly performed for a number of clinical indications, but primarily for the removal of malignant neoplasms, and is associated with significant blood loss, which may necessitate the use of red blood cell (RBC) transfusions. Technical improvements, resulting in decreased blood loss, as well as evidence of the detrimental effects of RBC transfusions in other areas of medicine, has led to a decline in transfusion prevalence

over the past few decades. In a high-volume, single-centre study, transfusion rates decreased from 83% between 1986 and 1990, to 43% between 1995 and 2001.² A National Surgical Quality Improvement Program (NSQIP) study of liver resections in 2013 reported that the overall prevalence of transfusion was 22%.¹

Randomized controlled trials in critical care³ and orthopedic surgery⁴ have demonstrated that a restrictive transfusion protocol is at least equivalent, and potentially beneficial, when compared to a more liberal transfusion protocol. In general surgical patients, a number of retrospective studies have demonstrated an association between RBC transfusions and infectious complications,^{2,5,6} as well as early cancer

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recurrence.^{7–9} The hypothesized pathophysiology of this association involves transfusion-related immunomodulation (TRIM). The immunomodulatory effects of blood transfusions were first demonstrated clinically in the 1970s by Opelz *et al.* when they showed improved survival of kidney transplant grafts with increasing number of pretransplant transfusions.¹⁰ Transfusions have been shown to suppress the immune system by impairing natural killer cell cytotoxicity¹¹ and lymphocyte activity.¹² This effect has largely been attributed to leukocytes, and has been a driving force in the implementation of leukocyte-reduced blood products in many modern blood banking systems.¹³

Given the high prevalence of transfusions in liver resection, and the potential deleterious effects of transfusions on important clinical outcomes, this systematic review aims to highlight the current scientific evidence available pertaining to the effects of RBC transfusions on major post-operative complications and long-term cancer survival.

Methods

This systematic review was performed in accordance with PRISMA guidelines.¹⁴ The protocol was prospectively registered with the PROSPERO database (CRD42015026132) and has been published.¹⁵

Study identification

The Medline, Embase, and Cochrane Central Register of Controlled Trials databases were searched on December 15, 2015 in collaboration with a medical librarian. The search strategy included a combination of MeSH and text words for liver resection and blood transfusion (Appendix 1). Searches were restricted to human studies published in English or French that involved only adult patients (>18 years old). Included study types were clinical trials, cohort studies, or case–control studies. Titles and abstracts were screened by one reviewer, and full text review was performed by two independent reviewers. Disagreement was resolved by discussion, or a third party.

Eligibility criteria

The population of interest was adult patients undergoing elective liver resection for any indication. The analytic cohort excluded emergency liver resection and patients receiving a liver transplantation. Included studies must have had a primary objective of comparing patients receiving any RBC transfusion during their hospitalization for liver surgery to those not receiving an RBC transfusion. Studies looking exclusively at transfusion of other blood products were not included.

Data collection

Data from the included studies were entered by two independent reviewers into a data extraction spreadsheet developed a priori. The outcomes of interest included transfusion prevalence, post-

operative mortality, post-operative morbidity (including infectious complications, acute liver insufficiency, acute renal failure, cardiovascular events, cerebrovascular events, and thromboembolic events), and long-term cancer outcomes, such as overall survival (OS) or disease-free survival (DFS).

Quality assessment

All included studies were scored on their methodological quality by two independent reviewers using A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI).¹⁶

Analysis

Descriptive summary statistics were collected and reported as whole numbers, proportions, or means, as appropriate. Transfusion proportions were calculated using the DerSimonian-Laird inverse variance weighted random effects model. Studies found to be at critical risk of bias on the ACROBAT-NRSI were described, but not included in any formal analysis. Subgroup analysis was done by disease type. Unadjusted and adjusted effects and their 95% confidence intervals are presented for each study. Pooling of the adjusted odds ratios (OR) or hazard ratios (HR) was done when available and when there was acceptable clinical and statistical homogeneity. Analysis was performed using RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

The initial literature search yielded 1906 citations (Fig. 1). A pilot screening of 100 titles and abstracts by two independent reviewers yielded excellent agreement, with a Cohen's kappa of 0.85. One reviewer screened the remaining titles. From the 1906 citations, 55 potentially eligible studies were identified for full text review. Full text review was done by two independent reviewers, and resulted in 22 papers meeting eligibility^{1,7,17–36} (Table 1). The included papers were published between 1992 and 2015, and comprised a total of 6832 patients undergoing liver resection. No prospective clinical trials were identified. The indications for resection varied by paper: 10 papers studied only patients with HCC (n = 2828), 7 papers studied colorectal metastases (CRM) (n = 2837), 1 studied cholangiocarcinoma (n = 66), and 4 papers included multiple indications (n = 1101). One paper included both hepatic and pancreatic resections,²³ but the liver-specific data was made available to us through personal correspondence with the authors.

Assessment of methodological quality

Using the ACROBAT-NRSI, no study was scored as a low risk of bias. Eighteen of the 22 scored moderate risk of bias, 1 study was scored as serious risk of bias, and 3 studies as critical risk of bias (Appendix 2).

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