The use of perioperative red blood cell transfusions and their appropriateness in liver resection

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1. Introduction & Thesis Outline

Liver resection, or hepatectomy, is a major abdominal surgery performed most often for the removal of malignant tumors of the liver, either primary or metastatic. It is often associated with significant blood loss and therefore, with blood transfusions. While transfusions are common, there is incomplete knowledge of their effects on clinical outcomes. Furthermore, both current practices and best practices in perioperative blood management, including blood product administration, are not well defined. This manuscript-based thesis will examine the clinical impact, current practices, and appropriate use of perioperative red blood cell transfusions for patients undergoing liver resection. It consists of the following five manuscripts, four of which are either published or being prepared for publication in peer-reviewed medical journals:

1. The impact of perioperative red blood cell transfusions in patients undergoing liver resection: a systematic review protocol
2. The impact of perioperative red blood cell transfusions in patients undergoing liver resection: a systematic review
3. Current practices in perioperative blood management for patients undergoing liver resection: a survey of surgeons and anesthesiologists
4. Using the RAND/UCLA Appropriateness Method - this paper is a modified version of a term paper previously written for EPI5343 (May 4, 2016), used by permission of Prof. Ian McDowell.
5. The Ottawa Criteria for Appropriate Transfusions in Hepatectomy (OCATH): using the RAND/UCLA Appropriateness Method

The published systematic review protocol aims to minimize publication bias by disseminating the methods a priori. The systematic review itself provides an introduction to the idea that blood transfusions, through immunomodulation, and pro-inflammatory mechanisms, may contribute to an increased risk of post-operative morbidity and mortality, and long-term cancer recurrence. It summarizes the best available current evidence to help shed light on this incompletely understood problem. The survey of Canadian liver surgeons and anesthesiologists describes the current landscape of perioperative blood management: what is currently practiced, what clinical information is used to make decisions, and who are the primary decision makers. Finally, the OCATH combines the best available evidence from the systematic review with multidisciplinary, multi-institutional expert opinion to develop clinical practice guidelines for the appropriate use of blood transfusions in liver resection.

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

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2.1. Abstract

Background: Liver resection is commonly performed for malignant and benign disease, and is associated with frequent use of intraoperative and postoperative blood transfusions. Blood transfusions are potentially life-saving, but they have many adverse effects; some well understood, and others less so. Some of the poorly understood side effects include increased risk of postoperative complications and possibly worse oncologic outcomes. The objectives of this systematic review are to provide estimates of transfusion prevalence and the effects of perioperative blood transfusion on post-operative mortality and morbidity, and long-term cancer outcomes in patients undergoing liver resection.

Methods/Design: The Cochrane, Medline, and EMBASE databases will be searched for any randomized controlled trial or observational cohort study comparing liver resection patients that received intraoperative or postoperative allogeneic red blood cell transfusions to those who did not. Outcomes include post-operative mortality, post-operative morbidity (infectious, liver failure, renal failure, cardiovascular/cerebrovascular events, and thromboembolic events), and long-term disease-free and overall survival. Only studies with adult, human patients (>18 years old) undergoing liver resection, in which the primary intervention of interest is blood transfusion will be included. Data will be extracted by two reviewers in duplicate and synthesized into a narrative review. Risk of bias will be assessed. When clinically and methodologically appropriate, meta-analysis will be performed.

Discussion: Our review will synthesize the literature pertaining to the potential beneficial and detrimental effects of red blood cell transfusion in patients undergoing liver resection. It will be an important step in the development of guidelines for the appropriate use of blood transfusions in patients undergoing liver resection.

Systematic review registration

PROSPERO CRD42015026132

Keywords: liver resection, hepatectomy, blood transfusion, outcomes, survival

2.2. Background

Liver resection is a major intraabdominal surgery performed for a number of indications, but most commonly for removal of malignant neoplasms. The liver receives approximately 25% of the cardiac output[1], and therefore resection is associated with moderate or significant blood loss, at times life threatening, and not uncommonly results in the use of intraoperative or postoperative blood transfusions. The loss of blood from the intravascular space results in decreased oxygen-carrying capacity and decreased delivery of oxygen to the tissues, however numerous physiologic adaptations occur to cope with these changes. The amount of tolerable blood loss is difficult to define precisely, and is influenced by individual patient and disease-related factors. The estimation of surgical blood loss is also difficult, and many different methods and calculations of blood loss have been studied and described[2,3]. Furthermore, the decision to replace blood volume by way of blood transfusion is one that requires

multiple pieces of clinical and laboratory-based information. Typically, intraoperative blood volume replacement is done by the anesthesiologist, but communication with the surgical team is critical. In making this decision, multiple factors are considered including the patient's hemodynamic status, cardiovascular disease status, hemoglobin concentration, hematocrit, the estimated blood loss, and the perceived rate of blood loss[2].

Blood transfusions have been shown to suppress the immune system in a number of ways, including impaired natural killer cell cytotoxicity[4] and lymphocyte activity[5]. The immunomodulatory effects of transfusions were first highlighted clinically by Opelz et al when they showed improved survival of kidney transplant grafts with increasing number of pretransplant transfusions[6]. There has been a number of observational, retrospective studies showing association between blood transfusion and infectious complications[7-10], as well as early cancer recurrence[11-13]. A 2012 Cochrane review of 36 studies demonstrated an increased odds ratio of 1.42 (95% CI, 1.20 to 1.67) for recurrence of colorectal cancer in patients receiving perioperative blood transfusions[12]. Despite this, there is much conflicting evidence in the literature pertaining to blood transfusions and cancer recurrence. This remains an area where blood transfusions have a perceived negative consequence without high-quality evidence to support such a claim.

Blood transfusions are administered to approximately one third of patients undergoing liver resections[14-18], and this rate appears to be decreasing over time. In a series of 1351 patients undergoing liver resection for colorectal liver metastases between 1986 and 2001 at a single centre, Kooby et al found that 55% of patients received a blood product transfusion (red blood cells, platelets, or plasma) either intraoperatively or

during their postoperative hospitalization[10]. They also demonstrated a reduction in the use of blood products over time, with 83% of patients between 1986-1990, 54% of patients between 1991-1994, and 43% of patients between 1995-2001 receiving blood. They found that non-transfused patients experienced fewer serious postoperative complications (33% vs 46%), and that patients transfused more than 2 units of blood experienced more complications than those transfused 1 or 2 units (51% vs 42%). Blood transfusion remained a significant predictor of complication after multivariate analysis (OR 1.5), along with larger resections and male gender. Blood transfusion was also found to be an independent predictor of 60-day mortality on multivariate analysis (OR 3.7), but not to have a significant impact on long-term survival beyond the 60-day postoperative period. More recent data demonstrates that the trend towards less blood transfusion continues. In a study of 2448 patients undergoing liver resection in 2013, the rate of blood transfusion for the entire cohort was 22.1%[19].

2.3. Objective

The primary objective of this review is to synthesize the evidence surrounding the prevalence and impact of intraoperative and postoperative transfusions of allogeneic red blood cells on key clinical outcomes in patients undergoing liver resection. The key clinical outcomes of interest include transfusion prevalence, post-operative mortality, post-operative morbidity (infectious complications, liver failure, acute renal failure, cardiovascular and cerebrovascular events, and thromboembolic events), and long term overall and disease-free survival.

2.4. Methods/Design

Our systematic review was designed using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[20]. A PRISMA-Protocol checklist was followed (see Appendix A). The protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42015026132).

2.4.1. Population

The population of interest is adult patients, over the age of 18, undergoing elective liver resection for any indication. This does not include patients having emergency liver resection for trauma or bleeding. It does include patients undergoing partial liver resection in order to be a transplant donor, but does not include patients receiving liver transplants. Studies that include liver resection in addition to other procedures will be included if the liver resection data can be extracted from the rest, either from the paper directly or through communication with the corresponding author.

2.4.2. Intervention

The intervention being studied is the administration of allogeneic red blood cell transfusions during the liver resection (intraoperative), or during the immediate hospitalization following liver resection (postoperative). This review will not focus on the administration of other types of blood products, such as autologous transfusions, platelets, plasma, or cryoprecipitate.

2.4.3. Comparators

Any randomized controlled trial (RCT) or observational cohort study comparing patients who received red blood cell transfusions to those who did not will be included in this review.

2.4.4. Outcomes

The outcomes of interest include transfusion prevalence, post-operative mortality, post-operative morbidity, and long term cancer survival outcomes. As post-operative mortality can be defined at a number of time points, all will be acceptable and will be categorized and described in the review. Post-operative morbidities that will be included are overall morbidity, infectious complications (surgical site infection, pneumonia, urinary tract infection), acute liver failure/insufficiency, acute renal failure, cardiovascular events, cerebrovascular events, and thromboembolic events. Severity of complications will be considered and categorized in subgroups, using the Clavien-Dindo Classification, if available from the reported data. Long term cancer survival outcomes will include overall survival, disease-free survival, as well as disease recurrence. Studies that report any, or all, of these outcomes will be considered for inclusion.

2.4.5. Search Strategy

The search strategy was created by the primary investigator (SB) and an expert medical librarian (RS). The Medline (1946 – Present), Embase and Embase Classic (1947 –

Present) and the Cochrane Central Register of Controlled Trials will be searched from inception until December 2015 for articles using a combination of MESH and text words for liver resection and blood transfusion (see Appendix B). Searches are restricted to human studies with adult (>18 years old) patients. Study inclusion will be limited to titles written in English or French. Reference lists will be reviewed for additional studies. Grey literature and conference proceedings will not be searched specifically, although abstracts identified in the search strategy will be considered for inclusion to minimize the impact of publication bias. To avoid duplicate study selection, author names will be compared, and if there is uncertainty, corresponding authors will be contacted.

2.4.6. Study Selection

After a pilot screening evaluation conducted by two independent investigators (SB and LB) of 100 titles and abstracts to establish excellent agreement (kappa > 0.75), one investigator (SB) will conduct the initial title and abstract screen for the remainder. Two investigators (SB and LB) will then conduct the full text review to identify studies meeting inclusion/exclusion criteria. Disagreements will be resolved via consensus where possible, and by a third reviewer, if necessary (GM).

2.4.7. Data extraction

Two investigators (SB and LB) will extract data in duplicate from the included studies into a spreadsheet developed a priori. Data will include publication details, study design,

study size, patient demographics, outcomes used, confounding variables controlled for on multivariate analysis, and effect of treatment on outcomes.

2.4.8. Quality Assessment

Two investigators (SB and LB) will independently assess the included studies for risk of bias and quality of reporting. Disagreement will be resolved via consensus or a third investigator, when necessary. The included studies are expected to all be observational cohort studies, with no RCTs. Should there be any RCTs, they will be assessed using the Cochrane Handbook "Risk of Bias" assessment tool[21]. The observational cohort studies will be assessed using the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI)[22]. This will evaluate risk of bias due to confounding, selection, measurement, and interpretation. The quality of reporting will be assessed using the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) checklist[23].

2.4.9. Data Synthesis

The data will be entered and interpreted into a narrative synthesis. The narrative synthesis will be grouped by outcome of interest (post-operative mortality, post-operative morbidity, and long-term cancer outcomes). Within each outcome group, the studies will be sub-grouped by liver pathology (primary liver tumors, metastatic disease, and donor hepatectomy), as these each have their own distinct clinical characteristics

when it comes to blood transfusion. Other subgroupings of interest may include date of publication, methodological quality, and extent of adjustment for confounding.

It is unlikely that a quantitative meta-analysis will be feasible due to expected lack of controlled clinical trials, and clinical and statistical heterogeneity, however this will be considered once the data is collected. Where possible, given the availability of data, and the clinical and statistical homogeneity, a quantitative meta-analysis of observational studies may be performed. If a meta-analysis is possible, the effect of blood transfusion will be stratified by outcome, using a random effects model. We will also evaluate the impact of important clinical and methodological characteristics through the conduct of subgroup analyses. Planned subgroup analyses include indication for surgery (benign, primary malignant, metastatic), risk of bias score, and method of multivariate analysis. We will also explore sources of potential heterogeneity through visual inspection of overall pooled analyses and inspection of Q and I^2 statistics. Quantitative meta-analysis will be performed using OpenMetaAnalyst software (Brown University, School of Public Health).

2.5. Discussion

There have been a number of recent calls for guidelines on the appropriate use of blood transfusions during liver resection[1,24]. Given the potential life-saving benefit of blood transfusions, as well as the possibility of negative clinical consequences when given inappropriately, this is an important future direction. While general guidelines on perioperative blood management do exist[25], none are specific to liver surgery.

Furthermore, there is published evidence of practice variability in the use of blood conservation methods during liver resection[26], as well as in the use of blood transfusions during liver transplant[27].

A thorough synthesis of the current body of literature is a necessary initial step in this process. One previous systematic review and meta-analysis showed blood transfusions had increased post-operative mortality, post-operative morbidity, and cancer recurrence after liver resection; but only studied patients with hepatocellular carcinoma[28]. The proposed review will expand the patient population to include patients undergoing liver resection for all indications, in particular for colorectal liver metastases, which is the most common indication for liver resection in North America[19,29]. Furthermore, this previous review included studies up until 2012, and an update to include the past three years of literature will be important.

The strengths of the proposed systematic review will be a very broad search strategy, rigorous inclusion/exclusion criteria, a focus on only studies where blood transfusion is the primary intervention of interest, and the inclusion of all indications for elective liver resection. Limitations of this review will likely include a lack of RCTs and significant clinical and statistical heterogeneity between studies. This will likely prevent the conducting of a quantitative meta-analysis.

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

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3.1. Abstract

Importance: Liver resection is associated with a high proportion of patients receiving red blood cell transfusions. There is a proposed association between perioperative transfusions and increased risk of complications and tumor recurrence.

Objective: The objective of this study was to review the evidence of the association between blood transfusions and post-operative mortality, morbidity, and long term cancer outcomes in adults undergoing liver resection.

Evidence Review: A search of Medline, EMBASE, and Cochrane databases to December 15, 2015 included MeSH terms “liver neoplasms”, “hepatectomy”, and “blood transfusion”. Included were clinical trials or observational studies of patients undergoing elective liver resection, with the primary objective of comparing patients who did and did not receive a perioperative red blood cell transfusion. Excluded were studies on emergency resections and liver transplants. Studies were assessed for risk of bias using the Cochrane Risk of Bias Assessment Tool. Outcomes were mortality, complications, and cancer survival.

Findings: Twenty-two studies involving 6832 patients were included. All studies were retrospective cohorts, with no clinical trials identified. No studies were scored as low risk of bias. The overall proportion of patients receiving a transfusion was 38.3%. After multivariate analysis, only 1 of 5 studies demonstrated an association between transfusion and increased mortality; 5 of 6 studies demonstrated an association

between transfusion and increased post-operative complications; and 10 of 18 studies demonstrated an association between transfusion and decreased cancer survival.

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

3.2. 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 1986-1990, to 43% between 1995-2001[2]. A National Surgical Quality Improvement Program (NSQIP) study of liver resections in 2013 reported that the overall prevalence of transfusion was 22.1%[1].

Blood transfusions can be life saving. However, randomized controlled trials in critical care[3] and orthopedic surgery[4] 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 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 cytotoxicity[11] 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 its potential deleterious effects 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.

3.3. 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].

3.3.1. Study Identification

Medline, Embase, and Cochrane Central Register of Controlled Trials databases were searched on December 15, 2015 in collaboration with a medical information specialist. The search strategy included a combination of MeSH and text words for liver resection and blood transfusion (Appendix B). Searches were restricted to human studies published in English or French that involved only adult patients (>18 years old). We included any clinical trial, cohort study, or case-control study. 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.

3.3.2. 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.

3.3.3. 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).

3.3.4. 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].

3.3.5. Analysis

Descriptive summary statistics were collected and reported as whole numbers, proportions, or means or medians and associated standard deviations, 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).

3.4. Results

The initial literature search yielded 1906 citations (Figure 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 hepatocellular carcinoma (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 through personal correspondence with the authors.

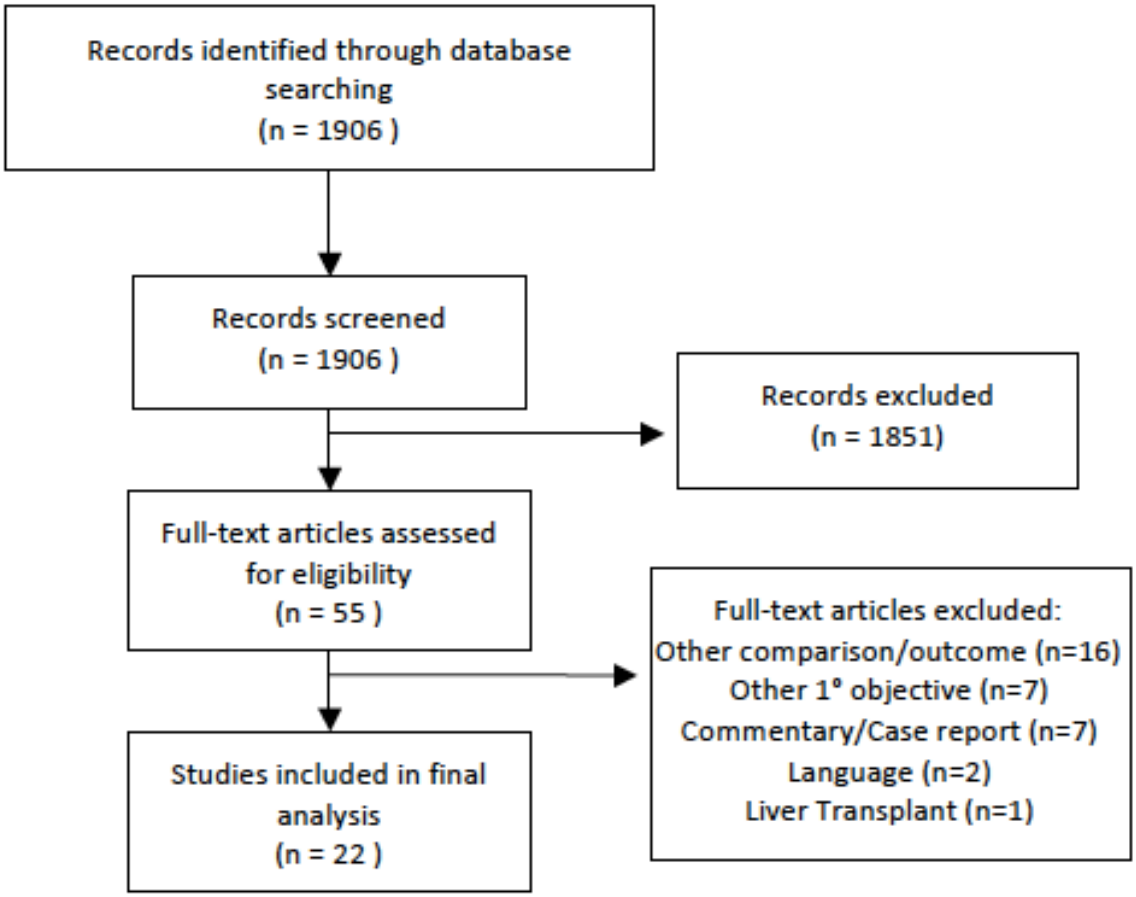

Figure 1. PRISMA flow diagram showing study selection process

3.4.1. 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 (Table 2).

3.4.2. Proportion Transfused

Transfusion proportions were presented in all studies except one[20]. The overall proportion of patients receiving at least one RBC transfusion in the remaining cohort of 6624 patients was 38.3% (29.7-46.9, 95% CI), with a range of 9.1%[26] to 65.4%[28]. Subdivided by decade of publication, there was a trend towards decreased transfusion utilization since 2010. Studies published in the 1990s (n=5) had a transfusion prevalence of 42.6% (21.3-63.9, 95% CI); studies published from 2000-2009 (n=6) had a transfusion prevalence of 49.1% (42.9-55.4, 95% CI), while studies published from 2010-2015 (n=11) had a transfusion prevalence of 29.6% (21.8-37.5, 95% CI). There was little difference noted in transfusion practices based on geographic region. Specifically, European (n=3), North American (n=7), and Japanese (n=12) studies reported transfusion prevalences of 46.4% (27.9-64.9, 95% CI), 37.4% (25.9-48.9, 95% CI), and 36.8% (25.2-48.3, 95% CI), respectively. Only one study[7] reported on whether or not leuko-reduced blood products were used.

Sixteen papers looked at demographic and clinical factors associated with a higher risk of receiving a blood transfusion. The most common factor associated with increased risk of receiving a blood transfusion was “estimated blood loss” (n=13 papers). Other factors associated with increased risk of transfusion were increased tumor size (n=5), cirrhosis (n=4), larger resections (n=4), preoperative anemia (n=3), and female sex (n=2).

3.4.3. Association between Transfusion and Surgical Mortality

Five of the included studies (n=2925) directly compared the post-operative mortality of patients who did and did not receive a transfusion[1,20,24,26,35] (Table 3). Kooby et al[1] defined post-operative mortality within 60 days of surgery, or in-hospital mortality. The overall mortality in this study was 3.7%. Before adjusting for any confounding factors, transfused patients had an over 4-fold increased hazard ratio of death (HR=4.2, 2.0-9.0, 95%CI). After multivariate analysis, transfusion remained an independent predictor of mortality, with a HR of 3.7 (1.7-8.4, 95%CI). Major hepatic resection (defined as 3 or more segments) was the only other independent predictor of mortality. Park et al[20] defined operative death as "any death resulting from a complication of the operation". These authors reported no significant difference in operative deaths when comparing 104 transfused patients (0 deaths) to 104 non-transfused patients (1 death), matched for age, comorbidities, extent of resection, and estimated blood loss. Kuroda et al[26] noted a significantly higher 30-day mortality rate among transfused versus non-transfused patients on univariate analysis (3.9% vs 0%, respectively; $p<0.001$). However, after propensity score matching for a number of important factors (see Table 3), the effect of transfusion on mortality was not significant in the matched cohort of 120 patients (5% vs 0%, $p=0.242$). Schiergens et al[24] noted an overall 30-day mortality rate of 5%, which was not significantly different among those who did and did not receive a transfusion (6% vs 4%, $p>0.05$). Reporting on 90-day mortality, Cannon et al[35] reported a mortality of 2.5% in their overall cohort. Mortality was not statistically different between the transfused (4.7%) and the non-transfused (1.7%) groups ($p=0.193$) in unadjusted analysis.

3.4.4. Association between Transfusion and Surgical Complications

Nine of the included studies (n=3340) performed a comparison of post-operative complications among transfused and non-transfused patients. Three studies[21,30,33] (n=606) were assessed as having critical risk of bias due to the lack of control for confounding, and thus their head-to-head comparisons are not further described.

The six papers that did attempt to control for known confounders in their analysis of post-operative complications are presented in Table 4. These papers used multivariable analysis, matched cohorts, or propensity score analysis to control for confounding. Five of the papers (n=2526) demonstrated transfusion to be a significant, independent predictor of total complications; with one performing analysis only of patients with cirrhosis[17]. Ejaz et al[23] demonstrated a dose-response relationship, with increasing risk of complication with 3 or more units transfused versus 1-2 units transfused. The sixth paper[20], using a matched cohort, did not find a statistically significant difference in total complications for patients who did and did not receive a transfusion. These authors did however describe a non-significant trend towards higher rates of major complications among patients who received a transfusion (24% vs 11.5%, p=0.09). Other factors reported to be predictors of post-operative complications were resection of a lobe or more[1], male sex[1], and a Charlson Comorbidity Index (CCI) above 4[23].

3.4.5. Association between Transfusion and Survival

Twenty papers reported either OS,DFS, or both (n=6497). Two papers did not control for any confounders[21,33], placing these reports at critical risk of bias and therefore the

results too problematic for inclusion. The 18 papers that did attempt to control for confounding are presented in Table 5. On univariate analysis, all but four papers demonstrated that transfusion was associated with worse OS, DFS, or both. After controlling for numerous known confounders, 7 papers identified transfusion as a negative independent prognostic factor for survival; 3 papers identified transfusion as a negative factor in only a certain subset of the cohort, and 8 papers did not find any association between transfusion and survival. The 7 papers that did demonstrate an association were mostly recent, with 6 of the 7 papers being published in 2009 or later. These reports included patients with various disease processes, with 4 being focused on HCC, 2 on CRM, and one on cholangiocarcinoma. The hazard ratio range for OS was 1.74-3.38 and the HR for DFS ranged from 1.46-2.84. All 7 papers used the Cox multivariate proportional hazards regression model, but 2 of the papers also performed propensity score matching analysis[19,26]. Both of these papers identified transfusion as a negative independent predictor for OS and DFS using the Cox model. In one, this relationship was not seen for either OS or DFS when propensity score methodology was used[26]. In the other, transfusion was found to be a negative predictor for DFS (HR 1.45, 1.0-2.1, 95%CI) but not for OS[19]. Three papers identified transfusion as a negative independent factor in specific cohort subgroups; cirrhotic patients with HCC[17], HCC patients with portal vein invasion[31], or early stage HCC patients[32].

Grouping by disease, only 1 of 6 CRM papers reported an association between transfusion and worse OS on multivariate analysis; 2 of the 3 CRM papers reporting DFS noted an association. In HCC, 3 of 5 papers described an association between transfusion and worse OS. Eight HCC papers reported DFS, with 3 reporting an

association for the whole cohort, and 2 others reported an association within a subgroup of patients.

3.5. Discussion

Liver resection is the only curative treatment for many malignant liver lesions, both primary and metastatic. While there is evidence of decreasing prevalence of perioperative blood transfusions in liver resection, transfusion remains a common intervention. In modern blood banking systems, the concerns over infectious transmission and incompatibility reactions are almost entirely mitigated[37], however those involving the immunomodulatory effects of transfusions are not. In the perioperative setting, these concerns involve the potential for increased risk of complications and cancer recurrence. The current study systematically reviewed the literature pertaining to the effects of blood transfusion on post-operative mortality, complications, and long-term cancer survival in patients undergoing liver resection. In existing studies, with moderate levels of evidence, a negative effect of transfusions on post-operative complications can be seen, independent of known confounders. In contrast to complications, there was no convincing evidence that perioperative transfusion was associated with increased post-operative mortality. The literature pertaining to the association between transfusions and long-term cancer survival (OS and DFS) was mixed, although there was some evidence that suggested a negative effect of blood utilization on long-term outcomes.

The potential deleterious effects of blood transfusions on patients undergoing liver resection have been previously reported by Liu et al, in a meta-analysis that focused exclusively on HCC[38]. These authors concluded that in patients with HCC, perioperative transfusion was associated with an OR of 1.60 (1.47-1.73, 95%CI) for 5-year all cause mortality, and an OR of 1.16 (1.08-1.24, 95%CI) for 5-year tumor recurrence. Unfortunately, this analysis was performed on a number of non-randomized papers, unadjusted for confounding or indication bias, and the link to causality was not well-supported. Without controlling for important confounders, the association between transfusion and recurrence is at high risk of bias.

Likely the best available evidence of the effect of transfusions on cancer recurrence is based on literature relating to colorectal cancer, as noted in a Cochrane review by Amato[8]. Of the 23 studies in this review that attempted to control for confounding, 14 noted a detrimental effect on cancer recurrence. The review included 7 prospective trials, with a combined OR of 1.42 (1.20-1.67, 95%CI) for risk of recurrence with a transfusion. The authors concluded there was an association between transfusion and cancer recurrence, although a causal link was difficult to determine due to heterogeneity and the inability to control for some important confounders in the non-randomized studies. A recent systematic review on the topic in patients undergoing pancreatic resection also demonstrated a decreased 5-year OS in patients receiving transfusions[39] with a pooled odds ratio of 2.43 (1.90-3.10, 95%CI) unadjusted for confounding. After controlling for confounding, 9 of 19 studies in this review reported an association between transfusion and OS.

The contrasting argument in favour of transfusion can be seen in two recent publications. De Almeida et al[40] performed an RCT of 198 patients admitted to the intensive care unit (ICU) following major abdominal surgery for cancer. The authors noted that a restrictive trigger for postoperative RBC transfusion (hemoglobin < 70g/L) resulted in a higher composite endpoint of 30-day death or severe clinical complications than did a liberal transfusion trigger (hemoglobin < 90 g/L) (35.6% versus 19.6%, p=0.012). All of the patients included in the cohort were unplanned ICU admissions due to physiologic abnormalities, and the majority of deaths were due to septic shock, which may be a subgroup that potentially benefits from RBC transfusions[41]. Furthermore, only 2% of patients in this series had a liver resection, and a total of 20 patients had a deviation from their intended treatment protocol, with no per-protocol sensitivity analysis performed. The other paper of interest is a meta-analysis of clinical trials for perioperative or critically ill patients[42]. Seventeen clinical trials were identified in the perioperative setting (9 orthopedic, 5 cardiac, 1 vascular, 1 abdominal oncology, 1 obstetrics), and these reports demonstrated a slight benefit towards a liberal transfusion trigger in terms of all-cause mortality (OR 0.81, 0.66-1.00, 95%CI). The 10 papers on critically ill patients had a near-significant finding in the opposite direction, favouring restrictive transfusion (OR 1.10, 0.99-1.23, 95%CI).

The current study focused on three main outcomes: post-operative mortality, post-operative complications, and long-term survival (OS and DFS). The evidence does not support an effect of transfusion on post-operative mortality. In 5 studies, only one demonstrated such an association[1]. One important issue with this finding, however, is that this paper also showed a significant decrease in transfusion prevalence over time,

but did not control for the time period in the multivariate analysis. Those more likely to receive transfusions were earlier in time, and therefore also less likely to benefit from the many advances in patient care over the past decades. In terms of post-operative complications, there is evidence of an association between transfusions and higher risk of complications. On multivariate analysis, 5 of the 6 papers reported that transfusion was an independent, negative predictor of total complications. The one paper that did not find transfusions to be a negative predictor was a matched cohort with 104 patients in each arm[20]. This report did, however, demonstrate a trend towards significance when comparing the 24% major complication rate in transfused patients to the 11.5% rate in non-transfused patients (p=0.09), suggesting a power issue. When it comes to OS and DFS, similar to the other systematic reviews mentioned above, the majority of papers in this review showed worse survival with transfusions on univariate analysis. This is not surprising, as there are many patient and disease factors that could confound the association. After multivariate analysis, there are 10 of 18 papers that demonstrate a negative effect on OS or DFS, or both, either in the entire cohort (n=7), or in a subgroup (n=3). These data indicate that there may be an important association between transfusion and cancer recurrence, however a causal link cannot be made based on these retrospective reports.

Despite being unable to draw causal links between transfusion and adverse outcomes, the implication of the current paper is that it lends support towards a more restrictive use of perioperative transfusions. In their large multicentre study, Kooby et al reported that 43.1% of liver resection patients who received a transfusion received only 1 or 2 units[1]. It is conceivable that a large proportion of these patients could be spared a

transfusion through the use of a more restrictive transfusion threshold; therapeutic modalities such as tranexamic acid; or through the use of perioperative blood conservation methods, such as low central venous pressure, acute normovolemic hemodilution or intraoperative whole blood phlebotomy. Ejaz et al demonstrated that a more restrictive transfusion strategy in patients undergoing liver and pancreas resection could reduce the number of transfusions by 25.7%, with no difference in the OS or DFS of patients receiving transfusions under either strategy[23]. The restrictive trigger was considered to be an intraoperative hemoglobin value below 100 g/L, and a postoperative value below 80 g/L, but very little research has been done to identify what an appropriate transfusion trigger might be.

The current study has several limitations. Primarily, there is inherent heterogeneity involved with including studies that focus on different diseases. The biology of primary HCC and metastatic colorectal cancer are very different, and each disease may behave differently in the setting of a perioperative transfusion. In addition, each study controlled for slightly different confounding factors. Furthermore, these are studies spanning 23 years, with many changes in surgical and adjuvant therapies. It was primarily because of this heterogeneity that a formal meta-analysis of the aggregated data was not performed. As a consequence of this, another limitation is that an overall estimate of association cannot be provided other than presenting the effect sizes of the various included studies. An important finding, and limitation, is that no clinical trials were identified in the literature. All of the included studies were retrospective and non-randomized, leading to the possibility of selection bias, publication bias, or bias due to confounding. Most studies attempted to control for confounding to various degrees, as

has been discussed. Measurement bias is also an important factor, primarily for the outcome of post-operative complications. Within-study, and between-study variability is likely to occur as to what is classified as a complication. Finally, given the presumed importance of leukocytes on the immunomodulatory effects of blood transfusions, it was interesting that only one paper[7] mentioned whether or not leuko-reduced blood products were used.

3.6. Conclusions

This systematic review lends support to the growing body of literature linking perioperative blood transfusions to negative short and long term patient outcomes. The most convincing association seen in patients undergoing liver resection is between perioperative transfusion and post-operative complications, with some association seen with long-term cancer outcomes, and no convincing association with post-operative mortality. The conclusions support the implementation and continued research of restrictive transfusion triggers and perioperative blood conservation techniques. Furthermore, the authors support the call by others[43,44] for the development of perioperative transfusion triggers by means of clinical trials, systematic reviews, and expert consensus conferences.

Table 1. Clinical characteristics and transfusion prevalence of studies included in the systematic review

Author	Pub. Year	QRS	N	BT+	BT-	% BT	Mean age	% male	Disease	Overall Risk of Bias
Rosen[28]	1992	3	280	183	81	65.4	59	62.0	CRM	Moderate
Matsumata[34]	1993	3	126	54	72	42.9	57.6	83.3	HCC	Moderate
Yamamoto[36]	1994	3	252	74	178	29.4	NR	79.4	HCC	Moderate
Gozzetti[17]	1995	3	522	325	197	62.3	55.6	58.4	Multiple (40.4% HCC, 22.2% CRM)	Serious
Asahara[32]	1999	3	175	23	152	13.1	60.1	76.0	HCC	Moderate
Makino[31]	2000	3	195	117	78	60.0	60.8	80.0	HCC	Moderate
Kwon[33]	2001	3	108	53	55	49.1	61.8	76.8	HCC	Critical
Kooby[1]	2003	3	1351	749	602	46.0	NR	58.0	CRM	Moderate
Hanazaki[18]	2005	3	368	210	158	57.1	62.4	75.5	HCC	Moderate
Park[20]	2007	3	208	104	104	NA	56.1	39.7	Multiple (8.4% HCC, 59% CRM)	Moderate
Sugita[25]	2007	3	224	101	123	45.1	63.2	76.8	HCC	Moderate
Shiba[22]	2009	3	66	22	44	33.3	NR	84.8	HCC	Moderate
Gruttadauria[30]	2011	3	127	51	76	40.2	63	56.7	CRM	Critical
Kuroda[26]	2012	3	835	76	759	9.1	63.5	76.9	HCC	Moderate
Cannon[35]	2013	3	239	64	175	26.8	61.4	NR	CRM	Moderate
Shiba[29]	2013	3	65	27	38	41.5	64.1	69.2	CRM	Moderate
Ejaz*[23]	2015	3	185	58	127	30.8	63	52.4	Multiple	Moderate
Hallet[7]	2015	3	483	133	350	27.5	63	61.9	CRM	Moderate
Harada[19]	2015	3	479	91	388	19.0	67.3	66.6	HCC	Moderate
Kimura[27]	2015	3	66	29	37	43.9	68.5	65.1	Hilar cholangiocarcinoma	Moderate
Schiergens[24]	2015	3	292	106	186	36.3	64.5	66.0	CRM	Moderate
Wehry[21]	2015	3	186	53	133	28.5	60.7	NR	Multiple (13.4% HCC, 47.6% CRM)	Critical

*liver specific data from this paper was retrieved through personal communication

Pub = publication; QRS = Quality Rating Scale[45] (1:Randomized Controlled Trial, 2:Prospective Cohort, 3:Retrospective Cohort, 4:Case Series, 5:Case Report/Opinion); BT+ = patients who received blood transfusion; BT- = patients who did not receive blood transfusion; %BT = proportion of patients receiving blood transfusion; HCC = hepatocellular carcinoma; CRM = colorectal metastases; NA = not applicable; NR = not reported

Table 2. Risk of bias by study using the ACROBAT-NRSI

	Bias due to:							
Study	**Confounding**	**Selection of participants**	**Measurement of interventions**	**Departures of intended interventions**	**Missing data**	**Measurement of outcomes**	**Selection of reported result**	**Overall Risk of Bias**
Rosen[28]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Matsumata[34]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Yamamoto[36]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Gozzetti[17]	Serious	Low	Low	Low	Moderate	Moderate	Serious	**Serious**
Asahara[32]	Moderate	Low	Low	Low	Low	Moderate	Moderate	**Moderate**
Makino[31]	Moderate	Low	Low	Low	Low	Moderate	Moderate	**Moderate**
Kwon[33]	Critical	Low	Low	Low	Low	Moderate	Low	**Critical**
Kooby[1]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Hanazaki[18]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	**Moderate**
Park[20]	Moderate	Moderate	Low	Low	Low	Moderate	Low	**Moderate**
Sugita[25]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Shiba[22]	Moderate	Low	Moderate	Low	Low	Moderate	Low	**Moderate**
Gruttadauria[30]	Critical	Low	Low	Low	Low	Moderate	Serious	**Critical**
Kuroda[26]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Cannon[35]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Shiba[29]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Ejaz*[23]	Moderate	Low	Low	Low	Low	Moderate	Moderate	**Moderate**
Hallet[7]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Harada[19]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Kimura[27]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Schiergens[24]	Moderate	Low	Low	Low	Low	Moderate	Low	**Moderate**
Wehry[21]	Critical	Serious	Low	Low	Critical	Moderate	Moderate	**Critical**

ACROBAT-NRSI definitions - Moderate risk: the study appears to provide sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial; **Serious risk**: the study has some important problems; **Critical risk**: the study is too problematic to provide any useful evidence on the effects of intervention

Table 3. Studies comparing effect of transfusion on post-operative mortality

Study (Year)	Disease	N	Overall mortality	Mortality (BT+)	Mortality (BT-)	Unadjusted findings	Confounders adjusted for	Findings, adjusted for known confounders
Kooby (2003)[1]	CRM	1351	3.7%[a]	5.8%	1.6%	BT assoc. w/ increased mortality (HR 4.2, 2.0-9.0, 95% CI)	bilateral resection, ≥ 1 lobe resection, positive resection margin, disease-free interval ≤ 12 months	**BT is an independent predictor of mortality (HR 3.7, 1.7-8.4).** Only other predictor is lobe or more resection
Park (2007)[20]	Multiple	208	0.5%[b]	0%	1%	NA	Age, comorbidities, extent of resection, estimated blood loss	**No difference between matched cohorts**
Kuroda (2012)[26]	HCC	835	0.36%[c]	3.9%	0%	Sig diff (p<0.001)	Propensity model: age, sex, anti-HCV Ab, LFTs, tumor size/number/grade, vascular invasion, extent of resection	One-to-one propensity score matched cohort (n=120) found **no sig diff in mortality (5% vs 0%, p=0.242)**
Cannon (2013)[35]	CRM	239	2.5%[d]	4.7%	1.7%	**No sig diff (p=0.193)**	NA	NA
Schiergens (2015)[24]	CRM	292	5.0%[c]	6%	4%	**No sig diff (p>0.05)**	NA	NA

BT+ = patients who received blood transfusion; BT- = patients who did not receive blood transfusion; CRM = colorectal metastases; HCC = hepatocellular carcinoma; HR = hazard ratio; anti-HCV Ab = anti-hepatitis C virus antibody; LFT = liver function tests;
a = 60-day mortality (or any same admission, in-hospital mortality beyond 60-days)
b = any death related to a complication of the surgery
c = 30-day mortality
d = 90-day mortality

Table 4. Studies comparing effect of transfusion on post-operative complications

Study (Year)	Disease	N	Overall comp.	Comp (BT+)	Comp (BT-)	Unadjusted findings	Confounders adjusted for:	Findings, adjusted for known confounders
Gozzetti (1995)[17]	Multiple	522	25.9%	34.8%	11.2%	More complications in BT patients (p<0.01)	length & year of operation, tumor size, Child-Pugh class (Only analyzed cirrhotic patients)	**BT in cirrhotics is the only predictor of complications**: OR 2.2 (1.7-2.9) (only reported for cirrhotic patients)
Kooby (2003)[1]	CRM	1351	40%	46%	33%	More comp in BT, + dose response: 0 units = 33%, 1-2u = 42%, >2u = 51% (p=0.03)	age, gender, bilateral rsx, ≥ 1 lobe resection, length of operation, EBL, tumor size	**BT is an independent predictor of complications**: OR 1.5 (p=0.0008) (also significant is ≥ 1 lobe resection, males)
Park (2007)[20]	Multiple	208	61.5%	63.5% (24% major)	59.6% (11.5% major)	No unadjusted findings. Study was a matched cohort.	Cohorts matched on: age, comorbidities, extent of resection, EBL	**No difference in total complications**. Non-significant difference in major comps (p=0.09)
Kuroda (2012)[26]	HCC	835	9.2%	27.6%	7.4%	More complications in BT patients (p<0.001)	Propensity score matching (n=120): age, sex, anti-HCV Ab, LFTs, tumor size/number/grade, vascular invasion, extent of resection	**BT patients still had more complications than non-BT after propensity score matching** (26.7% vs 8.3%, p=0.016)
Cannon (2013)[35]	CRM	239	42.7%	57.8%	37.1%	More complications in BT patients (p=0.004)	Tumor size	**BT is the only independent predictor of non-bleeding complications** OR 1.98 (1.09-3.58)
Ejaz (2015)[23]	Multiple	185	8.6%	17.2%	4.7%	More comp in BT, + dose response: 0 units = 4.7% 1-2u = 12.5% 3+u = 27.8% (p=0.003)	Age, ASA, CCI, serum albumin, EBL	**BT is a predictor of complications** (+ dose response relationship) 1-2u: OR 3.3 (1.5-7.2) 3+u: OR 9.1 (3.9-22.1) CCI > 4 also significant

Comp = complications; BT = red blood cell transfusion; CRM = colorectal metastases; HCC = hepatocellular carcinoma; OR = odds ratio; EBL = estimated blood loss; CEA = carcinoembryonic antigen; anti-HCV Ab = anti-hepatitis C virus antibody; LFTs = liver fuction tests; ASA = American Society of Anaesthesiologists' Physical Status Classification System; CCI = Charlson Comorbidity Index

Table 5. Studies comparing effect of transfusion on long term cancer survival

Study (Year)	Disease	N	Unadjusted findings	Variables in Cox regression analysis	Adjusted Findings
Rosen (1992)[28]	CRM	280	BT had sig lower 5-year OS (21% vs 32%, p=0.03)	Primary tumor stage, method of diagnosis, metastatic configuration (single, multiple, satellite), extrahepatic nodal status, extrahepatic disease	**BT not an independent predictor of OS** (included only 60-day survivors, n=261). Sig predictors: extrahepatic nodal status, method of diagnosis, metastatic configuration
Matsumata (1993)[34]	HCC	126	No difference in OS (p=0.47) or DFS (p=0.16)	Age, sex, HbsAg, AFP, albumin, AST, ALT, bilirubin, ICGR15, platelets, preop Hgb, type of resection, length of operation, EBL, cirrhosis, tumor size, intrahepatic metastases	**BT had no effect on OS or DFS.** Significant predictors of DFS: albumin < 3.5g/dl, intrahepatic metastases
Yamamoto (1994)[36]	HCC	252	BT had sig lower DFS (25.7% vs 50%, p=0.0001)	Age, gender, tumor number/size/capsule/invasiveness, surgical margin, liver parenchyma, extent of resection, EBL	**BT is an independent predictor of recurrence (HR 1.7, 1.19-2.42).** Other predictors: tumor invasiveness (either portal invasion or hepatic mets), cirrhosis
Gozzetti (1995)[17]	Multiple	522	BT had sig. lower 3 and 5-year OS in patients with and without cirrhosis	length & year of operation, C-P class, extent of resection, ascites, postop complication, tumor recurrence (**note:** controlling for complication and recurrence is overadjustment, as these are intermediate variables on the causal pathway to survival)	**BT had sig worse survival only in cirrhotic patients with HCC. No effect on non-cirrhotic pts with HCC, or in CRM.**
Asahara (1999)[32]	HCC	175	BT = lower 5-yr OS (27.9% vs 45.7%, p=0.08) and DFS (7.3% vs 25.2%, p=0.003)	age, sex, tumor size, capsular formation, portal invasion, intrahepatic metastases, Edmondson's histological grade, extent of resection, margin status, ICGR15	**BT is a significant negative independent predictor for DFS in stage I-II (p=0.006) but not stage III-IV (p=0.99).** Other negative predictors: extent of resection, ICGR15 (stage I-II), portal invasion (stage III-IV)
Makino (2000)[31]	HCC	195	BT had no significant effect on 1,3, and 5 year DFS (p=0.175)	gender, preop Hgb, liver disease, number of tumors, tumor size, EBL, C-P class, vascular invasion, intrahepatic metastases	**BT not a significant predictor of DFS** (Subgroup: BT was an independent predictor of intrahepatic recurrence in HCC patients with portal vein invasion)
Kooby (2003)[1]	CRM	1351	BT had significantly decreased OS (primarily in the first 60-days, although still significant after)	gender, bilobar resection, > 1 lobe resection, age, operative time, EBL, tumor size, margin status, disease-free interval, CEA, nodal status, site of primary disease	**BT no longer a significant predictor of OS (HR 1.1, 0.9-1.3)** Sig. predictors: positive resection, node positive primary, multiple liver lesions, size >5cm, extrahepatic disease
Hanazaki (2005)[18]	HCC	368	BT had significantly lower 3 and 5 year OS (p=0.019) and DFS (p=0.0061)	vascular invasion, major resection, AFP, tumor size, gender, age, C-P class, AST, ALT, albumin, ICGR15, EBL, TNM stage, cirrhosis, number of tumors	**BT no longer a significant predictor of OS or DFS**
Sugita			BT= no diff in DFS (p=0.28), except in tumors >5cm	Age, gender, cirrhosis, AST, AFP, tumor size, portal vein invasion, tumor grade	**BT is not a predictor of DFS**

Shiba (2009)[22]	HCC	66	BT = significantly decreased OS (p=0.001) and DFS (p=0.038)	age, gender, ICGR15, C-P class, MELD score, T stage, type of resection, operative time, EBL, hepatitis status	**BT remains a sig. negative prognostic factor for OS (p<0.001) and DFS (p=0.002)** Other neg. predictors: female gender, T stage
Kuroda (2012)[26]	HCC	835	BT = sig. lower 5-yr OS (23.1 vs 56.3%, p<0.001). Sig. lower 5-yr DFS (22.8% vs 32.9%, p=0.009)	cirrhosis, anti-HCV, PT, bilirubin, albumin, ICGR15, AFP, C-P class, tumor size, number of tumors, MVI, extent of resection, EBL	**BT: independent poor predictor of OS (HR 1.74, 1.29-2.34) on Cox regression model Propensity matching (n=120): no diff seen in OS (p= 0.47) and DFS (p=-0.62)**
Cannon (2013)[35]	CRM	239	BT = no diff in OS (p=0.11) or DFS (p=0.28)	Age, BMI, CEA, number/size of lesions, Fong score, type of resection	**BT not a prognostic predictor of OS or DFS**
Shiba (2013)[29]	CRM	65	BT had sig lower 5-year OS (HR 2.54, 1.15-5.58)	Tumor distribution, number of nodal mets, FFP transfusion	**BT not an independent predictor of OS (HR 1.86, 0.67-5.19).** Sig predictors: bilobar tumors, ≥ 4 nodal mets, FFP transfusion
Ejaz (2015)[23]	Multiple	185	BT associated with sig worse OS and DFS (data not available)	age, sex, race, ASA, CCI, albumin, Hgb, EBL, type of resection	**BT not a predictor of OS (HR 4.1, 0.69-24.5) or DFS (HR 1.08, 0.58-2.01)**. Only factor that is negatively predictive is low albumin for DFS.
Hallet (2015)[7]	CRM	483	BT: sig. lower 5-yr OS (45.9% vs 61%, p<0.0001) and DFS (15.5% vs 31.6%, p<0.0001) Significant dose-response relationship for both.	age, gender, preop Hgb, preop chemo, Clinical Risk Score (CRS): primary tumor N stage, number & size of liver lesions, CEA level, disease-free interval, time period (03-07 vs 08-12)	**BT: ind. neg predictor of OS (HR 2.24, 1.60-3.15)**. Other OS predictors: CRS, time period. BT also a neg predictor of DFS (HR 1.71, 1.28-2.28). Other DFS predictors: preop chemo, CRS
Harada (2015)[19]	HCC	479	BT had significantly lower 5-yr OS (55.4 vs 73.9%, p<0.0001) and DFS (24.3 vs 37.7%, p=0.002)	age, cirrhosis, AFP, tumor size, EBL, gender, anti-HCV, ICGR15, number of tumors, grade, vascular invasion, extent of resection	**Cox Model: BT remains a significant independent predictor of worse OS** (HR 1.76, 1.16-2.62) and DFS (HR 1.46, 1.10-1.91) **IPTW propensity scoring: no sig impact on OS (HR 1.33, 0.8-2.2), but DFS remained significant (HR 1.45, 1.0-2.1)**
Kimura (2015)[27]	CCA	66	BT is a sig predictor of decreased OS (p=0.002) and DFS (p=0.007)	Gender, CA 19-9, pre-op portal vein embolization, type of resection, nodal status, post-op max bilirubin, MVI, LVI	**BT is an ind. predictor for decreased OS (HR 3.38, 1.50-7.64).** Also predictive: + margin BT is the only independent prognostic factor for DFS (HR 2.84, 1.37-5.88)
Schiergens (2015)[24]	CRM	292	BT = sig shorter median DFS: 0 units = 72 mth, 1-2u = 37 mth, >2u = 27 mth (p=0.005) Non-sig shorter median OS (48 vs 63 mths, p=0.09)	DFS: CCI, number of metastases, EBL, margin positivity OS: Age, CCI, complications, extent of resection	**BT is an independent poor prognostic indicator for DFS (HR 1.65, 1.05-2.61).** Other predictors: >3 mets, + margins BT is not a predictor of OS. Predictors were age>70, CCI>8, and major resection

HCC = hepatocellular carcinoma; CRM = colorectal metastases; CCA = cholangiocarcinoma; BT = red blood cell transfusion; OS = overall survival; DFS = disease-free survival; HCC = hepatocellular carcinoma; CRM = colorectal metastases; HbsAg = hepatitis B surface antigen; AFP = alpha fetoprotein; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ICGR15 = indocyanine green retention rate at 15 minutes; Hgb = hemoglobin level; EBL = estimated blood loss; C-P = Child-Pugh; CEA = carcinoembryonic antigen; HR = hazard ratio; MELD = Model for End Stage Liver Disease; anti-HCV = anti-hepatitis C virus antibody; PT = prothrombin time; MVI = microvascular invasion; BMI = body mass index; FFP = fresh frozen plasma ASA = American Society of Anaesthesiologists' Physical Status Classification System; CCI = Charlson Comorbidity Index; ; IPTW = inverse probability of treatment weighting;CA 19-9 = carbohydrate antigen 19-9; LVI =

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2. Current practices in perioperative blood management for patients undergoing liver resection: a survey of surgeons and anesthesiologists

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2.1. Abstract

Background: The development of new techniques and blood management strategies in liver resection, the lack of large clinical trials and synthesized evidence, and the multidisciplinary nature of perioperative transfusion decision-making, creates an opportunity for practice variation within and between centres. The aim of this study was to describe the current practices in perioperative blood management, and explore differences between surgeons and anesthesiologists.

Methods: A standardized survey was circulated to Canadian liver surgeons and anesthesiologists. The survey focused on management of pre-operative anemia, blood conservation strategies, estimation of blood loss, and transfusion decision-making in a multidisciplinary setting.

Results: 198 physicians received the survey and 117 responded (59.1%). Most responding surgeons (66.7%) perform over 20 liver resections per year, while most responding anesthesiologists (90%) take part in less than 20 per year. The most common blood conservation strategy used is administration of anti-fibrinolytics (63% used them at least occasionally). The most important factor for anesthesiologists when deciding on an intraoperative transfusion was hemoglobin value (47.2%); for surgeons, it was patient hemodynamics (33.4%). Compared to when they started their career, 60.5% of respondents felt they were less likely to transfuse a patient in their current practice.

Discussion: The results of our survey provide insights into current transfusion practice and decision-making in liver resection, including important differences between anesthesiologist and surgeon transfusion behaviour.

2.2. Introduction

Perioperative blood management for patients undergoing liver resection has changed a great deal over the past several decades. Advances in surgical and anesthestic techniques, and alterations in the definitions of resectability have changed how patients are managed before, after, and during surgery. Currently, manipulation of the central venous pressure (CVP), vascular clamping techniques, dissection devices, topical hemostatic agents, and pharmacologic agents such as anti-fibrinolytics, are used to reduce blood loss in liver surgery[1]. The introduction of these techniques, in addition to changes in transfusion hemoglobin thresholds over time[2], appears to have decreased transfusion rates overall, with a large, single-centre study demonstrating a decrease in transfusion prevalence from 83% in the late 1980s, to 43% in the late 1990s[3]. Current evidence suggests that approximately 22% of liver resection patients in North America receive a perioperative transfusion[4]. There is limited high-quality evidence on the impact of blood loss and blood transfusions in liver resection, although some retrospective data suggest transfusions may lead to increased complications and cancer recurrence, independent of known confounders[3,5,6]. Evidence from other areas of surgery and medicine suggest that a more restrictive use of red blood cell (RBC) transfusions is at least equivalent, or possibly beneficial[2,7], compared to liberal transfusion practices.

Despite the numerous techniques and interventions that can be employed in the perioperative blood management of patients undergoing liver resection, there is little guidance for best practices, and little is known about the current transfusion practices of both surgeons and anesthesiologists. Previous work has demonstrated variability amongst surgeons in regards to diagnostic, surgical, and post-operative management for liver and biliary procedures[8]. Our overall objective was to assess the current status of perioperative blood management amongst Canadian surgeons and anesthesiologists involved in liver resections, including, techniques employed, information used for decision-making, and the dynamic of having multidisciplinary decision-makers involved in transfusion decision-making.

2.3. Methods

2.3.1. Survey generation and testing

This study received approval from the Ottawa Health Science Research Ethics Board (20160063-01H). A web-based, 14-question survey was developed using a systematic approach, focusing on perioperative blood management decision-making. First, survey items were generated based on a review of the literature and interviews with clinical experts. Next, the survey was distributed amongst study authors and item reduction was performed for clarity and feasibility. Finally, the survey was piloted by two surgeons and two anesthesiologists to ensure content validity, clarity, and understanding.

Basic demographics, type of training, years in practice, type of practice, and practice volume were collected. Clinical questions pertained to management of preoperative

anemia, the use of perioperative blood conservation techniques, techniques to estimate blood loss, information used when deciding to transfuse, and the decision-making dynamics amongst care providers. The survey was written in both French and English, and was hosted on fluidsurveys.com.

2.3.2. Target Population

Thirty-one hospitals across Canada were identified as performing liver resections. Within these 31 centres, a link to the survey was distributed via email to 75 surgeons who were identified as performing liver surgery. For distribution to anesthesiologists, one point of contact within the anesthesiology department was made for each hospital. Surveys were then circulated to each member who provides anesthesia for liver resections. The survey was distributed to 123 anesthesiologists. Because the purposes of our study were primarily descriptive, we did not specify a specific sample size, but instead attempted to define and access a sample frame that was representative of perioperative physicians involved in liver surgery on a national basis, and attempted to optimize our response rate through provision of a reminder email which was circulated 4 weeks after the initial email. The survey was closed after 8 weeks.

2.3.3. Analysis

Descriptive data were collected and analyzed using the fluidsurveys analytics tool. Comparative statistical analyses (Chi-square, t-test) between surgeons and

anesthesiologists were performed using SAS 9.3 (SAS Institute Inc., Carry, NC, USA). A p-value of less than 0.05 was considered statistically significant.

2.4. Results

The survey was distributed to 75 surgeons, with 42 respondents (56%); and 123 anesthesiologists, with 75 respondents (61%). Overall response rate was 59.1%. Three anesthesiologists responded that they did not participate in liver resections, therefore 72 completed the full survey. Participant demographics are presented in Table 1. The majority of surgeons and anesthesiologists practice in an academic university-affiliated centre (87%) that performs over 25 liver resections per year (91%). The majority of surgeons (66.7%) perform at least 20 liver resections themselves per year, while the majority of anesthesiologists (90%) participate in less than 20. Most surgeons (86%) are fellowship-trained, primarily in hepatobiliary/transplant, with several in surgical oncology. A slightly smaller proportion of anesthesiologists have fellowship training (62.5%), with a wider variety of fellowship types. Overall, there was a wide range of years in practice (1 to 36). Mean (standard deviation(SD)) number of years in practice for the entire cohort was 13.7 (9.05).

2.4.1. Preoperative blood management

According to anesthesiologists, pre-operative anemia was most commonly managed by another practitioner (37.5%) or by way of a blood conservation program (27.8%).

Surgeons primarily prescribed no specific preoperative treatment (45.2%) or oral iron therapy (19%). Of total respondents, 14% selected “other”, citing individualized approaches and insufficiently brief time frames between assessment and the scheduled operation (Figure 1).

2.4.2. Intraoperative blood management

Practitioners were asked about their frequency of use of intraoperative blood conservation techniques (Figure 2). Overall, the most commonly used was the administration of anti-fibrinolytics, with 63% using it at least “occasionally”. Intraoperative cell salvage was used at least occasionally by 51% of respondents. Much less commonly used techniques included acute normovolemic hemodilution (ANH) (20%) and intraoperative whole blood phlebotomy (14%).

The frequency of use for various ways to estimate blood loss is seen in Figure 3. Nearly all anesthesiologists reported that they either “always” or “most of the time” used each of the five techniques (observing surgical field, observing surgical sponges, observing suction canister, hemoglobin lab value, patient hemodynamics). Most surgeons also used all five techniques at least “most of the time”. They were less likely to report “always” using hemoglobin values ($p=0.002$), and patient hemodynamics ($p=0.0003$).

The most important factor when deciding to give an RBC transfusion (Figure 4) was patient hemodynamics for surgeons (33.4%), and hemoglobin lab values for anesthesiologists (47.2%). Both groups ranked their “estimation of accumulated and ongoing blood loss” as the second most important factor. “Discussion with the other

physician” was the most important factor for 19% of surgeons and 0% of anesthesiologists. Nine responded “other”, all commenting that it is a combination of these factors.

In the operating room, the anesthesiologist was most commonly reported as being the primary decision-maker for transfusions, by both surgeons and anesthesiologists (76% vs. 99%, $p<0.0001$). In the post-anesthesia care unit (PACU), anesthesiologists continued to report themselves as the primary decision maker (97%), while 57% of surgeons reported this to be true ($p<0.0001$); the remainder reporting the surgeon or surgery resident as primary decision maker. On the inpatient ward, there was little difference between the two groups of respondents, with 71% of all respondents reporting the surgeon as primary decision maker, and 28% reporting the surgery resident (Figure 5).

When asked how likely they are to transfuse a patient now, compared to the start of their career, 8.3% of anesthesiologists reported “more likely”, 40.3% “as likely”, and 51.4% “less likely”. Conversely, no surgeons reported being more likely, with 23.8% and 76.2% reporting “as likely” and “less likely”, respectively. Among all 114 respondents, the mean number of years (SD) in practice for those who answered “more likely” or “as likely” to transfuse was 9.2 (7.1), compared to 16.7 (9.0) years for those who are “less likely” to transfuse ($p<0.00001$).

2.5. Discussion

Our survey of Canadian surgeons and anesthesiologists outlines current practices in perioperative blood management in Canada for patients undergoing liver resection. Overall, physicians may be less likely to transfuse packed red blood cells now than in the past, yet wide variation in the management of pre-operative anemia as well as the use of intraoperative blood conservation techniques was demonstrated. Importantly, the primary decision maker regarding transfusion was perceived to vary depending on the phase of the perioperative period, which highlights the complexities and multidisciplinary nature of perioperative blood management in the setting of liver surgery.

Perioperative blood management and transfusion decision making is complex, especially in the setting of liver resection, where substantial blood loss can occur rapidly in the context of the steady ongoing blood loss often associated with parenchymal resection. Our findings highlight several important themes that inform this complex process. First, the primary decision maker for transfusion appears to vary in the different phases of the perioperative period. Interestingly, neither surgeons nor anesthesiologists appear to be substantively involved in the management of preoperative anemia, which may be the primary risk factor for intraoperative transfusion[6,9,10]. This may be an important opportunity for increased detection and management of preoperative anemia, possibly with the involvement of hematology or internal medicine. Intraoperatively, transfusion decisions are most commonly made by the anesthesiologist. Furthermore, responding anesthesiologists did not appear to approach this decision in consultation with the surgical team. While this may be rational

in the setting of rapid blood loss and hemodynamic instability, with the surgeon focussed on addressing the source of losses and the anesthesiologist with resuscitation, this is not the context for all transfusions in the operating room. In the postoperative phase, transfusion decisions in the PACU appear to be more evenly shared between surgeons and anesthesiologists, while on the inpatient unit surgeons were almost exclusively responsible.

In addition to the perceived differences in which clinician was the primary decision maker, differences also emerged regarding reasons to transfuse. Anesthesiologists reported relying on intraoperative hemoglobin values most often, while surgeons tended to favor reasons of hemodynamic status. The operating room is one of the few settings in medicine where there is more than one most responsible physician, however, there is limited literature on collaborative decision-making between surgeons and anesthesiologists. Regardless of the reason to transfuse, however, nearly two-thirds of all respondents reported that they are less likely to transfuse a patient now compared to when they started their career. Therefore, despite an overall behavioural trend toward decreasing transfusion, which is supported by clinical studies, this decision-making dynamic, and evidence that each provider utilizes somewhat different information, highlights the importance of effective team communication and the development of clinical practice guidelines for decisions such as blood transfusions in this setting.

Blood loss is an independent predictor of morbidity and mortality in liver resection[11], emphasizing the importance of enhancing blood conservation strategies. As noted, neither surgeons nor anesthesiologists appear to be routinely involved in the treatment of preoperative anemia. In the intraoperative phase, the current study demonstrates

very infrequent use of ANH, similar to a 2014 survey of Canadian liver surgeons[8]. This may reflect the findings of a 2012 Cochrane review[12] that found ANH to not significantly reduce blood loss, although, it can reduce use of allogeneic RBC transfusions. We did find that an increasing number of respondents are using anti-fibrinolytics and cell salvage either “occasionally” or “most of the time”. The use of anti-fibrinolytics in liver resection is supported by a randomized controlled trial which found tranexamic acid to be associated with reduced blood loss and transfusions compared to placebo[13], while another recently completed clinical trial of tranexamic acid in liver resection is awaiting publication[14]. Whole blood phlebotomy, a technique similar to ANH but without crystalloid replacement, appears also to be used infrequently in Canada. It has been described more so in liver transplantation[15], but a clinical trial in liver resection is also underway[16].

Overall, the majority of liver resections are performed at academic health science centres, and most responding surgeons performed more than 20 liver resections per year, which suggests that most Canadian liver resection patients may be benefiting from centralized high volume surgeons[17-19]. However, most responding anesthesiologists cared for fewer than 20 liver resection patients per year. Although response bias could explain the high volume surgeon findings, our response rate of 60% suggests that this is not entirely the case. Recent evidence in the liver transplantation literature suggests that anesthesiologist experience can significantly impact patient outcomes[20]. Therefore, future efforts to improve the care and outcomes of patients undergoing liver resection through decreases in practice variation, including blood management, could consider engaging high-volume perioperative teams.

This nationwide survey of providers is strengthened by its favourable response rate of 59%, leading to a reasonable representation of the population of interest, and a decrease in non-response bias. This response rate is similar to other surveys of Canadian surgeons and anesthesiologists[8,21,22], and is slightly higher than the mean physician response rate reported in a systematic review of surveys[23]. The sample size of 114 is a good representation of care providers across the country. Furthermore, the survey methods followed best practice recommendations[24], including rigorous piloting by both surgeons and anesthesiologists before being circulated.

Limitations of the study primarily include those inherent to surveys, namely sampling bias, nonresponse bias, and measurement bias. Sampling and non-response bias were limited by the good response rate, however those providers with a more specific interest in blood management may have been more likely to complete the survey. Potential measurement bias was limited by piloting the survey before distribution. As the same survey was circulated to both surgeons and anesthesiologists, there were no questions regarding specific surgical techniques such as parenchymal transection technique or portal pedicle clamping. Furthermore, the survey did not explore regional variations. Delivery of hepatobiliary surgery in Canada is highly centralized[25], and therefore the survey findings may be less applicable to countries performing more liver resections in lower volume centres. As noted by Truong et al[8], many Canadian anesthesiologists and hepatobiliary surgeons receive training abroad and participate in international conferences, thereby lending increased generalizability to the findings.

In summary, our survey describes the commonalities and differences between surgeons and anesthesiologists in perioperative blood management for patients undergoing liver

resection. It may give providers a common understanding from which to improve upon team communication skills in the operating room. The findings reflect trends toward restrictive transfusion strategies, and promote the development of improved blood conservation techniques and clinical practice guidelines.

Table 1. Practice pattern of survey respondents

		Surgeons (n=42)	Anesthesiologists (n=72)	Total cohort (n=114)
Years in practice	**0-5**	8 (19%)	15 (20.8%)	23 (20.2%)
	6-10	11 (26.2%)	15 (20.8%)	26 (22.8%)
	11-15	8 (19%)	15 (20.8%)	23 (20.2%)
	16-24	7 (16.7%)	12 (16.7%)	19 (16.7%)
	25+	8 (19%)	15 (20.8%)	23 (20.2%)
Type of practice	**Academic**	37 (88.1%)	62 (86.1%)	99 (86.8%)
	City/community	3 (7.1%)	10 (13.9%)	13 (11.4%)
	Small community	1 (2.4%)	0	1 (0.9%)
Fellowship	**Yes**	36 (85.7%)	45 (62.5%)	81 (71.1%)
	No	6 (14.3%)	27 (37.5%)	33 (28.9%)
# of liver resections performed (per year)	**1-5**	5 (11.9%)	27 (37.5%)	32 (28.1%)
	6-10	2 (4.8%)	22 (30.5%)	24 (21.0%)
	11-20	7 (16.6%)	16 (22.2%)	23 (20.2%)
	21-39	17 (40.5%)	6 (8.3%)	23 (20.2%)
	40+	11 (26.2%)	1 (1.4%)	12 (10.5%)
# of liver resections performed at your hospital (per year)	**1-10**	1 (2.4%)	1 (1.4%)	2 (1.8%)
	11-25	3 (7.2%)	5 (6.9%)	8 (7.0%)
	26-50	10 (23.8%)	19 (26.4%)	29 (25.4%)
	51-99	14 (33.3%)	23 (31.9%)	37 (32.5%)
	100+	14 (33.3%)	20 (27.8%)	34 (29.8%)
	NR	0	4 (5.6%)	4 (3.5%)

NR = no response

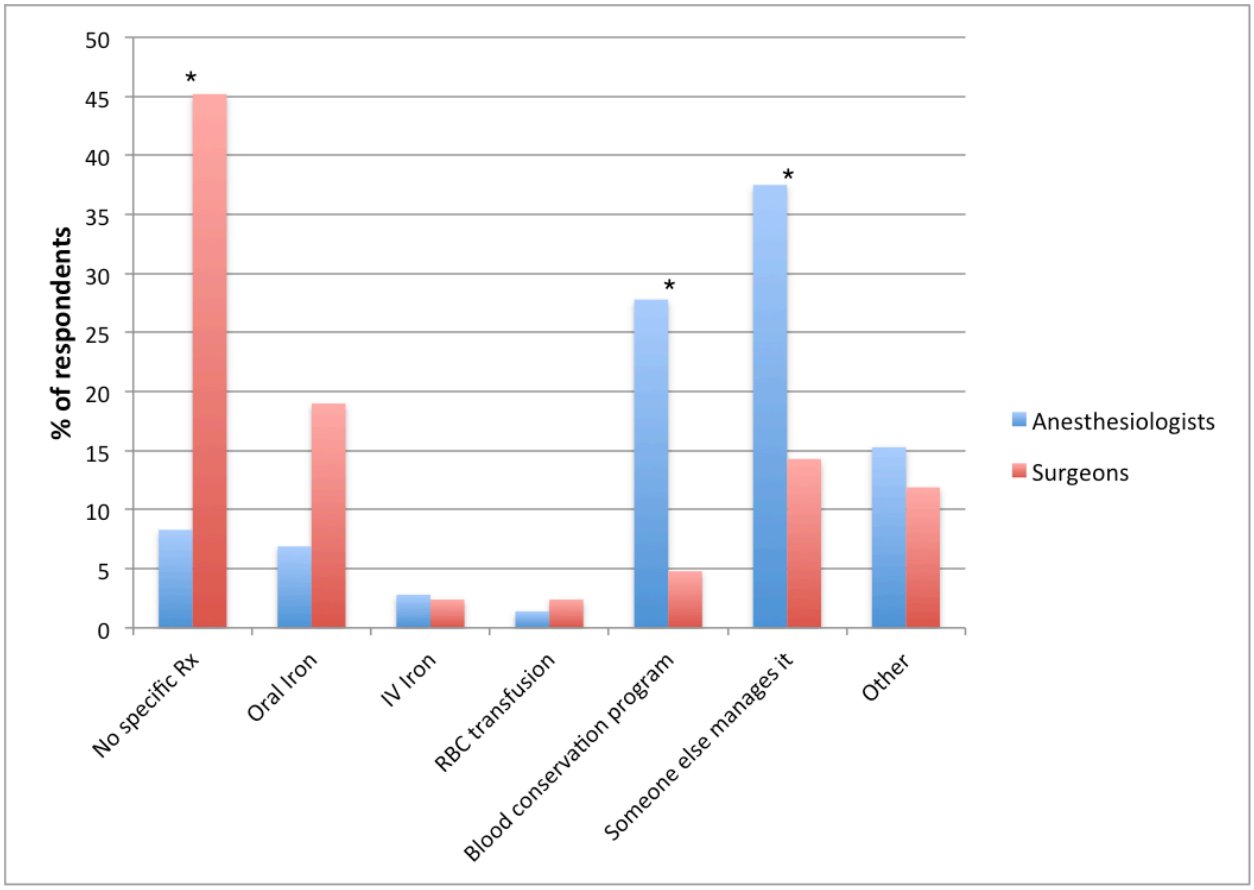

Figure 1. Responses to the question "How do you typically manage pre-operative anemia?" Rx = treatment, IV = intravenous, RBC = red blood cell. (*$p<0.05$)

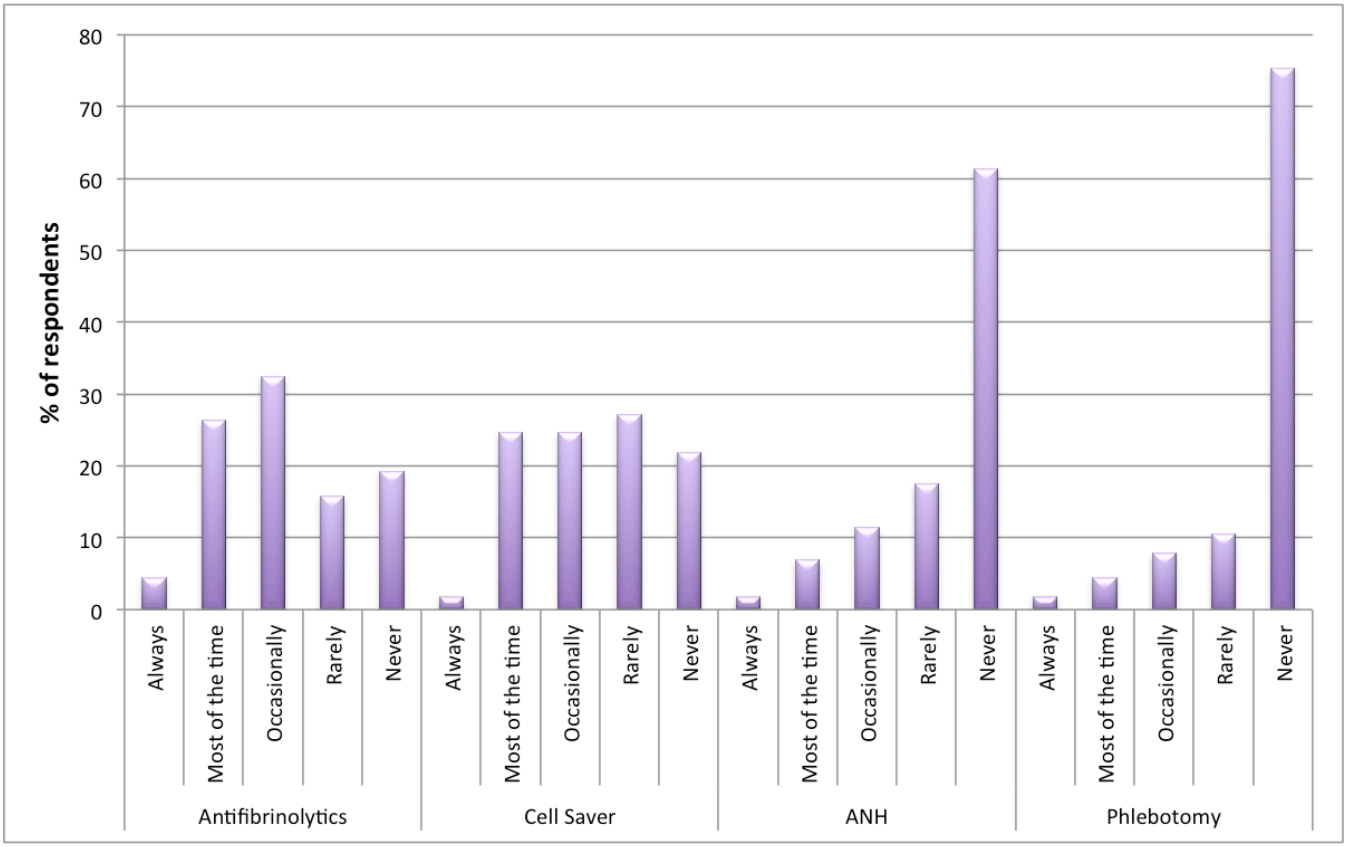

Figure 2. All responses to the question "Do you ever employ the following perioperative blood conservation techniques?"; ANH = acute normovolemic hemodilution, Phlebotomy = intraoperative whole blood phlebotomy

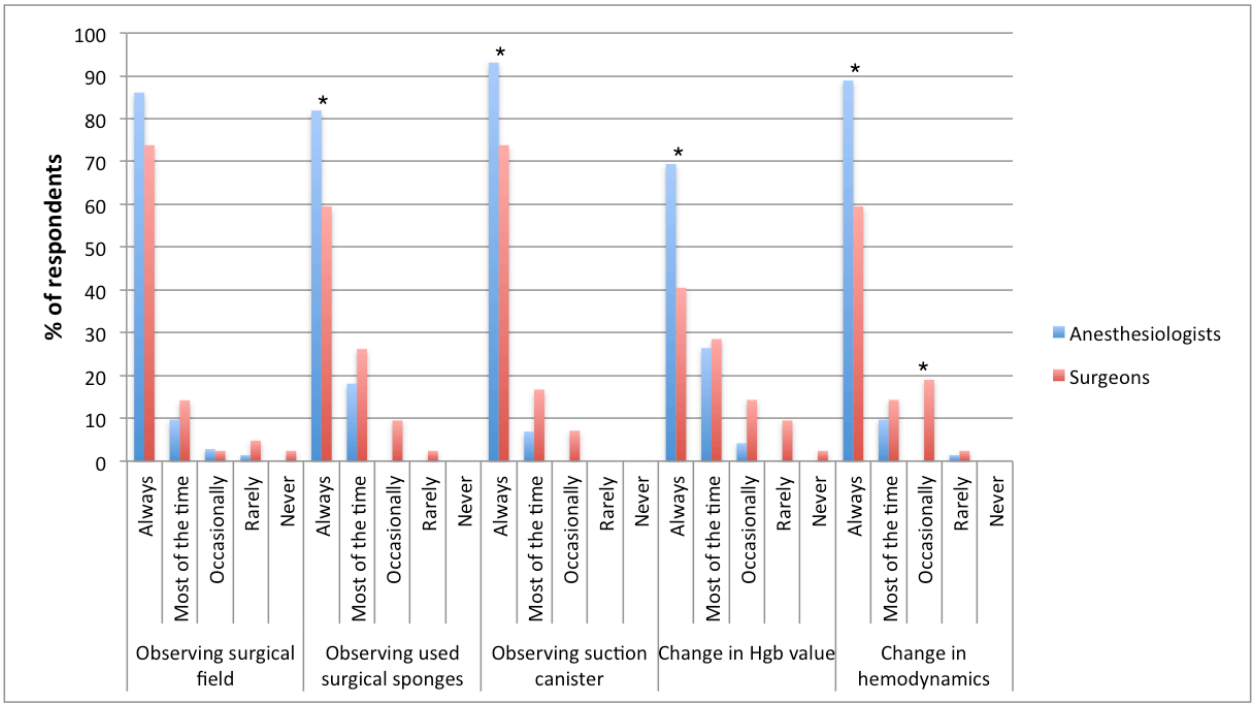

Figure 3. Responses to the question "What techniques do you use to estimate intraoperative blood loss in liver resections?"; Hgb = hemoglobin. (*p<0.05)

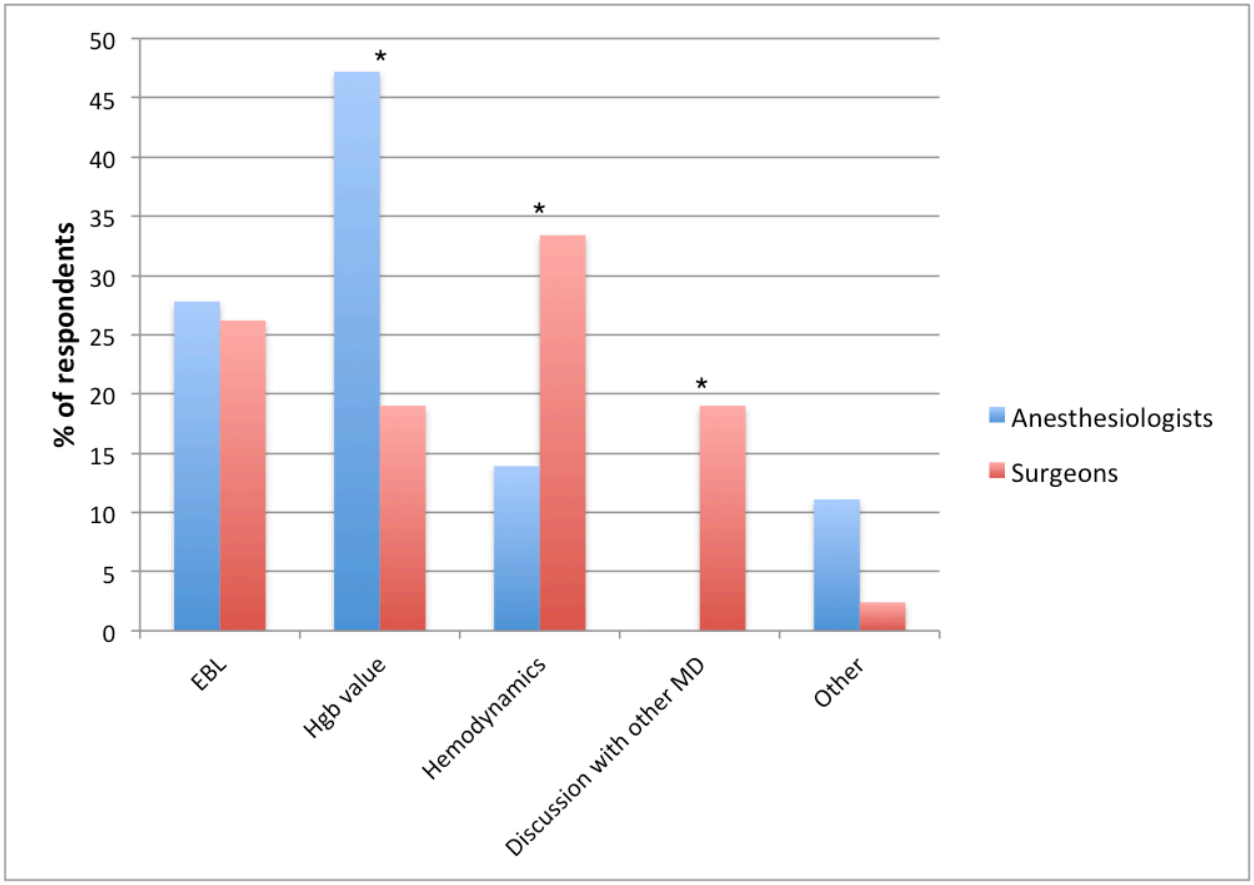

Figure 4. Responses to the question "What is the most important information you use to decide on intraoperative blood transfusion?"; EBL = estimated blood loss, Hgb = hemoglobin, MD = medical doctor (*$p<0.05$)

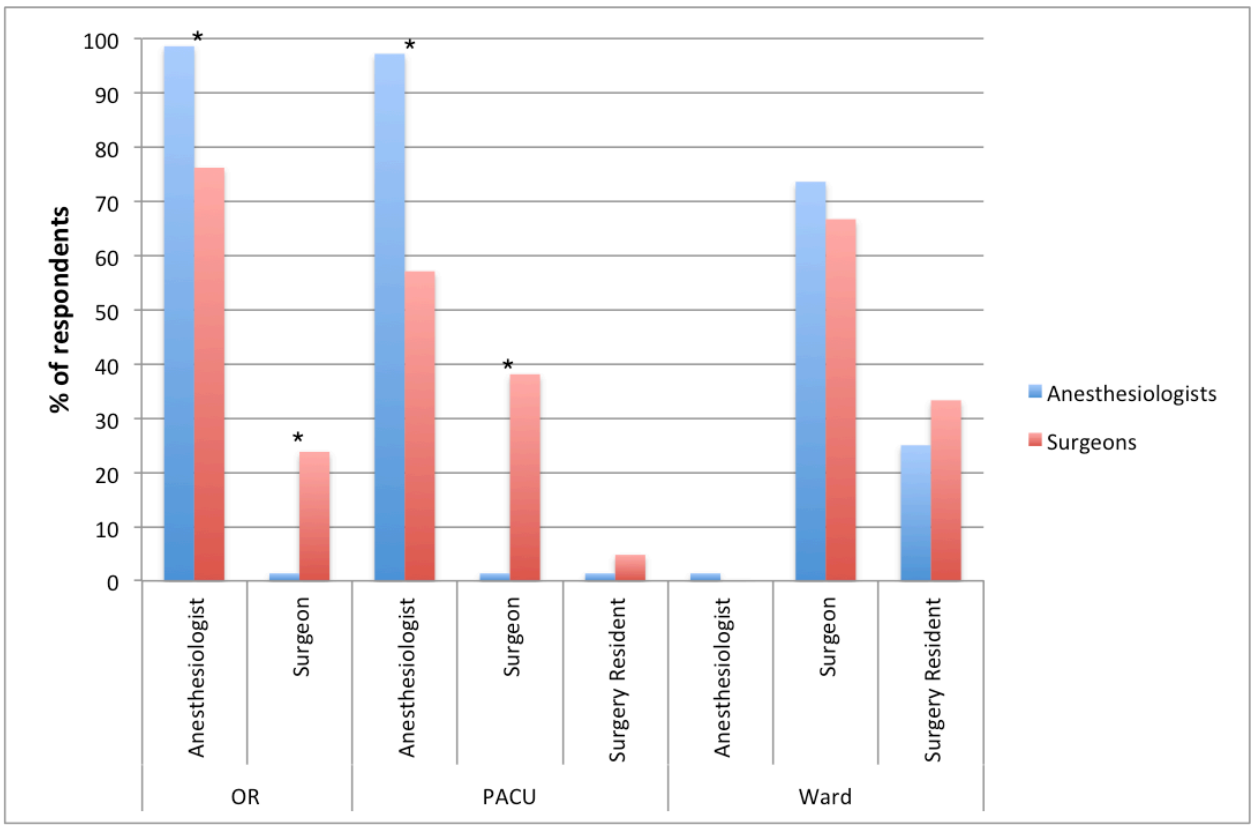

Figure 5. Responses to "Who is the primary decision maker regarding blood transfusions?"; OR = operating room, PACU = post-anesthesia care unit (*p<0.05)

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3. Using the RAND/UCLA Appropriateness Method

~This chapter is a modified version of a term paper previously written for EPI 5343 (May 4, 2016). Used by permission of Prof. Ian McDowell~

3.1. Introduction

The RAND/UCLA Appropriateness Method (RAM) aims to identify the clinical scenarios for which a given intervention of interest is either appropriate or inappropriate. It was first developed in the 1980s as a technique to measure the overuse or underuse of medical interventions. The technique begins with a systematic review of the literature, followed by the creation of multiple clinical scenarios that would be expected to be encountered, and for which the intervention would be considered. Both the systematic review and the list of clinical indications are sent out to a multidisciplinary group of experts, identified by the researchers. In addition, instructions on how to rate the scenarios and any definitions used are circulated as well. The panelists then rate each scenario in two iterations: initially by themselves, and then in an in-person, moderated panel session during which they can discuss the scenarios, particularly areas of disagreement, and alter their responses. The method does not require consensus, in fact, areas of uncertainty and disagreement can inform future research. The scale used in the RAM is a 1 to 9 ordinal scale, with 1 meaning “highly inappropriate”, and 9 meaning “highly appropriate”. Based on the median score,

each scenario is then classified as either inappropriate (1-3), uncertain (4-6), or appropriate (7-9)[1].

The RAM has been used for multiple medical and surgical interventions; even for routine procedures seen in every emergency department and inpatient unit, such as urinary catheters and intravenous catheters[2,3]. A 2011 systematic review found that in the United States alone, the RAM had been used to develop appropriateness criteria for 16 separate surgical procedures: coronary artery bypass grafting (CABG), bariatric procedures, abdominal aortic aneurysm surgery, carotid endarterectomy, hysterectomy, nephrectomy for metastatic renal cell cancer, cholecystectomy, upper endoscopy, colonoscopy, cataract procedures, tympanostomy tube placement, sinus procedures, low back surgery for sciatica, sentinel lymph node biopsy for melanoma, tonsillectomy, and carpal tunnel release[4]. Furthermore, these appropriateness criteria were used to assess for overuse and underuse of various populations in 27 different studies. The authors compared the procedures for which an appropriateness criteria had been created to a list of the most commonly performed inpatient and outpatient surgical procedures in the USA. They concluded that appropriateness criteria exist for 10 of the 25 most commonly performed inpatient procedures, and 6 of the 15 most commonly performed outpatient procedures. Examples of some of the inpatient and outpatient procedures lacking appropriateness criteria include knee arthroplasty, appendectomy, colorectal resection, inguinal hernia repair, and breast surgery[4].

3.2. Reliability and Validity of the RAM

A 2013 systematic review evaluated the reliability and validity of the RAM for surgical procedures[5]. The review screened 395 articles, and included 37 articles; 5 assessed reliability, 21 validity, and 17 assessed the effect of changing the composition of the panel. The studies were published between 1987 and 2006.

3.2.1. Reliability

Four studies were identified that assessed the test-retest reliability of the RAM. These studies involved patients undergoing carotid endarterectomy[6], coronary artery bypass grafting[7], total hip replacement[8], and total knee replacement[9]. The panelists in each study were asked to re-rate between 2-25% of the scenarios 6 months to 1 year after the initial rating. Three of the studies used a weighted kappa, demonstrating a range from 0.64 to 0.78. This is an indication of good agreement. The final study chose to report Spearman rank correlation coefficients, and showed a range from 0.75 to 0.96[6]. In no study did they find any evidence of discordance, where a given scenario changed from being rated appropriate to inappropriate, or vice versa.

To test between-panel reliability, one study reported the findings of two appropriateness studies performed with two completely different panels, for both

CABG and hysterectomy. Using a three-way weighted kappa, these scored 0.52 and 0.51 respectively, consistent with moderate agreement[10].

3.2.2. Face Validity

Medical decision-making is done by healthcare practitioners. Their decision-making is typically informed by their training, their experience, their assessment of the medical literature, and clinical practice guidelines. The RAM utilizes the best available evidence from the medical literature in combination with the opinion of medical experts (based largely on their training and experience) to create a type of clinical practice guideline. Therefore, at face value, the RAM technique is certainly valid at determining the appropriateness of medical interventions in various scenarios.

3.2.3. Construct Validity

Eight studies were identified that aimed to compare the results of RAM appropriateness studies to published guidelines using other methods. These studies demonstrated very similar results. One example classified 1115 patients undergoing upper endoscopy. Using appropriateness criteria, reported rates of appropriate and inappropriate use were 90.1% and 6.7%, respectively. Using the American Society of Gastrointestinal Endoscopy (ASGE) guidelines, the reported rates were 93.5% and 3.7%[11]. Thus the authors concluded that the RAM

demonstrates good construct validity when compared to widely accepted clinical guidelines. Furthermore, four of these studies concluded that the RAM technique was able to classify more patients than were classified by the guidelines[5].

3.2.4. Predictive Validity

In order to ascertain whether correctly applied appropriateness criteria can result in improved clinical results, four studies were identified that measured the predictive validity of the RAM. These were all done in patients undergoing coronary revascularization procedures. Studying only patients who were classified as being appropriate for revascularization, two studies demonstrated decreased mortality among patients who were revascularized versus those who were treated medically (9% vs 19% and 9.1% vs 23.3%, both $p<0.05$)[12,13]. For patients classified as inappropriate for CABG, one study demonstrated decreased mortality in those who did not undergo surgery versus those who did (11.9% vs 20%, $p<0.05$)[14]. These results clearly demonstrate that applying the appropriateness criteria to clinical decisions can improve patient care.

This systematic review of the literature clearly supports the reliability and validity of the RAM. In comparison to other methods of determining clinical appropriateness, such as clinical practice guidelines, decision analysis, and probability estimation; the RAM has much more published evidence on its

reliability and validity[5]. Most impressively, the RAM shows excellent predictive validity, showing that the appropriateness criteria can be directly applied to clinical situations with a demonstrable improvement in outcomes. Within the realm of transfusion medicine, the RAM was used with a multidisciplinary panel of 15 experts to assess appropriateness of RBC transfusion in stable, nonbleeding patients[15]. While being a different patient population than those undergoing liver resection, this clearly demonstrates feasibility of the RAM to study blood transfusion as the intervention of interest.

3.3. Conclusion

The appropriate use of perioperative blood transfusions in patients undergoing liver resection requires interpretation of multiple pieces of clinical data, laboratory data, and patient characteristics. This, in addition to the dynamic environment of the operating room, makes for a very difficult question to answer using prospective clinical trials. To address the multiple pieces of clinical information, and the many possible patients undergoing liver resection, an appropriateness study is ideal. As has been demonstrated, the RAND/UCLA Appropriateness Method is a well-established technique that has been used for over three decades. It has been used to assess multiple medical interventions for their appropriateness. Within the realm of surgery, the reliability and validity of the RAM has been demonstrated through multiple publications, and clinical guidance from appropriateness criteria has been used with improvements in clinical

outcomes. Furthermore, there is a paucity of appropriateness criteria for a number of commonly performed surgical interventions. Therefore, the door is open for further study using this technique.

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4. The Ottawa Criteria for Appropriate Transfusions in Hepatectomy (OCATH): using the RAND/UCLA Appropriateness Method

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4.1. Abstract

Objective: Develop practice guidelines for the appropriate use of blood transfusions in hepatectomy.

Summary background data: Hepatectomy is associated with a high prevalence of blood transfusions. A transfusion can be life-saving, but is associated with important adverse effects. Given their prevalence, their potential for benefit and harm, and the difficulty in conducting clinical trials, transfusion in hepatectomy is well-suited for a study of appropriateness.

Methods: This study used the RAND/UCLA Appropriateness Method. An international, multidisciplinary expert panel in hepatobiliary surgery, anesthesia, transfusion medicine, and critical care were asked to rate a series of 468 perioperative scenarios for transfusion appropriateness. Scenarios were rated individually, and again during an in-person moderated session. Median scores and level of agreement were calculated to classify each scenario as appropriate, inappropriate, or uncertain.

Results: 48% of scenarios were rated appropriate, 28% inappropriate, and 24% uncertain. The key recommendations for intraoperative transfusion were:
1) it is never inappropriate to transfuse for significant bleeding or ST segment changes, 2) it is never inappropriate to transfuse for an intraoperative hemoglobin $\leq$ 75g/L, and 3) without significant bleeding or ST changes, a transfusion for

hemoglobin ≥ 95g/L is inappropriate, and a transfusion for hemoglobin of 85g/L requires strong justification. The key postoperative recommendations were:
1) in a stable, asymptomatic patient, an appropriate transfusion trigger is 70g/L (without coronary artery disease) or 80 g/L (with coronary artery disease), and 2) it is appropriate to transfuse for a hemoglobin of 75 g/L either immediately post-operative, or with a significant decrease from the previous day (>15g/L).

Conclusions: Based on best available evidence and expert opinion, we have developed criteria for appropriate perioperative blood transfusions in hepatectomy.

4.2. Introduction

Hepatectomy, or liver resection, is associated with significant blood loss and the use of perioperative red blood cell transfusions. Changes in surgical technique and technology, as well as the potential adverse effects of blood transfusion, have resulted in a decrease of transfusion prevalence in hepatectomies over time. A large, single-centre study demonstrated that the proportion of patients receiving a transfusion decrease from 83% in the late 1980s, to 43% in the late 1990s[1]. Another study of hepatectomies in 2013 demonstrated that 22.1% of patients received a perioperative transfusion[2]. Blood transfusions have the ability to be life saving, but they are also associated with adverse effects, including allergic, febrile, hemolytic, and immunomodulatory reactions, as well as administrative errors.

Currently, there is a lack of evidence-informed clinical guidelines on the appropriate use of perioperative blood transfusions. American Association of Blood Banks (AABB) guidelines[3] focus solely on the hemodynamically stable patient, and draw their recommendations primarily from studies in critical care, cardiac surgery, orthopedic surgery, and acute gastrointestinal bleeding. While helpful, they cannot be fully applied to patients undergoing major abdominal or oncologic surgery. There have been calls for transfusion trials in major abdominal surgery, and liver surgery in particular[4], as well as for the development of patient-specific blood management protocols for optimal perioperative transfusion triggers[5].

Given its high prevalence, its ability for both benefit and harm, and the difficulty in studying its effects in a clinical trial, blood transfusion strategies for patients undergoing hepatectomy is an ideal intervention for a study of appropriateness. For a given intervention, appropriateness studies combine the best available scientific evidence and expert opinion, in the form of a consensus conference, to determine the indications for which "the expected health benefit (e.g. increased life expectancy, relief of pain, reduction in anxiety, improved functional capacity) exceeds the expected negative consequences (e.g. mortality, morbidity, anxiety, pain, time lost from work) by a sufficiently wide margin that the procedure is worth doing, exclusive of cost"[6]. The RAND/UCLA Appropriateness Method (RAM) is a widely used technique to measure the appropriateness of medical and surgical interventions[7-11]. In a systematic review of studies focusing on surgical procedures, the RAM has been shown to be both reliable and valid[12].

The objective of the current study is to utilize the RAM process to develop clinical guidelines for the appropriate use of perioperative red blood cell transfusions for patients undergoing hepatectomy.

4.3. Methods

4.3.1. The RAND/UCLA Appropriateness Method (RAM)

The specifics of the RAM have been previously published[13]. In brief, it consists of a systematic review of the literature; the creation of multiple realistic clinical scenarios for which the intervention of interest may be considered; and the rating of these scenarios in two iterations, by a multidisciplinary panel of experts from multiple centres. A rating for each scenario is completed using an ordinal 1 to 9 scale; 1 meaning “highly inappropriate”, and 9 meaning “highly appropriate”.

4.3.2. Systematic Review

We performed a systematic review of the literature pertaining to the epidemiology and impact of perioperative red blood cell transfusion on post-operative mortality, morbidity, and cancer survival in patients undergoing hepatectomy. The systematic review protocol[14] and the systematic review[15] have both been previously published. The systematic review results were distributed to the expert panel members.

4.3.3. Expert Panel

A multidisciplinary group of 8 clinical experts from 5 hospitals in Canada and the United States were identified and enlisted to participate. These experts represent leaders in the fields of hepatopancreatobiliary surgery, surgical oncology, anesthesiology, transfusion medicine, and critical care medicine. The panel member information is presented in Table 1.

4.3.4. Clinical scenarios to be rated

The panelists were asked to rate 468 distinct clinical scenarios using the 1-9 RAM scale. The scenarios were created through an iterative process with input from surgeons, anesthesiologists, and transfusionists, and were designed to represent, as widely as possible, the scenarios for which a blood transfusion may be considered. The scenarios were based on six main patient encounters (chapters), within which a number of important clinical modifiers were used to create the 468 scenarios. The chapters and modifiers are shown in Table 2. There are three intraoperative, and three post-operative chapters. Definitions of key terms were provided to the panelists, to ensure a uniform understanding of each scenario. These definitions are provided in Table 3.

4.3.5. Rating the scenarios

The 468 scenarios, along with instructions, definitions, and the systematic review, were circulated to the eight panelists for round 1 of scoring. Based on their clinical expertise, and the best available evidence, they were asked to rate the scenarios independently and return their scores to the researchers (SB,DF,GM). Median scores and levels of agreement were calculated (described below). A second round of ratings was performed on March 9th, 2016 during an in-person, moderated session in Ottawa, Canada. The panel moderator (PH) was selected for his experience with the RAM process, and extensive clinical expertise in transfusion medicine and critical care. During the second round session, panelists discussed the scenarios, the evidence, and the rationale for their scoring, focusing primarily on areas that lacked agreement. Panelists were then able to change their scores based on the discussion, but were not required to come to a consensus. Seven of the eight panelists attended in person, with one panelist attending via teleconference.

4.3.6. Data Analysis

From each of the panelists' individual scores, median scores were determined for each scenario. The median score determined whether transfusion was inappropriate (1-3), uncertain (4-6), or appropriate (7-9) in each scenario. Since the panel had an even number of members, potential median scores of either 3.5 or 6.5 were both considered to be in the uncertain range. Each scenario was also

classified on its level of agreement. Agreement was defined as having fewer than 3 panelists rating the scenario outside of the 3-point "appropriateness range" within which the median fell. Disagreement was defined as 3 or more panelists rating the scenario in the inappropriate range, and 3 or more in the appropriate range. Scenarios meeting the criteria for disagreement were considered to have an appropriateness grade of uncertain, regardless of their median score.

To determine the effect that various clinical factors had on the appropriateness score, comparisons were made between scenarios that did and did not feature the clinical factor of interest. For example, to assess the impact of blood loss on the appropriateness score, chapters 1 and 2 were compared to see in what proportion of scenarios was the appropriateness rating increased (from inappropriate to uncertain, or uncertain to appropriate). Chapter 1 and 2 are identical except for the volume and rate of blood loss (1000ml of consistent bleeding vs. ≥1500ml with major hemorrhage).

4.4. Results

4.4.1. Rater Agreement

After round 1, there was agreement on 268 of 468 (57.3%) scenarios. This was slightly lower for the intraoperative scenarios (54.5%) than the postoperative scenarios (61.7%). Following the round 2 panel session, agreement increased to 334 of 468 (71.4%), with intraoperative scenarios again showing slightly less agreement (69.1%) than postoperative (75%). The level of disagreement reduced

significantly after the round 2 panel session (4.1% to 0.4%). Disagreement after round 2 was found in two scenarios: 1) an 80 year old hemodynamically normal patient in the operating room without ST segment changes, with a history of coronary artery disease (CAD) but not cerebrovascular accident (CVA), 1000cc of fluid in the suction canister, and a hemoglobin (Hb) change from 125 g/L (pre-op) to 85 g/L (intraop); and 2) a 63 year old patient after major hepatectomy being assessed 3 hours post-operatively, with no history of CAD, heart rate above 110bpm, MAP of 55-60, and a Hb change of 120g/L to 85 g/L.

4.4.2. Overall Rating Results

Of the 468 scenarios rated after Round 2, 222 (47.4%) were assessed as appropriate, 132 (28.2%) were inappropriate, and 114 (24.4%) were uncertain. Of the 288 intraoperative scenarios, 165 (57.3%) were rated as appropriate, 40 (13.9%) were rated as inappropriate, and 83 (28.8%) were rated as uncertain. Of the 180 postoperative scenarios, 57 (31.7%) were assessed as appropriate, 92 (51.1%) were inappropriate, and 31 (17.2%) were uncertain. From Round 1 to Round 2, the median score for 71 scenarios (15.2%) changed by one point or more; 43 increased, 28 decreased, and 29 resulted in the median score moving from one category to another. Tables 4-9 provide the appropriateness scores for the various combinations of modifiers in the six patient chapters.

4.4.3. Estimated blood loss

Increased blood loss led to an upgrade of the transfusion appropriateness grade in 67.4% of possible scenarios (29 of 43). Looking at Chapter 2 (Table 5) alone (≥1500ml EBL with massive hemorrhage), only 1 of 96 scenarios received a grade of inappropriate. In all other scenarios, transfusion was considered either appropriate (72.9%) or uncertain (26%).

4.4.4. Hemodynamic abnormality

Intraoperatively, the presence of hemodynamic abnormality resulted in an increased appropriateness grade in 21 of 41 possible scenarios (51.2%) compared to scenarios with normal hemodynamics. In the immediate post-operative setting (Table 7), hemodynamic abnormality resulted in no change on the appropriateness grade at Hb lab values of 65, 95, or 105. At Hb values of 75 and 85, hemodynamic abnormality increased the appropriateness grade in 6 of 9 scenarios (66.7%). Similarly, in the POD 2 setting (Table 8), hemodynamic abnormality had no effect at Hb values of 65, 95, or 105. For Hb values of 75 and 85, hemodynamic abnormality increased the appropriateness grade in 6 of 9 scenarios (66.7%).

4.4.5. Intraoperative ST segment changes

Intraoperative ST segment changes resulted in an increased appropriateness grade in 30 of 44 possible scenarios (68.2%). Furthermore, of the 96 scenarios with ST segment elevation, no scenarios were considered inappropriate to transfuse. These scenarios were either appropriate (72.9%) or uncertain (27.1%).

4.4.6. History of CAD and CVA

Intraoperatively, a past medical history positive for CAD was associated with an increase in appropriateness grade in 36 of 73 scenarios (49.3%). History of CVA increased the appropriateness grade in 10 of 28 scenarios (35.7%).

In the immediate postoperative setting (Table 7), a history of CAD resulted in no change in appropriateness at Hb values of 65, 95, or 105 g/L. For Hb values of 75 or 85 g/L, a history of CAD increased the appropriateness grade in 6 of 9 scenarios (66.7%). On POD 2 (Table 8), history of CAD had no effect on appropriateness for Hb values of 65, 85, 95, or 105 g/L, and resulted in increased appropriateness grade in 2 of 3 scenarios (66.7%) with Hb 75 g/L. In the late postoperative setting (Table 9), history of CAD had no effect at Hb value of 95 and 105 g/L, or for asymptomatic patients at Hb 85 g/L. History of CAD resulted in an increased appropriateness grade for 10 of 10 scenarios with a Hb of 65, 75, or 85 g/L (with symptoms of lightheadedness and poor mobilization).

4.4.7. Hemoglobin lab value

Intraoperatively, the Hb lab value was not a major determinant of transfusion appropriateness in the presence of significant blood loss. This is evident in chapter 2 (Table 5), where only 1 of 96 scenarios was considered inappropriate. Of the 24 scenarios at the highest intraoperative Hb value (95 g/L), 25% were appropriate, and 71% were uncertain. At more moderate levels of EBL (Tables 4 and 6), transfusion for an intraoperative Hb value of 75 g/L or less was appropriate in 93% of cases and uncertain in 7%. Without ST segment changes, an intraoperative Hb of 85 was considered appropriate in 3%, uncertain in 78%, and inappropriate in 19% of cases. At Hb 95 g/L, without ST segment changes, transfusion was uncertain in 14%, and inappropriate in 86%.

In the immediate post-operative setting (Table 7), it was considered appropriate to transfuse for a Hb of 75 g/L in the majority of settings. Transfusion at a Hb of 85 g/L was mostly uncertain, or inappropriate in the hemodynamically normal patient without CAD. All scenarios with Hb $\geq$ 95 g/L were considered inappropriate.

On POD 2, all scenarios with Hb $\geq$ 95 g/L were inappropriate. At Hb of 85 g/L, transfusion was either inappropriate (33.3%) or uncertain (66.7%). For Hb of 75 g/L without history of CAD, the scenarios were either uncertain (50%) or appropriate (50%),.Comparatively, Hb of 75 g/L with a history of CAD was more often appropriate (83.3%) than uncertain (16.7%). Those with a Hb of 75g/L and a > 15g/L drop from the previous day were almost exclusively appropriate. A Hb of 65 g/L was considered appropriate in all scenarios.

On POD 6 (Table 9), all scenarios with Hb ≥ 95 g/L were inappropriate. All scenarios with Hb of 85 g/L were inappropriate, save for the patients with a history of CAD plus symptoms of anemia, which were uncertain.

4.4.8. Patient age

The effect of patient age on transfusion appropriateness can be seen in chapters 3 and 6 (Tables 6 and 9). In chapter 3, when comparing age 50 versus 80 in the intraoperative setting, there was little impact on transfusion appropriateness. Of 48 scenarios, older age resulted in an increased appropriateness grade in 6 (12.5%). In chapter 6, comparing ages 40, 60, and 80 in the late post-operative setting, there was no difference in the ratings between age 60 and 80. In patients without symptoms of anemia, a 40 year old patient was considered uncertain to transfuse at Hb 65 g/L (without CAD) or Hb 75 g/L (with CAD), whereas patients aged 60 and 80 were both considered appropriate in those circumstances. Otherwise, age did not affect the appropriateness ratings.

4.4.9. Post-operative functional status

In the late post-operative setting (Table 9), symptoms of anemia (lightheadedness, difficulty mobilizing) affected transfusion appropriateness when the Hb value was near a potential transfusion trigger. For patients without CAD, symptoms of

anemia increased the grade from inappropriate to unclear at Hb of 75 g/L. For those with CAD, this same increase was seen at Hb of 85 g/L.

4.5. Discussion

The current study combines the best available scientific evidence with multi-disciplinary expert opinion to create guidance for the appropriate use of perioperative red blood cell transfusions for patients undergoing hepatectomy (Fig 1). Intraoperatively, there are three main recommendations: it is never inappropriate to transfuse for either significant blood loss or ST segment changes; it is never inappropriate to transfuse for an intraoperative Hb value $\leq$ 75 g/L; and in the absence of major indications (significant bleeding, ST changes), transfusion for a Hb of 95 g/L is inappropriate, and transfusion at 85 g/L requires strong justification (ex. low MAP, history of CAD). For a hemodynamically stable patient in the late post-operative period, a reasonable transfusion trigger is 70 g/L for patients without CAD, and 80 g/L for patients with CAD. In the immediate post-operative setting, or with a decrease in Hb of more than 15 g/L later in the post-operative period, it is appropriate to transfuse for a Hb of 75 g/L or less. These recommendations are summarized in Fig 1.

As these recommendations are based on experts' clinical experience as well as their interpretation of the literature, there are many links to previously published works. Most notably, many of the post-operative recommendations are highly influenced by the TRICC[16] and FOCUS[17] trials. Performed in critical care

and orthopedic surgery patients respectively, these trials informed the recommendations for transfusion triggers of 70 g/L (without CAD) and 80 g/L (with CAD) in stable post-operative patients. In contrast, a more recent clinical trial of patients undergoing abdominal oncology surgery who required intensive care unit (ICU) admission, a transfusion trigger of 90 g/L was found to have decreased mortality at 30 and 60 days, compared to a trigger of 70 g/L[18]. These findings are contrary to the TRICC and FOCUS trials, which found no difference in their populations. Criticisms of this trial include a higher proportion of important comorbidities in the restrictive group (diabetes, chronic obstructive pulmonary disease, metastatic cancer, congestive heart failure, cerebrovascular disease), as well as a deviation of protocol in 10% of patients, without a per-protocol analysis. However, this trial certainly influenced our results, as can be seen by the high level of uncertainty towards transfusion at a Hb of 85 g/L in the majority of postoperative settings. Had the TRICC and FOCUS trials been the only clinical trials informing these recommendations, transfusion at 85 g/L would have likely been considered inappropriate in the majority of instances.

In the operating room, our transfusion recommendations have less basis in level 1 evidence, as there are no trials that target intraoperative transfusions specifically. From the second round panel discussion, scoring of intraoperative scenarios was primarily based on training, personal experience, and retrospective literature pertaining to the impact of blood transfusion. The first and second recommendations state that significant bleeding, ST segment changes, and an intraoperative Hb value of 75 g/L are never inappropriate indications to transfuse.

This viewpoint is based on the expert panel's medical training, experience, and the potential impact of severe anemia or blood loss on tissue ischemia, particularly the myocardium. The third intraoperative recommendation, that it is inappropriate to transfuse for a Hb of 95 g/L without significant bleeding or ST changes, is consistent with observational data for patients undergoing hepatic and pancreatic resection[19]. That paper found that a restrictive transfusion strategy did not impact morbidity or mortality, and had the added benefit of decreased resource-utilization and risk of adverse transfusion events. Their intraoperative restrictive transfusion threshold was defined as less than 100 g/L, although this was considered to be a conservative threshold, in order to account for the possibility of active bleeding.

Our study also demonstrates very comparable findings to the only other RAM transfusion appropriateness study, which focused on stable, nonbleeding medical and surgical patients[7]. Transfusion for a Hb between 80 and 99 g/L was found to be inappropriate in 71.3% of their scenarios, and in 72.2% of our post-operative scenarios. Overall, they identified that transfusion was uncertain in 28.9% of their scenarios, comparable to 24.4% found in our study. Similarly, they also found patient age to not be a significant factor in determining transfusion appropriateness.

In addition to the key recommendations, other findings require further analysis. It was found that in post-operative scenarios hemodynamic abnormality only increased the appropriateness rating in scenarios with a Hb value of 75 or 85 g/L; and in those scenarios, it increased the rating in nearly all of them. At a Hb of 65 g/L, nearly every patient will be receiving a transfusion regardless of their

hemodynamic status; and at Hb values of 95 or 105 g/L, there are likely factors other than blood loss contributing to the hemodynamic abnormalities. Similarly, a history of CAD impacted the appropriateness rating only in scenarios with a Hb level near the potential transfusion triggers (75 or 85 g/L). It can be seen as well that there is increased reliance on the Hb value in the post-operative settings compare to the intraoperative. This likely relates to the fact that an intraoperative Hb reading may not be as good a representation of the true value, considering the time required for Hb equilibration after acute blood loss. Therefore, in the intraoperative settings, more reliance was placed on the pre-operative Hb starting point in combination with the estimated blood loss.

One of the main strengths of the current study is the use of the RAM: an established, validated, reliable tool for determining appropriateness[12]. A significant benefit of the RAM process is the inclusion of a large number of scenarios, allowing for the consideration of multiple clinical factors when determining appropriateness. This allows wide generalizability to the majority of patients undergoing hepatectomy. Furthermore, the expert panel consisted of an international group of leaders from multiple discplines involved in perioperative blood management. This represents diverse training and knowledge, and further lends generalizability to the findings. The primary limitation in the current study is the lack of level 1 evidence specific to liver surgery, from which the panelists could base their appropriateness scores. The prospective clinical trials that informed this panel were from the fields of critical care, orthopedic surgery, and abdominal oncology. The literature relating to transfusion in hepatectomy is limited to

observational studies. The scenarios were selected in order to represent as wide a range of potential indications to transfuse as possible. Additional scenarios could have increased this range, or added granularity and detail, although this may have become unfeasible for the expert panel members. In particular, the Hb levels chosen were not ranges, but discrete points. This allowed better clarity and consistency for the panelists' ratings, however could lead to difficulty when interpreting a Hb value falling in between.

In addition to guiding clinicians with a difficult clinical decision, these appropriateness scores can also be used to study over and underuse of perioperative blood transfusions by applying them to a retrospective cohort of patients. A cohort of patients receiving inappropriate transfusions can be matched to one not receiving transfusions to study the clinical outcomes. Three studies in cardiac revascularization have demonstrated that patients treated in concordance with RAM appropriateness criteria had significantly lower mortality[20-22]. The current study also informs future prospective transfusion trigger trials by defining areas of uncertainty. This will help to identify the clinical scenarios with important unanswered questions.

In summary, we believe the Ottawa Criteria for Appropriate Transfusion in Hepatectomy will help inform clinical decision-making in the perioperative setting. By applying the OCATH, physicians can efficiently combine the best-available scientific evidence and clinical expert opinion to make an informed decision about a particular patient.

Table 1. Members of the RAND/UCLA expert panel for the OCATH

Name	Affiliation	Specialty
Jeffrey Barkun	McGill University, Montreal, Canada	HPB Surgery
Paul Karanicolas	University of Toronto, Toronto, Canada	Surgical Oncology
Guillaume Martel	University of Ottawa, Ottawa, Canada	HPB Surgery
Lauralyn McIntyre	University of Ottawa, Ottawa, Canada	Critical Care Medicine
Daniel McIsaac	University of Ottawa, Ottawa, Canada	Anesthesiology
Timothy Pawlik	Johns Hopkins University, Baltimore, USA	Surgical Oncology
Alan Tinmouth	University of Ottawa, Ottawa, Canada	Transfusion Medicine
Alexis Turgeon-Fournier	Université Laval, Quebec City, Canada	Anesthesiology
Paul Hebert (Moderator)	Université de Montréal, Montréal, Canada	Critical Care Medicine

HPB = hepatopancreatobiliary

Table 2. Chapters and categorical modifiers used in the RAND/UCLA Appropriateness Method

Chapters	Modifiers	# of scenarios
Ch. 1 (Intraop): 63 year old patient, 4-5 hour operation, consistent bleeding throughout, nearly finished parenchymal transection. EBL 1000cc	Pre-op Hb, Intraop Hb, CAD, ST changes, HD	96
Ch. 2 (Intraop): 63 year old patient. Major acute bleed from middle hepatic vein with variable control. 750cc EBL until now, plus 750cc from current bleeder.	Pre-op Hb, Intraop Hb, CAD, ST changes, HD	96
Ch. 3 (Intraop): Right hepatectomy for cholangiocarcinoma. Halfway through liver transection, moderate oozing throughout. 1000cc blood/bile in suction canister. Normal HD, no ST changes.	Pre-op Hb, Intraop Hb, CAD, CVA, Age (50 vs. 80)	96
Ch. 4 (Post-op): 3 hours post-op, assessing a 63 year old patient in PACU after major liver resection	Current Hb, Drop in Hb (from pre-op), CAD, HD	60
Ch. 5 (Post-op): 63 year old patient, POD 2 major resection. Ongoing ileus, moderate pain, minimal ambulation	Current Hb, Drop in Hb (from POD 1), CAD, HD	60
Ch. 6 (Post-op): POD 6 major resection, no significant change in Hb from previous day, HD normal	Current Hb, Age (40 vs 60 vs 80), Hx of CAD, Symptoms of anemia	60

Pre-op = pre-operative; Intraop = intraoperative, Hb = hemoglobin; CAD = history of coronary artery disease; HD = hemodynamic status; CVA = history of cerebrovascular accident; POD = post-operative day; symptoms of anemia = lightheadedness, poor mobilization

Table 3. Definitions used by the panel for rating of scenarios

Modifier	Definition used
History of coronary artery disease (CAD)	Previous history of significant CAD. Currently stable, no active angina.
History of cerebrovascular accident (CVA)	Previous history of significant CVA. Currently stable, no major neurological deficits.
ST segment changes	New (or presumed new) significant ST-segment T-wave changes or new left bundle branch block
Hemodynamic abnormality	Heart rate > 110bpm + Mean Arterial Pressure 55-60 mmHg
Major resection	Surgical resection of 4 or more liver segments

Table 4. Appropriateness scores for Chapter 1: 63 year old patient, 4-5 hour operation, consistent bleeding throughout, nearly finished parenchymal transection. EBL 1000cc

			No ST Changes		ST Changes	
Hb	**Hx CAD**	**Pre-Hb**	**Normal HD**	**Abnormal HD**	**Normal HD**	**Abnormal HD**
65	**+**	**95**	8.5	9	9	9
		110	9	9	9	9
		125	9	9	9	9
	-	**95**	7.5	9	9	9
		110	9	9	9	9
		125	9	9	9	9
75	**+**	**95**	8	8.5	9	9
		110	7.5	8.5	9	9
		125	7	8.5	9	9
	-	**95**	5.5	7.5	9	9
		110	5.5	7.5	9	9
		125	4.5	7.5	9	9
85	**+**	**95**	4	7	7.5	8
		110	3.5	6	7.5	7.5
		125	3.5	5.5	7.5	7.5
	-	**95**	1.5	3.5	6.5	6.5
		110	2	4	6	6
		125	1.5	4	5	6
95	**+**	**95**	1.5	5	7	7
		110	1	3.5	6	6
		125	1.5	4	5.5	6
	-	**95**	1	2.5	5	5
		110	1	2.5	4	4.5
		125	1	1.5	3.5	4

Colour-coded for appropriate (green), uncertain (yellow), and inappropriate (red). Hb = current hemoglobin value (g/L); Hx CAD = history of coronary artery disease; Pre-Hb = pre-operative hemoglobin value; Abnormal HD = heart rate > 110bpm, mean arterial pressure 55-60 mmHg

Table 5. Appropriateness scores for Chapter 2: 63 year old patient. Major bleed from middle hepatic vein with variable control. 750cc EBL until now, plus 750cc from current bleeder.

			No ST Changes		ST Changes	
Hb	**Hx CAD**	**Pre-Hb**	**Normal HD**	**Abnormal HD**	**Normal HD**	**Abnormal HD**
65	**+**	**95**	9	9	9	9
		110	9	9	9	9
		125	9	9	9	9
	-	**95**	9	9	9	9
		110	9	9	9	9
		125	9	9	9	9
75	**+**	**95**	8	9	9	9
		110	8	9	9	9
		125	8	9	9	9
	-	**95**	7	9	8.5	9
		110	7.5	9	9	9
		125	8	9	9	9
85	**+**	**95**	7	8	7.5	8.5
		110	6.5	8	8	9
		125	6	8	7.5	8
	-	**95**	5.5	7.5	6.5	8
		110	5	6	6.5	8
		125	4	6.5	6	7
95	**+**	**95**	5	7	7	8
		110	4.5	6	6.5	7
		125	4	6	5.5	7
	-	**95**	4.5	6	6	7
		110	4	5	6	6.5
		125	2.5	5	4.5	6

Colour-coded for appropriate (green), uncertain (yellow), and inappropriate (red). Hb = current hemoglobin value (g/L); Hx CAD = history of coronary artery disease; Pre-Hb = pre-operative hemoglobin value; Abnormal HD = heart rate > 110bpm, mean arterial pressure 55-60 mmHg

Table 6. Appropriateness scores for Chapter 3: Right hepatectomy for cholangiocarcinoma. Halfway through liver transection, moderate oozing throughout. 1000cc blood/bile in suction canister. Normal HD, no ST changes.

			No Hx of CVA		Hx of CVA	
Hb	**Hx CAD**	**Pre-Hb**	**Age = 50**	**Age = 80**	**Age = 50**	**Age = 80**
65	**+**	**95**	9	9	9	9
		110	9	9	9	9
		125	9	9	9	9
	-	**95**	8	9	9	9
		110	8	9	9	9
		125	8	9	9	9
75	**+**	**95**	7.5	8	7.5	9
		110	7	7.5	7.5	8.5
		125	7	8	8	8.5
	-	**95**	6	6.5	7	8
		110	5	7	7	8
		125	5.5	7	7	8
85	**+**	**95**	3.5	4.5	5	6
		110	3.5	4.5	5.5	6
		125	3.5	5	5.5	6
	-	**95**	2.5	3	4	5
		110	2	4	4	5.5
		125	2	4	4.5	5.5
95	**+**	**95**	1	2	2.5	3.5
		110	1	2	2.5	3.5
		125	1.5	2.5	2	3
	-	**95**	1	1	1.5	2
		110	1	1.5	1.5	2
		125	1	1	2	2

Colour-coded for appropriate (green), uncertain (yellow), and inappropriate (red). Hb = current hemoglobin value (g/L); Hx CAD = history of coronary artery disease; Pre-Hb = pre-operative hemoglobin value

Table 7. Appropriateness scores for Chapter 4: 3 hours post-op, assessing a 63 year old patient in PACU after major liver resection

		No History of CAD		History of CAD	
Hb	**Drop**	**Normal HD**	**Abnormal HD**	**Normal HD**	**Abnormal HD**
65	**-35**	9	9	9	9
	-25	8	9	9	9
	-15	7	9	9	9
75	**-35**	4	7	7.5	8.5
	-25	3.5	7	7	8
	-15	3	7	7	8
85	**-35**	2.5	4	4.5	6.5
	-25	1	3.5	4	6
	-15	1	3.5	4	6
95	**-35**	1	2	1.5	3
	-25	1	2	1.5	2.5
	-15	1	1	1	1.5
105	**-35**	1	1	1	1.5
	-25	1	1	1	1.5
	-15	1	1	1	1

Colour-coded for appropriate (green), uncertain (yellow), and inappropriate (red).

Hb = current hemoglobin value (g/L); Drop = change in Hb since pre-op; CAD = coronary artery disease; Abnormal HD = heart rate > 110bpm, mean arterial pressure 55-60 mmHg

Table 8. Appropriateness scores for Chapter 5: 63 year old patient, POD 2 major resection. Ongoing ileus, moderate pain, minimal ambulation

		No History of CAD		History of CAD	
Hb	**Drop**	**Normal HD**	**Abnormal HD**	**Normal HD**	**Abnormal HD**
65	**-35**	9	9	9	9
	-25	9	9	9	9
	-15	8	9	9	9
75	**-35**	7	8	7.5	8.5
	-25	6.5	7.5	7.5	8
	-15	5.5	6.5	6.5	8
85	**-35**	3.5	6	4	6
	-25	2.5	5	3	5.5
	-15	1.5	3.5	2.5	4.5
95	**-35**	1	2	1.5	3
	-25	1	1.5	1	2
	-15	1	1	1	1
105	**-35**	1	1	1	1
	-25	1	1	1	1
	-15	1	1	1	1

Colour-coded for appropriate (green), uncertain (yellow), and inappropriate (red).

Hb = current hemoglobin value (g/L); Drop = change in Hb since POD 1; CAD = coronary artery disease; Abnormal HD = heart rate > 110bpm, mean arterial pressure 55-60 mmHg

Table 9. Appropriateness scores for Chapter 6: POD 6 major resection, no significant change in Hb from previous day, HD normal

		No History of CAD		History of CAD	
Hb	**Age**	**Asymptomatic**	**Symptomatic**	**Asymptomatic**	**Symptomatic**
65	**80**	7	8.5	9	9
	60	7	8	8	9
	40	6	8	7.5	9
75	**80**	3	5.5	7.5	8
	60	2	5.5	7	7.5
	40	2	5	5	7.5
85	**80**	1	3	2.5	5.5
	60	1	2.5	2	4.5
	40	1	1.5	1	4
95	**80**	1	1.5	1	2.5
	60	1	1.5	1	2.5
	40	1	1	1	2
105	**80**	1	1	1	1
	60	1	1	1	1
	40	1	1	1	1

Colour-coded for appropriate (green), uncertain (yellow), and inappropriate (red).
Hb = current hemoglobin value (g/L); CAD = coronary artery disease; Symptomatic = lightheaded, poor mobilization

Intraoperative:

1. Significant bleeding and ST segment changes trump other factors. It is never inappropriate to transfuse for these reasons.
2. It is never inappropriate to transfuse for an intraoperative hemoglobin value $\leq$ 75 g/L.
3. Without major indications (significant bleeding, ST segment changes) transfusion for a hemoglobin of 95 g/L is inappropriate, and transfusion for a hemoglobin of 85 g/L requires strong justification.

Post-operative:

1. In a stable, asymptomatic patient, appropriate transfusion triggers are 70 g/L (without CAD) and 80 g/L (with CAD).
2. In the immediate post-operative setting, or with a hemoglobin drop of more than 15 g/L later in the post-operative period, it is appropriate to transfuse for a hemoglobin of 75 g/L.

Figure 1. Main OCATH appropriateness recommendations

4.6. References

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5. Conclusion & Future Directions

The above work synthesizes and describes much of what is known today about the use of blood transfusions for patients undergoing liver resection. The systematic review of the literature demonstrates a decreasing prevalence of transfusions over time and a lack of high-quality prospective data exploring the impact of transfusions on important clinical outcomes. From the retrospective data that is available, there appears to be a strong case to be made that transfusions independently contribute to increased post-operative complications, but not mortality. As for increased risk of cancer recurrence, the data is equivocal, with several studies both supporting and rejecting the association.

The survey of Canadian liver surgeons and anesthesiologists provides a much needed snapshot of the current practices in perioperative blood management. To improve practice, one must first understand what is currently being done. It also provides interesting information regarding how practitioners make decisions regarding transfusions, and how they balance the multidisciplinary nature of decision making in the care of surgical patients. The differences identified between surgeons and anesthesiologists in their perioperative blood management practices will provide an opportunity for shared understanding, with the potential to improve communication.

The OCATH appropriateness study combines the best available scientific evidence with the clinical knowledge of an international, multidisciplinary panel of experts in perioperative blood management and hepatobiliary surgery. Not only

does this study provide clear recommendations for clinical practitioners treating patients who are undergoing liver resection, it also identifies areas of uncertainty which will help to inform future clinical research. An immediate future project, following completion of this Master's thesis, will be to apply the appropriateness criteria to a retrospective cohort of patients who have undergone liver resection. This will allow us to measure overuse and underuse, as well as to examine the clinical outcomes for those transfused inappropriately.

6. Acknowledgements

The past two years have afforded me numerous opportunities to think, learn, develop, collaborate, and produce as a trainee surgeon-scientist. These are not opportunities that many trainees receive, and I have many people to thank for that.

Firstly to the Division of General Surgery at the University of Ottawa – thank you for the time away and the financial support that allowed me to complete this work. I hope you see value in what I have produced, and I look forward to continuing to contribute to the clinical and academic pursuits of the division. To the Clinician Investigator Program at the University of Ottawa – thank you for the opportunity and the guidance throughout the two years.

Returning to a traditional university education after two years as a surgical trainee is an interesting transition. I felt extremely welcomed by all the students, professors, and administrators at the School of Epidemiology, Public Health and Preventive Medicine at the University of Ottawa. Thank you for including me, and for teaching me the importance of not only research, but research done right!

To the expert panelists of the OCATH project, Drs. Karanicolas, McIntyre, Barkun, Pawlik, Turgeon-Fournier, and Hébert – thank you for being so gracious with your time, knowledge and insights. Working with you all was a pleasure.

To my Thesis Advisory Committee members, Drs. Alan Tinmouth, Daniel McIsaac, and Shane English – your contributions were invaluable. I feel very lucky to have access to your minds and expertise.

Most importantly, this project would not have been conceivable without the guidance of my thesis supervisors, Dr. Guillaume Martel and Dr. Dean Fergusson. Both superb researchers, they each contributed their own strengths to help mold the final product. With access to both their clinical and methodological expertise I was never without a compass. I look forward to continued collaboration in the future.

Thank you to my friends and family for the support and for always at least giving the impression of being interested in my work. Thank you Danielle for brightening my day, always.

Appendix A: PRISMA-P Checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	✓1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	✓2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	✓3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	✓3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	✓5a	Indicate sources of financial or other support for the review
Sponsor	✓5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	✓5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	✓6	Describe the rationale for the review in the context of what is already known
Objectives	✓7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	✓8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	✓9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	✓10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	✓11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	✓11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection	✓11c	Describe planned method of extracting data from reports (such as piloting

process		forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	✓12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	✓13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	✓14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	✓15a	Describe criteria under which study data will be quantitatively synthesised
	✓15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	✓15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	✓15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix B: Example of systematic review search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 exp Liver Neoplasms/su (20551)
2 Hepatectomy/ (23248)
3 hepatectom*.tw. (17035)
4 ((liver or hepatic or hepato*) adj2 resect*).tw. (14735)
5 or/1-4 (44945)
6 exp blood transfusion/ (85009)
7 ((rbc or blood$ or red cell$ or erythrocyte$ or plasma or platelet$) adj2 transfusion$).tw. (46072)
8 transfusion*.ti. (32101)
9 cryoprecipitate.tw. (1736)
10 or/6-9 (111774)
11 5 and 10 (1280)
12 remove duplicates from 11 (1264)

Appendix C: Blood Use in Liver Resections Provider Survey

1. **Do you perform liver resections or provide anesthesia for patients undergoing liver resections?**
   Yes-Surgery Yes-Anesthesia No *(If No, survey ends)*

2. **Approximately how many liver resection cases are you involved with per year?**
   1-5 6-10 11-20 21-39 40+

3. **Approximately how many liver resections are performed at your hospital per year?**
   1-10 11-25 26-50 50-99 100+

4. **What type of hospital setting do you work in?**
   Small community Large city, non-academic Academic

5. **Do you have fellowship training beyond residency?**
   Yes No

   If yes, what fellowship? _____

6. **How many years have you been working as a staff surgeon/anesthesiologist?**
   1-3 3-5 6-10 11-19 20+

7. **How do you typically manage preoperative anemia prior to elective liver resection?**
   No specific treatment Oral iron supplementation
   Intravenous iron supplementation Pre-op allogeneic blood transfusion
   Pre-operative blood conservation program
   Someone else manages it

8. **Do you ever employ perioperative blood conservation techniques?**
   Yes No

   If yes, which ones:
   Anti-fibrinolytic therapy: Always Occasionally Never
   Cell salvage: Always Occasionally Never
   Acute normovolemic hemodilution: Always Occasionally Never

Intraoperative phlebotomy with autologous transfusion: Always Occasionally Never

9. **What techniques do you use to estimate intraoperative blood loss in liver resections?**
   Observing surgical field: Always Occasionally Never
   Observing used surgical sponges: Always Occasionally Never
   Observing suction canister: Always Occasionally Never
   Change in Hemoglobin value: Always Occasionally Never
   Change in patient hemodynamics: Always Occasionally Never

10. **What is the most important information you use to decide on intraoperative blood transfusions?**
    Your estimation of accumulated and ongoing blood loss
    Hemoglobin lab values
    Patient hemodynamics
    Discussion with the other physician (surgeon or anesthesiologist)
    Other:_____

11. **In the operating rooms that you work in, who is the primary decision maker regarding blood transfusions?**
    Anesthesiologist Surgeon Anesthesia Resident Surgery Resident

    In the recovery room, who is the primary decision maker regarding blood transfusions?
    Anesthesiologist Surgeon Anesthesia Resident Surgery Resident

    On the inpatient ward, who is the primary decision maker regarding blood transfusions?
    Anesthesiologist Surgeon Anesthesia Resident Surgery Resident

12. **In comparison to when you started practicing, do you feel you are more or less likely to transfuse a patient now?**
    More likely Less likely As likely

Appendix D: OCATH Panelists Instructions for Rating

EXPERT PANEL ASSESSING THE APPROPRIATENESS OF RED BLOOD CELL TRANSFUSIONS IN LIVER RESECTION

Instructions for rating the scenarios

Attached are the clinical scenarios to be rated.

- **They are divided into 6 main "chapters" – 3 intraoperative & 3 postoperative.**
- **Each "chapter" is numbered from 1-6.**
- **Within each of these chapters, there are a number of modifiers, which creates 468 unique scenarios for which a blood transfusion might be considered.**
- **These modifiers are items like lab values, an important piece of clinical history, or variations in vital signs.**

You are being asked to assign each scenario with an appropriateness score, from 1 to 9. A score of 1 indicates that a blood transfusion would be highly inappropriate, and a score of 9 that it is highly appropriate. **Important:** you are rating appropriateness not necessarily how you practice but rather whether the degree to which you think it is appropriate or inappropriate.

From the RAND/UCLA Appropriateness Method User Manual, a treatment is considered appropriate if "The expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing, exclusive of cost". Consideration of cost should not enter into your judgment, and only clinical effectiveness is considered. **You are being asked to rate these based on your knowledge of the evidence (including the enclosed systematic review) and your own best clinical judgment.**

Please take some time to look at the 6 chapters, and how the various modifiers are combined to create each individual scenario. From experience, the first handful of scenarios takes the longest as you get used to the format.

Example: Look at the first 1-9 scale in the top left corner of Chapter 1

Chapter 1. 63-yr old patient, 4-5hr case, major resection, average bleeding throughout. Nearly finished parenchymal transection. EBL 1000cc

Pre-op Hgb was 95g/L, the patient has a history of coronary artery disease, a current intraoperative Hgb reading of 65g/L, normal hemodynamics, and no ST changes seen on the monitor.

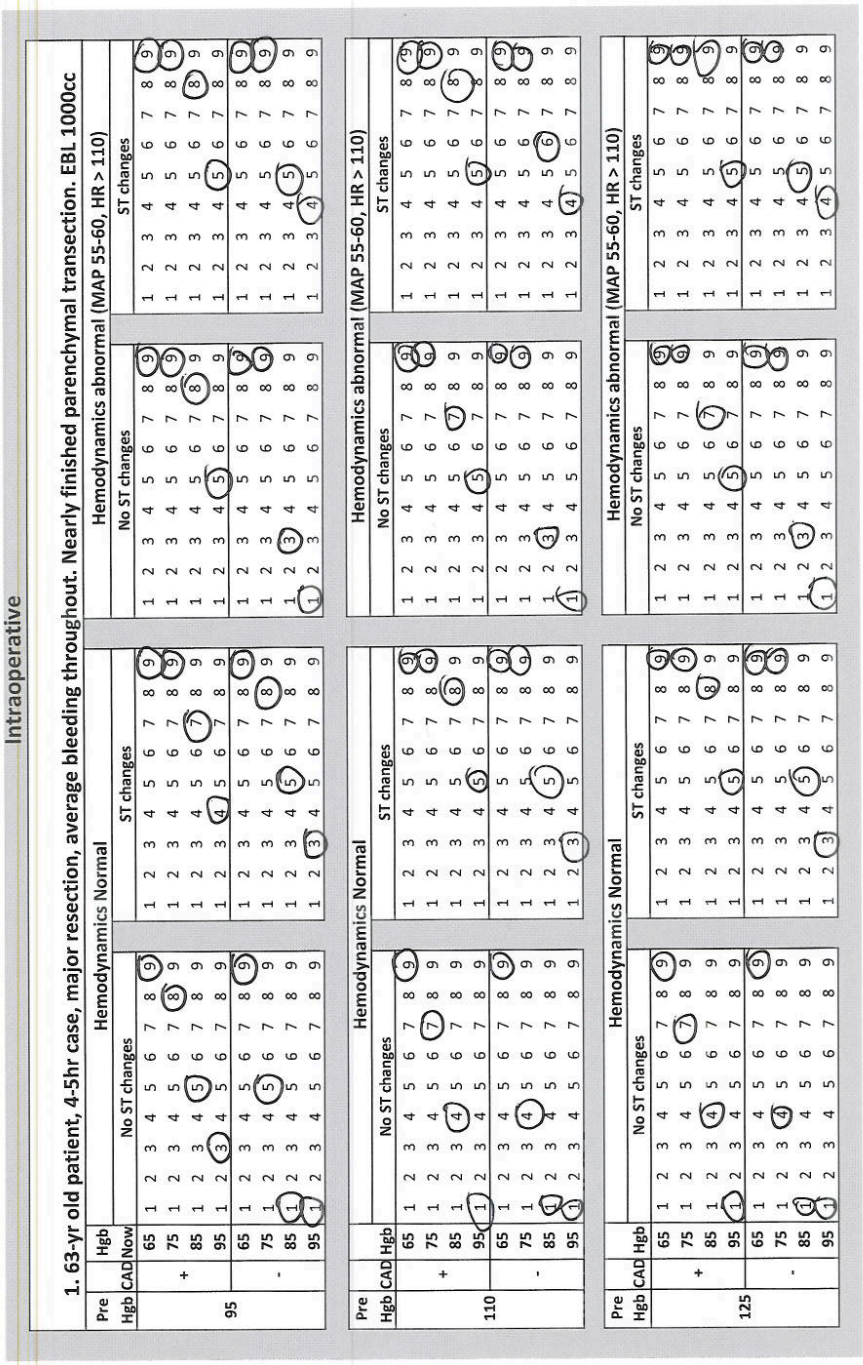
Circle how **appropriate** it would be to give a red blood cell transfusion to this patient.

1	2	3	4	5	6	7	8	9
Highly Inappropriate								Highly Appropriate

Important: During the rating process, you may come up with questions or feel that there are other important modifiers that aren't being captured here. We would encourage you to keep note of these, and they can be discussed at the panel meeting during round 2 of the appropriateness rating. At that time, depending on the discussion, some modifications may be made to these scenarios. Round 2 is also where you can make modifications to your Round 1 scoring depending on the panel discussion.

We will be in contact shortly after you receive these documents to follow up, but if you have any questions or concerns please don't hesitate to contact Sean Bennett at

Appendix E: Example of a Round 1 rating sheet (completed)



Name Montal

Intraoperative

1. 63-yr old patient, 4-5hr case, major resection, average bleeding throughout. Nearly finished parenchymal transection. EBL 1000cc

Pre Hgb	CAD	Hgb Now	Hemodynamics Normal: No ST changes	Hemodynamics Normal: ST changes	Hemodynamics abnormal (MAP 55-60, HR > 110): No ST changes	Hemodynamics abnormal (MAP 55-60, HR > 110): ST changes
95	+	65	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		75	1 2 3 4 5 6 (7) 8 9	1 2 3 4 5 6 (7) 8 9	1 2 3 4 5 6 7 (8) 9	1 2 3 4 5 6 7 (8) 9
		85	1 2 3 (4) 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 3 4 (5) 6 7 8 9
		95	1 (2) 3 4 5 6 7 8 9	1 2 3 (4) 5 6 7 8 9	(1) 2 3 4 5 6 7 8 9	1 2 3 (4) 5 6 7 8 9
	-	65	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		75	1 (2) 3 4 5 6 7 8 9	1 2 3 4 5 6 (7) 8 9	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		85	1 (2) 3 4 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 (3) 4 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9
		95	1 (2) 3 4 5 6 7 8 9	1 2 (3) 4 5 6 7 8 9	(1) 2 3 4 5 6 7 8 9	1 2 3 (4) 5 6 7 8 9
110	+	65	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		75	1 2 3 4 5 6 (7) 8 9	1 2 3 4 5 6 (7) 8 9	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		85	1 2 3 (4) 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 3 4 5 6 (7) 8 9	1 2 3 4 5 6 (7) 8 9
		95	(1) 2 3 4 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9
	-	65	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		75	1 2 3 (4) 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		85	(1) 2 3 4 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 (3) 4 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9
		95	(1) 2 3 4 5 6 7 8 9	1 2 (3) 4 5 6 7 8 9	(1) 2 3 4 5 6 7 8 9	1 2 3 (4) 5 6 7 8 9
125	+	65	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		75	1 2 3 4 5 6 (7) 8 9	1 2 3 4 5 6 (7) 8 9	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		85	1 2 3 (4) 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 3 4 5 6 (7) 8 9	1 2 3 4 5 6 (7) 8 9
		95	(1) 2 3 4 5 6 7 8 9	1 2 3 (4) 5 6 7 8 9	1 2 3 4 5 6 7 8 9	1 2 3 (4) 5 6 7 8 9
	-	65	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		75	1 2 3 (4) 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 3 4 5 6 7 8 (9)	1 2 3 4 5 6 7 8 (9)
		85	(1) 2 3 4 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9	1 2 (3) 4 5 6 7 8 9	1 2 3 4 (5) 6 7 8 9
		95	(1) 2 3 4 5 6 7 8 9	1 2 (3) 4 5 6 7 8 9	(1) 2 3 4 5 6 7 8 9	1 2 3 (4) 5 6 7 8 9

* Pre-Hgb = preoperative Hgb (expressed in g/L. Divide by 10 to convert to g/dL)
* Hgb Now = intra-op measurement (expressed in g/L. Divide by 10 to convert to g/dL)
* CAD = previous MI, unstable angina, angioplasty or CABG
* ST Changes = New or presumed new significant ST-segment T-wave changes or new LBBB
* EBL = estimated blood loss
* MAP = mean arterial pressure