Use of Transfusion Risk to Direct Blood Conservation Strategies in Hepatectomy

by

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Institute of Health Policy, Management, and Evaluation
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Abstract

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Peri-operative allogeneic red blood cell transfusions (RBCTs) are a common complication for patients undergoing hepatectomy. Use of RBCTs has notable disadvantages, including inferior morbidity, mortality, rates of cancer recurrence and substantial resource requirements.

Intraoperative cell salvage (ICS) is a strategy used to reduce RBCTs in other surgical procedures. Here, we evaluated the cost efficiency of ICS for patients undergoing hepatectomy and found it to be cost efficient for patients with a peri-operative RBCT risk of 25% or greater.

To predict patient risk of RBCT in the pre-operative setting, three transfusion risk scores (TRS) exist. These three TRS have limited assessment of external validity and are complex to use. None showed superior performance over a simplified Three Point TRS considering only pre-operative anemia, primary liver malignancy, and major resection.

This Three Point TRS should be used in the pre-operative setting to direct blood conservation strategies, including ICS, for patients undergoing hepatectomy.
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<table>
<thead>
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<th>Abbreviation</th>
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<tbody>
<tr>
<td>95% CI</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>ANH</td>
<td>Acute normovolemic hemodilution</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under (receiver operating characteristic) curve</td>
</tr>
<tr>
<td>CAD</td>
<td>Canadian dollar</td>
</tr>
<tr>
<td>CRLM</td>
<td>Colorectal liver metastases</td>
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<tr>
<td>ICS</td>
<td>Intraoperative cell salvage</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PABD</td>
<td>Preoperative autologous blood donation</td>
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<tr>
<td>RBCT</td>
<td>(Allogeneic) red blood cell transfusion</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristic curve</td>
</tr>
<tr>
<td>TRS</td>
<td>Transfusion risk score</td>
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<tr>
<td>USD</td>
<td>American dollars</td>
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Chapter 1: Background

Early attempts at hepatectomy

The liver is a large and highly perfused organ. Approximately three quarters of the blood supply enters through the portal vein carrying nutrients from the digestive tract, while the remaining quarter flows in from the hepatic artery. (1, 2) The middle hepatic vein divides the liver into the right and left lobe, which can be further divided into a total of eight segments defined by Couinaud. (3) A unique property of the liver is its ability to regenerate hepatocytes from unipotent cells. (1) This allows for liver regeneration following resection or trauma, and loss of up to 80% of liver tissue can occur without causing death. (4, 5)

Difficulty exposing the liver and high volumes of blood loss limited early efforts at hepatectomy, which were generally only attempted following trauma. (6) The first successful hepatectomy was performed by Langenbuch in 1888, which was complicated by a massive secondary hemorrhage requiring reoperation. (6) The importance of controlling blood loss in early hepatectomy is also demonstrated by the development of techniques such portal triad occlusion, named the Pringle maneuver after the inventor, which was developed in the early 1900s. (6) A more refined version of this technique remains in use today to temporarily limit blood flow to the liver during transection. Morbidity and mortality following hepatectomy remained significant for many years, with peri-operative mortality reported as high as 20% in the 1970s. (1, 7)

Indications for hepatectomy

Hepatic resection is performed for both primary and metastatic cancers. Primary cancers warranting hepatectomy include cholangiocarcinoma, originating in the bile ducts, and
hepatocellular carcinoma, originating in the hepatocytes. (8, 9) Risk factors associated with primary liver cancers include hepatitis B and C, exposure to aflatoxin, excessive alcohol consumption, smoking, and obesity. (9-11)

Hepatectomy is also increasingly performed on metastatic disease, most frequently for colorectal liver metastases (CRLM) where the primary tumour is a colorectal adenocarcinoma. (8, 12) Colorectal cancer is among the top most commonly diagnosed cancers in the world; however, survival is improving. (9, 10) Improvements in survival of metastatic colorectal cancer have been largely attributed to improved chemotherapy and increased hepatic resection. (13) Hepatectomy is also commonly performed on metastases originating from neuroendocrine primaries. (14, 15) Primary sites of neuroendocrine tumours include small bowel, colon, rectum, pancreas, and stomach. (15)

**Modern hepatectomy**

Improvements in surgical and anesthetic techniques have improved patient outcomes following hepatectomy; making it a more common procedure and available to a wider array of patients. (1, 4, 16-18) While early hepatectomy was limited to removing either the right or left lobe of the liver in its entirety, modern practice often uses a segmental approach where only affected segments are removed. (4, 6, 17) This saves healthy liver parenchyma, and allows for disease that is bilobar to be potentially resectable. To further maximize the remnant liver volume, non-anatomic resections have been increasing in use, allowing surgeons to remove only diseased tissue and leave behind healthy liver parenchyma. (4) In addition to advances in surgical dissection, multiple therapeutic options have become increasingly used in combination with hepatectomy, including systemic therapy, radiation, and ablative techniques. (3, 8, 19)

With such high complexity, decision making has become increasingly challenging and is subject to high variability between institutions and surgeons. (19, 20) Need for down-staging,
extent of intra and extrahepatic disease, accessibility of equipment, and patient factors contribute to variation in practice of hepatectomy. (19) With such complex and highly specialized care often involving multidisciplinary teams, liver surgery has been largely regionalized in North America to high volume centres. (21, 22) Development of hepatectomy into such highly specialized care has resulted in improved outcomes for patients. (4, 17, 21)

Modern perioperative mortality rates are typically reported under 5% for hepatectomy. (17, 23-25) Rates of major morbidity following hepatectomy are more variable but typically reported between 5 and 50%. (24, 25) Common complications following hepatectomy include post-operative fever/infections, liver failure, bile leakage, and hemorrhage. (25) Bleeding in the peri-operative setting may require correction with allogeneic (donor) red blood cell transfusions (RBCT). (1) Intra-operative blood loss and receipt of RBCT are important factors associated with poorer post-hepatectomy short and long term outcomes. (17, 26, 27) While in certain circumstances administering RBCTs may be necessary, there are notable risks, costs and limitations associated with their use, often warranting restrictive transfusion protocols.

Allogeneic red blood cell transfusions

Allogeneic red blood cells are provided by voluntary blood donors who meet highly restrictive screening criteria to ensure donated blood is safe for transfusion and to minimize risk to both donors and recipients. Modern practices have reduced risks of infection to extreme rarities, with risks of contracting human immunodeficiency virus (HIV) and hepatitis B and C virus from a RBCT in Canada in the range of one in five to eight million. (28) While strict criteria to assess potential donors are necessary to ensure the high safety standards of donated blood, restricting the donor pool limits the availability of blood products. These stringent measures as well as extensive testing and processing contribute to high costs. (29-32) The reported costs of one unit of red blood cells as collected by Canadian Blood Services is $435 (CAD, 2011) (1 unit
= 250 mL of packed red blood cells); however, a more comprehensive activity based cost analysis reported costs of $761 (USD, 2009) per unit once the donated blood is administered to the patient. (31, 32)

Despite the improved safety of modern day RBCTs, receipt of allogeneic red blood cells is associated with inferior outcomes. This has been attributed to immunomodulation following transfusion and has been shown to have multiple consequences although the mechanism is poorly understood. (33, 34) Receipt of RBCTs has been associated with increased risk of infection, poorer wound healing, extended length of stay, and higher rates of morbidity and mortality following major abdominal surgeries. (35-42) For patients undergoing resection of malignancies, peri-operative RBCTs have been associated with poorer long term outcomes, including higher rates of cancer recurrence and worse survival. (43-50)

Two studies have examined short term outcomes for all patients undergoing hepatectomy, one with over 2000 patients and another with 7500 patients. (51, 52) Both found receipt of RBCTs to be strongly associated with morbidity and mortality. Another study examined the impact of transfusions of any blood product for patients with CRLM undergoing hepatectomy, and found them to be detrimental to short term outcomes including a strong association with morbidity and mortality. (26) Furthermore, this was dependent on the number of units of transfused blood products. This group also examined the impact of transfusions on long term outcomes, and found poorer long term mortality for patients receiving transfusions that was similarly dependent on the quantity received.

Hallet and collaborators also examined long term outcomes for patients undergoing liver resection for CRLM, but specifically considered only RBCTs. (27) Overall survival was worse for patients who received peri-operative RBCTs, despite whether patients who died from surgical complications (defined as death within 90 days of surgery) were included or excluded (Figure
1). Further, patients receiving peri-hepatectomy RBCTs had poorer recurrence free survival (Figure 2). Survival was also dependent on the number of units of red blood cells transfused (Figure 3). These findings are echoed by another study examining recurrence rates for hepatocellular carcinoma, where patients undergoing liver resection for hepatocellular carcinoma who received RBCTs were associated with higher rates of cancer recurrence and poorer overall survival.(53)

For all of these reasons, restrictive transfusion protocols have gathered increasing evidence to support their use, and reducing use of RBCTs has been identified as a societal priority in healthcare.(54-56) Restrictive transfusion protocols typically use 7 g/dL as a trigger for RBCTs in otherwise well patients; however, use of this transfusion trigger has been shown to vary between institutions and hepatopancreaticobiliary surgeons.(56-58) Current research has found restrictive transfusion protocols to safely decrease the use of blood products.(59, 60) One randomized controlled trial examining short term (30 day) outcomes for patients who underwent resection for a malignancy did find superior outcomes for patients where a more liberal transfusion protocol was used (transfusion trigger of 9 g/dL).(61) This trial is limited in that it examines very short term outcomes and has not been supported by other research. Because of this, it has not changed current transfusion guidelines. Increased implementation and stronger adherence to restrictive transfusion protocols has resulted in reduced rates of RBCT over time; however, in order to continue to reduce rates of RBCT while using resources responsibly, current blood conservation strategies need to be utilized in the pre-operative setting for appropriate patients.(17, 30, 62)

Strategies to reduce blood loss and transfusions in hepatectomy

Multiple strategies exist to reduce blood loss and/or RBCTs in hepatectomy. Current evidence shows efficacy when targeted appropriately; however, use is highly variable.(20, 62,
Such strategies include intraoperative techniques, pharmaceuticals, and autologous blood products.

**Intraoperative Techniques**

A commonly employed method to reduce blood loss in hepatectomy is to maintain an intra-operative central venous pressure at or below 5 mm Hg. Low central venous pressure reduces blood loss occurring from venous backflow. This strategy is highly effective in reducing blood loss, but requires close monitoring by anesthesia to prevent hypovolemia and inadequate perfusion. Employment of this strategy has gained widespread use, but adds increased complexity to the anesthetic care of patients during hepatectomy.

Other intraoperative techniques are less universal, but can be used in appropriate patients. One such technique includes inflow occlusion during transection, first developed by Pringle in the early 1900s. Inflow occlusion can be employed using an array of different techniques; however, can be associated with ischemia and injury if prolonged. Intermittent clamping is often used, with a typical regimen of 15 minutes of clamping followed by 5 minutes of reperfusion, which can be safely repeated up to 90 minutes.

Other strategies to reduce blood loss have focused on the method for dissecting liver parenchyma. Some of these strategies can be quite simple and do not require specialized equipment. One such method is the finger fracture technique, where surgeons manually crush the liver to dissect delicate liver tissue while identifying and protecting larger vascular structures and bile ducts. This method fails to prevent bleeding from smaller vasculature, which can continuously bleed and accumulate to extensive blood loss. Alternatively, clamps can be used to crush the liver parenchyma, allowing for faster dissection with better direct visualization. More sophisticated devices have been developed in modern hepatectomies,
including Cavitron Ultrasonic Surgical Aspirator, radiofrequency dissecting sealers, and hydrojet devices that use ultrasound, radiofrequency, and pressurized water to allow skeletonizing of tiny vessels. (3) Another method to control blood loss is targeted at exposed, cut liver parenchyma. Fibrin or other substances can be applied onto the cut liver surface and left in situ, to promote clot formation and later dissolve. (75)

A number of intraoperative techniques have been developed to reduce blood loss during hepatectomy, which can be used alone or often in combination. These advances in technology allow more resources for surgeons to limit blood loss in hepatectomy; however, it can be challenging to identify the optimal combination of techniques for each patient.

**Pharmaceuticals**

Medications to reduce intra-operative blood loss include use of tranexamic acid, an anti-fibrinolytic agent. (76) Tranexamic acid is not currently routinely used by the majority of Canadian hepatopancreaticobiliary surgeons, and its ability to reduce RBCTs in this setting continues to be studied. (20) Risks associated with tranexamic acid are limited to a theoretical concern regarding increased venous thromboembolism rates; however, current research has not supported this concern. (77, 78) Widespread use of tranexamic acid in hepatectomy has been discussed and is currently under evaluation in a double blinded, randomized controlled trial. (79) Aprotinin is another pharmacologic strategy with potential for reducing blood loss during surgery, but with higher risks of thrombosis, renal complications, and death. (62, 76)

**Autologous Blood Products**

Another approach to avoiding allogeneic transfusions is to re-transfuse patient’s own (autologous) blood. Pre-operative autologous blood donation (PABD) allows patients to donate one or more units of blood, recover, and subsequently undergo their planned surgery with their
own autologous blood available if required.(80) This strategy has been shown to reduce the need for allogeneic RBCTs, and avoids some risks although improved long term outcomes have not been identified.(81, 82) PABD has a number of disadvantages, including potential for operative delay as patients recover from reduced hemoglobin levels as well as considerable costs and wastage.(66, 80, 83) Additionally, it cannot be employed in a number of patients who present with anemia or hypovolemia.(81, 84) Likely due to all of these restrictions, this strategy has not been routinely employed by Canadian surgeons.(20)

Acute normovolemic hemodilution (ANH) is a technique where a calculated volume of blood is removed immediately pre-operatively and replaced with crystalloids or colloids.(76) This allows for diluted blood to be shed intra-operatively and the patient’s own blood, with a higher concentration of red blood cells, to be available for transfusion if required.(76, 85) This strategy takes advantage of the fact that the majority of transfused patients in hepatectomy require only 1-2 units of red blood cells; however, it is limited to patients with sufficiently high hemoglobin levels pre-operatively.(85) ANH has been shown to be effective in reducing allogeneic transfusions; however, only in patients who experience significant blood loss and have a relatively high risk of transfusion.(67, 80, 85-87) Patients undergoing ANH are exposed to notable safety risks, particularly regarding the impact of major hemorrhage while hemoglobin and coagulation factors are diluted, risking major ischemia and/or blood loss.(80) Patients who do not require re-transfusion of the pre-operatively collected blood will be exposed to these risks without potential benefits and contribute to wastage.(88)

Intraoperative cell salvage (ICS) involves the collection, filtration and re-transfusion of shed blood during surgery.(89) In a recent review of other surgical procedures with significant blood loss, use of ICS has been associated with a relative risk of allogeneic transfusion of 0.62 (95% CI 0.55-0.70).(90) ICS has historically been avoided in oncologic surgeries due to theoretical fear of transfusing malignant cells and promoting diffuse metastases; however, this
has not been supported by recent clinical and biochemical evidence.(91-96) ICS takes advantage of blood that is naturally shed during the operation, avoiding issues associated with drawing additional blood from patients.

These three strategies attempt to use patients’ own blood to avoid the negative outcomes associated with immunomodulation following receipt of RBCT. Each, however, is associated with high costs and resource utilization and may introduce safety risks for patients. Directing these resources only to patients who will benefit is crucial. In order to facilitate this, accurate prediction of patients at elevated risk of transfusion is necessary.

**Predicting Transfusion Risk for Hepatectomy Patients**

While some patients may experience high volumes of blood loss during hepatectomy, many others will not. With such a complicated procedures and diverse patient populations, predicting which patients are at risk of extensive blood loss can be challenging. Factors associated with increased blood loss include gender, body mass index, extent of resection, location of the tumor, prothrombin time, and use of hemostatic devices during the procedure.(97-99) These factors are insufficient to assess need for transfusion, however, as they do not consider the patient’s capacity to tolerate and/or recover from extensive blood loss. Factors associated with transfusion in hepatectomy include: pre-operative hematocrit, pre-operative albumin, comorbidities and anticoagulation/bleeding disorder.(58) Methods to predict patients who will require RBCT during or following hepatectomy have been explored by four groups, each developing a transfusion risk score (TRS).

**Methods for Developing Transfusion Risk Scores**

Four TRSs have been developed to predict an individual patient’s risk of RBCT.(100-103) Each model was developed by examining the unadjusted relationship between pre-operative factors and receipt of RBCT using a univariable logistic regression model. Factors showing a statistically significant relationship were included in a multivariable model, and
independent predictors of RBCT were assigned points to create a TRS for each patient. These predictive factors and methods to calculate each TRS are shown in Table 1.

The accuracy of each TRS to distinguish between patients who receive a transfusion and those who do not, or the discriminative ability, was assessed by each model. Discrimination is evaluated by examining two patients, one who received a RBCT and one who did not, and assessing the likelihood that the patient who received the RBCT has a higher TRS.(104, 105) The discrimination can be assessed by examining a receiver operating characteristic curve, or ROC. The ROC curve plots the sensitivity (true positive rate) rate against 1 – specificity (false positive rate). In other words, it displays the number of correct predictions across different thresholds of false positive rates. The discriminative ability of the ROC curve can be quantified using the area under the ROC curve (AUC). The AUC of a predictive model lies between 0.5, indicating no predictive advantage over assuming a 50% probability of either outcome, and 1.0, indicating perfect predictive ability of the model to predict the outcome.(104)

Some TRSs also assessed the calibration of the model. Calibration refers to how well the model reflects the dataset, and is often evaluated by examining the degree of agreement between predicted and actual probabilities.(104, 105) The degree of agreement can be visually assessed using scatterplots of the actual and predicted probabilities, where a slope of 1 would be observed for perfect agreement.(104, 106) The predicted probabilities are calculated from the logistic regression model. The actual probabilities are derived from local regression of the actual outcome, receipt of RBCT.(104, 106, 107) Local regression applies a non-parametric fit to data that do not adhere to commonly used parametric models (linear, quadratic, etc.) In this instance, it is used to provide a fit for binary data (receipt or no receipt of RBCT).

In order for TRSs to be applicable to a wider population, they must be both reproducible and generalizable.(107) A model that is reproducible is internally valid, indicating the same results are found when it is repeatedly applied to different samples within the same setting.(107)
A common way to assess this is using a split sample design, where the model is derived on a portion of the data and the performance of the model is compared between the sample on which is was derived and the remaining portion. Another important factor to consider is whether the model is applicable to a wider population. This requires the external validity to be assessed, which evaluates the performance of the model outside of the setting on which it was derived (ideally on an independent dataset).(107) It is important for a model to be externally valid for other groups to apply the model to their own setting. Differences in patient populations, institutional characteristics, and geographical and temporal restrictions are some factors that can threaten external validity.(107)

**Yamamoto's Transfusion Risk Score**

Yamamoto and colleagues developed a TRS to predict receipt of intra-operative RBCT for patients with hepatocellular carcinoma undergoing hepatectomy.(100) The model was developed on 168 patients who underwent hepatic resection between 2001 and 2010, where 38 (22.6%) received an intra-operative RBCT. Predictive factors in this model were: α-fetoprotein ≥80 ng/mL, tumor size ≥4 cm, platelet count <100 x 10^9/L, and a major hepatectomy (Table 1). Scores of 0 to 5 were possible, with transfusion rates ranging from 3% in patients with zero points up to 45% in patients with a score of 3 or greater. Discriminative ability was high, with an AUC of 0.758. There was no assessment of internal or external validity. As this model only included patients with hepatocellular carcinoma and was limited to identifying receipt of intraoperative transfusions alone, it applies only to a small subset of hepatectomies.

**Cockbain's Transfusion Risk Score**

Cockbain and colleagues developed a TRS on a cohort of 589 patients undergoing hepatectomy at a single centre the United Kingdom between September 2004 and March 2008.(101) Peri-operative RBCT, defined as occurring within the first 48 hours from the time of surgery, occurred in 17% of patients. Seven factors were identified in a multivariable logistic regression model and assigned one point each in a TRS: coronary artery disease, pre-operative
biliary drainage, prior liver resection, tumour size greater than 3.5 cm, hemoglobin <12.5 g/dL, resection of five or more segments, and diagnosis of cholangiocarcinoma (Table 1). The reported Area Under the Curve (AUC) was 0.77. Neither internal nor external validity was assessed.

**Sima’s Transfusion Risk Score**

Another TRS was developed by Sima and colleagues from 1204 patients having hepatectomy between 1995 and 2000 and subject to temporal validation at the same centre on an additional 555 hepatectomies between 2001 and 2003. The overall peri-operative RBCT rate was 46%. Predictors in the nomogram included the number of segments resected (1 point for 2-3, 4 points for 4-6), primary liver malignancy (1 point), extrahepatic resection (1 point), anemia (<12 g/dL for women, <14 g/dL for men, 2 points) and thrombocytopenia (<125 x10^9/L, 1 point) (Table 1). The AUC was 0.70. The calibration of the model was found to be good, showing high agreement between the expected and observed probabilities.

**Pulitanó’s Transfusion Risk Score**

Pulitanó and colleagues from San Raffaele, Italy derived a TRS using a cohort of 480 hepatectomies between January 1996 and April 2006. A split sample design was used to assess internal validity. The model was derived on 360 patients with a RBCT incidence of 37.7% and identified five predictive factors each assigned one point: hemoglobin ≤12.5 g/dL, exposure of the vena cava, cirrhosis, extra-hepatic resection, and tumour size >4 cm (Table 1). The AUC reported was 0.89 in the validation cohort of 120 patients. Pulitanó’s model was subject to an independent external validation using a cohort of 205 patients having a hepatectomy between 2008 and 2009 in Paris, France with a lower RBCT incidence of 23.4%. The AUC reported in the external validation was 0.68.

These four transfusion risk scores have largely not been incorporated into clinical practice. There are a number of limitations to these TRSs that currently exist. Firstly, calculation of each TRS requires four to seven factors to be assessed, variable numbers of points to be
assigned and for the total points to be associated with a risk of RBCT. Such a process may be too complex to be practical for use in a busy, clinical environment. Secondly, no comparative studies have been performed to identify a superior TRS that should be used by surgeons. And finally, information on external validity is limited, making it unclear whether each TRS will be applicable to independent groups of hepatectomy patients. All of these issues are preventing the translation of TRSs into clinical practice. One simple yet universal TRS would allow for better uptake by surgical teams to assess patient risk of transfusion and direct resources accordingly to reduce overuse of RBCTs.

**Objectives**

Multiple strategies exist to prevent blood loss and reduce RBCTs in hepatectomy. Targeting these resources to appropriate patients is highly complex and increasingly challenging. Here, we aimed to determine whether one strategy, ICS, could be cost minimizing when used in hepatectomy and targeted to patients with a particular risk of receiving a RBCT. Additionally, we aimed to identify the optimal strategy to assess patients undergoing hepatectomy’s risk of RBCT in the pre-operative setting; one that is both highly accurate and easy for clinicians to use in a busy clinical environment. Our specific aims are to:

i. Evaluate the cost efficiency of intraoperative cell salvage in hepatectomy.

ii. Assess the external validity of currently existing transfusion risk scores on a multicentre, contemporary cohort of patients undergoing hepatectomy.

iii. Create a simplified transfusion risk score that will enable use in the clinical environment without limiting predictive value.
Chapter 2: A Decision Model and Cost Analysis of Intra-operative Cell Salvage during Hepatic Resection

Abstract

Background Intraoperative cell salvage (ICS) can reduce allogeneic transfusions but with notable direct costs. This study assessed whether routine use of ICS is cost minimizing in hepatectomy and defines a subpopulation of patients where ICS is most cost minimizing based on patient transfusion risk.

Methods A decision model from a health systems perspective was developed to examine adoption and non-adoption of ICS use for hepatectomy. A prospectively maintained database of hepatectomy patients provided data to populate the model. Probabilistic sensitivity analysis was used to determine the probability of ICS being cost-minimizing at specified transfusion risks. One-way sensitivity analysis was used to identify factors most relevant to institutions considering adoption of ICS for hepatectomies.

Results In the base case analysis (transfusion risk of 28.8%) the probability that routine utilization of ICS is cost-minimizing is 64%. The probability that ICS is cost-minimizing exceeds 50% if the patient transfusion risk exceeds 25%. The model was most sensitive to patient transfusion risk, variation in costs of allogeneic blood, and number of appropriate cases the device could be used for.

Conclusions ICS is cost-minimizing for routine use in liver resection, particularly when used for patients with a risk of transfusion of 25% or greater
**Introduction**

Surgical resection remains the mainstay for curative-intent treatment of liver tumors. Improvements in anatomic approaches, surgical technologies, anesthetic and peri-operative care have produced superior outcomes in modern hepatic surgery; however, blood loss remains a frequent complication. Allogeneic (donor) transfusions (RBCT) may be required to correct significant bleeding events, and occur in up to 50% of liver resections. RBCT have a generally acceptable safety profile in countries with well-developed blood-banking systems, but are associated with the transmission of infectious disease, transfusion reactions, and immunosuppression. For liver resection of colorectal metastases, receipt of RBCTs has been associated with higher rates of post-operative complications and cancer recurrence. Limited availability of donors and high processing costs place further constraints on the use of RBCTs. As such, safe and cost-efficient alternatives to RBCTs are highly desirable for health care providers and their patients.

Intra-operative cell salvage (ICS) offers an attractive method for reducing allogeneic blood transfusion and has been demonstrated multiple surgical contexts. ICS with autotransfusion allows for shed blood to be collected during a surgical procedure. Once a volume of 400-600 mL of blood has been collected, it can be washed, filtered, concentrated, and re-transfused into the patient. Traditionally, ICS has been avoided in oncologic surgery because of concerns regarding the dissemination of tumor cells in shed blood. However, recent literature has provided convincing evidence that standard ICS devices remove malignant cells during filtration. A recent meta-analysis has shown the receipt of autotransfused blood from ICS has not been associated with higher rates of cancer recurrence, dispelling historical concerns.

Use of ICS has been shown to reduce the need for RBCTs in surgical procedures by 38% (RR 0.62; 95% CI 0.55 to 0.70). While ICS may offer the opportunity to reduce costs
associated with intra-operative RBCT, use of the device is accompanied by notable direct medical costs. Optimal utilization of the cell salvage device requires the sterile collection system to be set-up pre-operatively rather than once extensive intra-operative bleeding is identified in order to maximize collection of shed blood. Given the notable set-up costs for the ICS apparatus and the proportion of patients that experience minimal blood loss (and would not require transfusion in any case), several authors have demonstrated that routine application of ICS is not cost-effective for procedures associated with low average blood loss. (113-115) The direct incremental costs of ICS would be considerable for patients with a very low risk of RBCT, but would lessen as the risk of transfusion increases and the potential for reduction of RBCTs becomes more significant. (90) Predictive nomograms for risk of transfusion in hepatic resection based on pre-operative characteristics are available to help identify patients who are likely to require an allogeneic blood transfusion. (100, 102, 103, 108)

In order to determine optimal resource utilization and inform decision-making regarding the use of ICS in hepatectomies, a detailed cost analysis was performed and a decision model constructed to compare the costs associated with adoption and non-adoption of ICS. Costs were compared across a range of transfusion rates to identify the patient transfusion risk where use of ICS becomes cost-minimizing over just providing allogeneic transfusions alone.

**Methods**

**Decision Model**

A decision analytic model was created to examine two scenarios: 1) adoption of routine use of ICS and 2) non-adoption during hepatic resection (Figure 4). Both scenarios were populated with risks and costs associated with each decision to allow for comparison between the two scenarios. A cost-minimization approach was used and assumes equivalent clinical outcomes between patients receiving autologous and allogeneic blood products; therefore, only
which scenario was less expensive was examined. A health system perspective was used to incorporate all incremental costs incurred by the hospital from the patients’ surgery until discharge regardless of length of stay.

The reference population for transfusion risks and quantities of transfused blood was derived from an institutional database of all patients undergoing hepatic resection at a single high-volume hepatobiliary surgical center (Sunnybrook Health Sciences Centre, Toronto, Canada), from 2003 to 2012 (Table 2). Twelve patients were excluded as information on post-operative RBCT use could not be determined. RBCTS were required for 28.8% of patients, with a median of 2 units (range 1-25 units). Probabilities were populated based on the reference population, and supplemented with literature values where required (Table 3). Autologous blood refers to blood collected using ICS; the use of pre-operative autologous donation was not included in the model. Current institutional guidelines recommend RBCT for hemoglobin levels below 7 g/dL, symptomatic non-bleeding patients, or to maintain hemoglobin of 7-8 g/dL in patients who are actively bleeding.

In the pathway without ICS use, the probability of the patient receiving RBCT is determined by a specified transfusion risk, defined as 28.8% in the reference case. There are no costs associated with no ICS use and no allogeneic transfusion. If allogeneic blood is transfused, transfusion quantities were stratified as 1 unit, 2 units, 3 units, 4 units, 5 units, a large transfusion of 6-10 units, or a massive transfusion of 11-25 units. The risk of receiving a specified transfusion volume was determined from the database cohort.

In the pathway with ICS use, three branches exist: no autotransfusion, autotransfusion but no allogeneic transfusion, and autotransfusion plus allogeneic transfusion. The relative risk of allogeneic transfusion with ICS was defined as 0.62 (95% CI 0.55-0.70) based on a published systematic review and meta-analysis for various other surgical procedures. (90) The model
assumes that ICS is set-up at the beginning of each case and that a minimum estimated blood loss of 750 cc was required for autotransfusion. (92)

**Cost Analysis**

The economic evaluation considers all direct medical costs associated with ICS and RBCT that were individually identified, costed and summed. All costs were initially collected in Canadian dollars (CAD) and converted to American dollars (USD) (1.00 CAD = 0.87869 USD, 2014).

The cost of the cell salvage device, Sorin Xtra, was based on the purchase price with an additional 10% for maintenance fees. The total cost was divided over the number of cases it currently services, an average of 117 per year over a lifespan of ten years. Unit costs of consumables related to the use of ICS were determined from institutional purchasing data and product manufacturers. The personnel time to operate the ICS device was evaluated based on the average reported salary of anesthesia assistants and perfusionists. (116) The cost of a single unit of allogeneic red blood cells used in the analysis was based on a published activity-based cost from a health system perspective. (32)

When ICS is not used, only the costs of RBCTs are considered. When ICS is used, the costs of set up and collecting blood with ICS are considered (Table 3). When autologous blood is re-transfused, the cost of filtration and transfusion are added to costs of collection, including additional personnel time and disposable material costs. When autologous and allogeneic blood is transfused, the costs of the allogeneic transfusion are added.

**Sensitivity Analysis**

Probabilistic sensitivity analysis was used to examine the impact of parameter uncertainty on the outcomes of the decision model. In this technique, distributions are assigned
to the costs and probabilities within the model. A Monte Carlo simulation was performed, where in each simulation a value for each parameter was selected based on the assigned distributions and a total cost per simulation was determined for each arm in the model (use of ICS and no use of ICS). The costs per simulation in each arm were compared, and the cost minimizing option identified. This was repeated for a total of 10,000 simulated patients to generate a probability that ICS is the cost minimizing option.

The use of probabilistic sensitivity analysis allows for the results to better reflect the uncertainty around each parameter experienced in reality. In this study, parameters assigned a distribution include the number of units of allogeneic blood transfused to patients in the large and massive transfusion groups based on the reference population. The cost of an ICS device was given variation based on retail costs and the negotiating potential of the institution. Costs of anesthesia assistant time were expanded to allow for variation between personnel. The probability of sufficient blood collection to allow for autotransfusion was varied by broadening the definition of estimated blood loss required to allow for autotransfusion. The relative risk of receiving an allogeneic transfusion when ICS is used and costs of RBCTs were derived from the literature; therefore they were assigned a distribution based on the reported variation.(32, 90) All 10,000 simulations were repeated at multiple patient risks of transfusion (from 0% to 100%) to construct a likelihood of ICS being the cost minimizing option based on the patient transfusion rates

Factors that may be significant for outside institutions considering adoption of ICS for liver resection were identified and their impact on the final results was evaluated using one-way sensitivity analysis. Important factors were considered to be those that caused the most fluctuation in the results. While many of the same factors were considered in the probabilistic sensitivity analysis, the one way sensitivity analysis allows for the absolute variation specific to each individual factor to be considered. This may be important for institutions considering
adoption of use of ICS in hepatectomy, as the relative variability of each factor can be easily compared. Personnel time was extended from 5 to 20 minutes for autologous blood collection and 10 minutes to 60 minutes for filtration and re-transfusion. The capital costs were varied to assume that an ICS device must be purchased for hepatic resection alone, and varied based on the yearly number of liver resections performed (between 30 and 200). (117, 118) The transfusion risk was varied from 20% up to 50% to evaluated differences in patient and institutional transfusion rates. Finally, relative risk of transfusion when ICS is used and costs of allogeneic blood transfusion were assigned upper and lower limits based on the reported literature values. (32, 90)

Results

The base case was defined as having a transfusion risk of 28.8%, the percentage of patients transfused in the institutional database. At this transfusion rate, ICS was found to be cost-minimizing over supplying RBCTs alone 64% of the time. In other words, the probability that ICS was cost-minimizing at a transfusion risk of 28.8% was 0.64. The average incremental cost savings of use of ICS at a transfusion risk of 28.8% was $45.54 (95% CI, $43.23-$47.85) per patient, with the mean direct costs associated with adoption of ICS averaging $689.83 (95% CI, $686.13-$693.53) and the non-adoption of ICS costing an average $735.38 (95% CI, $729.52-$741.22).

The individual transfusion rate was varied over a wide range and probabilistic sensitivity analysis was used to determine the threshold where routine use of ICS would become cost-minimizing in over 50% of cases (the equivalence point) (Figure 5). When the patient’s transfusion risk is low, the probability that use of ICS is cost-minimizing over as-needed RBCT alone is minimal. This is depicted for patients with 10% transfusion risk, where the probability ICS is cost minimizing is 0.11%, with the average cost of ICS utilization nearly $136.39 (95% CI, $135.54-$137.24) over as-needed allogeneic transfusions. As the transfusion risk increases, the
probability that ICS is cost minimizing also increases. The equivalence point was reached at a transfusion risk of 24.6% (Figure 5). For patients with a transfusion risk of 50%, the probability that ICS is cost minimizing reaches 89.67% representing an average cost savings of $253.96 (95% CI, $249.92-$258.00) with the use of ICS over as-needed allogeneic transfusions.

One-way sensitivity analysis was used to evaluate the impact of institution-specific factors that may influence decision-making for adoption of ICS in hepatic surgery (Figure 6). The analysis was found to be highly sensitive to transfusion risk, causing the results to vary by $290.68. Institutional differences in the cost of allogeneic transfusions cause the results to fluctuate by $133.76. The volume of liver resections/other procedures the device could be used for varied the results by $123.24, which the relative risk of transfusion when ICS is used cause fluctuation of $110.04. The results showed lesser sensitivity to personnel costs, varying the results by only $7.67 for collection of blood and $22.74 for the costs of filtering and re-transfusion of the collected blood.

**Discussion**

ICS is increasingly available yet it has failed to achieve widespread use in oncologic surgeries, largely because of theoretical concerns of tumor dissemination leading to increased local and distant recurrence.(20) Recent outcome-driven literature has shown at minimum comparable rates of cancer recurrence when ICS is used.(89, 91, 93, 112) This evidence is also supported by cytopathological studies that have failed to detect malignant cells in blood that was collected and filtered using modern filtration techniques.(92) Complications of RBCT are well established and include transfusion reactions, transmission of infectious diseases and increased rates of post-operative infections.(28) Furthermore, high costs of provision and limited blood supply challenge the use of RBCT. While incompletely understood, accumulating evidence supports the detrimental impact of RBCT on rates of cancer recurrence and overall survival.(26, 27, 43) Although limitations exist, theoretical concerns of increased cancer recurrence with ICS
have not been supported by evidence and may be well offset by mitigating the better established detrimental impact of RBCT on cancer recurrence and survival.(27, 43)

Optimal application of ICS requires pre-operative identification of patients at greatest risk of significant intra-operative blood loss in order to have the device available to collect shed blood. In the model, the probability that ICS was cost-minimizing exceeded 50% in individual patients or patient populations with a pre-operative risk of RBCT that exceeded 25%. Due to the significant fixed costs of ICS, application in patients at a lower risk of transfusion was not cost-minimizing when compared to the strategy of as-needed RBCT alone. Naturally, greater probabilities that ICS are cost-minimizing are achieved at greater patient-specific risks of transfusion. These findings suggest that use of ICS would be cost minimizing for hepatectomy populations with an overall transfusion risk of 25% or greater. To be most cost efficient, surgical teams can target ICS use only in patients with a pre-operative transfusion risk of 25% or greater. This would avoid use of ICS in patients that are less likely to require RBCT and where routine use of ICS is expected to be more expensive that providing RBCT alone, further increasing the cost efficiency of ICS in hepatectomy.

Predicting pre-operative risk of RBCT is aided by previously reported predictive models. A transfusion risk score is provided by Sima et al. based on an American hepatectomy population with a transfusion risk of 46%.(102) This predictive model allows the individual hepatectomy patient’s peri-operative risk of RBCT to be calculated based on the patient’s preoperative hemoglobin and platelets levels, number of segments resected, whether an extra-hepatic resection was planned, and the diagnosis.(102) Another transfusion risk score was developed in Italy and validated in France that uses pre-operative hemoglobin, cirrhosis, exposure of the vena cava, associated surgical procedures and size of the tumor to predict RBCT risk for hepatectomy patients.(103, 108)
The model was designed from a health systems perspective to assist surgical teams’ decision-making when considering costs associated with ICS use in liver resection. A societal perspective was not adopted, which would consider the costs incurred by society as a whole rather than just limited to the hospital. In particular, this would consider time spent by allogeneic blood donors, and thus a societal perspective would be expected to favor the use of ICS. Additionally, reducing RBCTs has been identified as a societal priority in healthcare, giving hospitals considerations other than cost to reduce the use of RBCTs. This decision model is the only cost tool available for surgical oncology teams interested in incorporating ICS use into routine practice. The design of the model allows the cost impact of ICS to be determined in the pre-operative setting to aid surgical teams in planning for use of ICS. With other considerations for use of ICS other than cost including reducing allogeneic blood units, individual institutions may have reason to consider the use of ICS more widely.

The costs included in this analysis are specific to a large tertiary referral hepatobiliary center with a high volume of liver resections, approximately 100 per year. This allows the institution to benefit from economies of scale, where a cell salvage device dedicated to liver surgery would become less expensive across many liver operations. If this is unreasonable for other institutions based on volume of liver resections, it may be beneficial to share cell salvage costs with other types of surgical cases. There are other institutional factors that may compromise the external validity of the model, including transfusion rates and the variable institutional costs associated with allogeneic blood transfusions. This was explored using one way sensitivity analysis to assist institutions with decision making regarding the cost impact of incorporating ICS into hepatectomy.

This decision model was limited to considering only the cost impact of allogeneic transfusions, and clinical outcomes resulting from receiving salvaged and allogeneic blood were not incorporated. The costs of an adverse event following allogeneic transfusion such as
transfusion reaction were not included in the model. Incorporation of these events into the decision model would increase the costs associated with RBCT, and favor use of ICS. Additionally, the decision model assumes a uniform decrease in RBCT rates but does not account for a decrease in quantity of transfused blood. This has shown to be significant in other blood conservation strategies, and could underestimate the cost savings potential of ICS. Allogeneic blood transfusions have been associated with higher rates of cancer recurrence and post-operative complications following liver resection for colorectal metastases. It is unclear whether use of salvaged over allogeneic blood would have similar consequences, but this could certainly alter decision-making regarding the use of ICS in liver resection for both avoiding and reducing quantities of allogeneic blood transfused. Other blood salvage techniques were not incorporated into the decision model, and this analysis examines only a piece of comprehensive strategies to reduce blood loss in practice.

The incorporation of ICS in oncologic surgeries has the potential to be cost saving by reducing the number of allogeneic blood transfusions. This was shown to be a cost-minimizing strategy for patients undergoing liver resection, although dependent on transfusion rates, the number of surgical procedures the cell salvage device will be used for, and the costs associated with allogeneic transfusion. Use of cell salvage in this hepatectomy population was found to be a cost minimizing strategy if used for all hepatectomies. However; to be most cost efficient, patients undergoing liver resection with a predicted transfusion risk of 25% or greater should be targeted.
Chapter 3: Three Point Transfusion Risk Score in Hepatectomy

Abstract

Objectives To compare the predictive ability of currently existing transfusion risk scores (TRSs) in a multicentre cohort of patients and to develop a simplified TRS for easier use.

Summary Background Data Peri-operative red blood cell transfusion (RBCT) is common in patients undergoing hepatectomy. Previous research has developed three TRSs to assess a patient’s risk of peri-operative RBCT.

Methods A database of patients undergoing hepatectomy at four specialized centres between 2008 and 2012 was developed. Discrimination and calibration were used to assess external validity. The discrimination was evaluated using the area under the receiver operating characteristic curve (AUC). Calibration was evaluated by the degree of agreement between predicted and actual RBCT probabilities. A simplified TRS using variables common to the three models was created and evaluated for discrimination and calibration.

Results There were 1287 hepatectomy patients included in this study, with 341 (26.5%) receiving a RBCT. Discriminative ability was similar between the three TRSs, with AUCs of 0.66-0.68 and all with good calibration. A new, “Three Point” TRS was developed based on factors present in all models: hemoglobin ≤12.5 g/dL, primary liver malignancy, and major resection (≥4 segments). Discriminative ability and calibration of the Three Point model was similar to the three existing models, with an AUC of 0.66.

Conclusion The Three Point TRS simplifies assessment of peri-operative transfusion risk in hepatectomy without sacrificing predictive ability. This TRS should be incorporated into clinical assessments to identify patients at higher risk of receiving a RBCT; to appropriately target interventions and reduce RBCTs.
**Introduction**

High volumes of blood loss and requirement for transfusion remain a significant risk for patients undergoing hepatectomy.\(^{(62)}\) Peri-operative red blood cell transfusions (RBCTs) are associated with poorer outcomes following hepatectomy, including higher risk of morbidity, mortality, and cancer recurrence.\(^{(26, 27, 40, 52, 53)}\) RBCTs are a limited resource, reliant on availability of donors and restricted to a short shelf life, in addition to being costly, totalling an estimated $721 (US dollars, 2009) per unit.\(^{(29, 32, 109)}\) RBCTs may be subject to overuse, and reduction of RBCTs has been identified as a societal priority.\(^{(55, 119)}\)

Current strategies to reduce intra-operative blood loss and peri-operative RBCTs in hepatectomy include intra-operative cell salvage (ICS), pre-operative autologous donation (PABD), acute normovolemic hemodilution (ANH), and medications.\(^{(80, 81, 90, 120)}\) These interventions are effective but require substantial resource utilization and are associated with risks of adverse events, limiting their routine use. To appropriately direct resources, accurate prediction of patients who will require RBCT during or after hepatectomy is imperative.

Three transfusion risk scores (TRSs) have been developed to address this issue, using pre-operative factors to assess risk of receiving a peri-operative RBCT for patients undergoing hepatectomy.\(^{(101-103)}\) Each model was developed from patients having surgery at a single institution, making the validity of the TRS on the wider population unknown. In order to gain widespread use by surgical teams, the TRSs must be able to accurately predict peri-operative RBCT on a diverse population of patients undergoing hepatectomy, and must be simple and easy-to-use in the pre-operative clinical setting. In this study, an independent external assessment of the validity of currently existing hepatectomy-specific was performed TRSs using a multicentre database of patients undergoing hepatectomy. An additional aim was to determine whether the models could be further simplified without sacrificing performance in order to promote their use in a busy clinical environment.
Methods

Transfusion Risk Scores

A literature review was conducted using Ovid MEDLINE (1996 to 2016) and EMBASE (1980 to 2016) database to identify studies that developed a predictive model or method to assess individual patients' peri-operative transfusion risk when undergoing hepatectomy. The search terms “hepatectomy” and “transfusion” were combined with either “predict,” “predictor,” “risk,” or “score” to elicit relevant literature. References of pertinent articles were cross-referenced to identify additional articles. Articles were excluded if they were specific to liver transplant donor or recipients, limited to subpopulations of patients (i.e. only patients with hepatocellular carcinoma), evaluated receipt of intra-operative transfusions alone, or if they were not peer reviewed. A total of 129 articles were identified, of which three predictive models were included. Each developed a TRS by assigning points based on pre-operative factors. These three models, developed by Cockbain, Sima, and Pulitanó, were each constructed using a multivariable logistic model on a population of patients undergoing hepatectomy at a single centre. The predictive factors included in each model are compared in Table 4; three factors that were common to all three models were: pre-operative anemia, liver disease, and extent of resection.

External Validation Dataset

A multicentre database of patients undergoing hepatectomy at four specialized hepatopancreatobiliary Canadian institutions was developed (Sunnybrook Health Sciences Centre, Toronto; Foothills Medical Centre, Calgary; London Health Sciences Centre, London; The Ottawa Hospital, Ottawa). All sites’ institutional research ethics boards approved this study. All adult (≥18 years) patients undergoing partial hepatectomy between January 1, 2008 and December 31, 2012 were included.
Peri-operative RBCT was defined as the receipt of allogeneic red blood cells intra or post-operatively during the patients’ hospital stay. Pre-operative laboratory values were recorded as the most recent prior to surgery. Tumor size was determined from pre-operative imaging; in a minority of patients where imaging reports were unavailable, the lesion size from the final pathology report was used. Extent of resection was based on the liver segments resected in the operative note. Exposure of the inferior vena cava (IVC) was defined as occurring in in the following procedures: left hepatectomy, left trisectionectomy, right hepatectomy, right extended hepatectomy, right posterior sectionectomy, or any resection including the caudate. Diagnosis and presence of cirrhosis were defined based on the final pathology report. Pre-operative biliary drainage was not collected in this database, and was not accounted for despite being identified as a predictive factor in the model developed by Cockbain.

Model Evaluation

Descriptive analysis was performed to compare the patient characteristics assessed in the TRSs (the derivation cohorts) with our cohort (the validation cohort). Frequencies were reported as an absolute number (n) with proportion (%) for patients who received and did not receive a RBCT, and were compared using Chi square test. Continuous variables were reported as mean and standard deviation and compared using t-tests. The frequencies of patients among each RBCT risk level were compared between those in the validation and derivation cohorts using Chi square tests. Statistical significance was considered for p≤0.05.

Model performance was evaluated based on discrimination and calibration in the validation cohort. Discrimination is the ability of the model to accurately predict the outcome, in this case, the receipt of a peri-operative RBCT.(104) Here the discrimination was assessed using the area under the receiver operating characteristic (ROC) curve, or AUC. The AUC of a
predictive model lies between 0.5, indicating no predictive advantage over assuming a 50% probability of either outcome, and 1.0, indicating perfect predictive ability of the model. (104) Statistically significant differences in AUC values were detected using DeLong’s nonparametric technique to compare AUC values, where statistical significance was considered at \( p \leq 0.05 \). (121)

Calibration refers to the degree of agreement between predicted and actual probabilities. (104) We evaluated the calibration using scatterplots; ideally, a slope of 1 would be observed if the predicted probabilities perfectly match the actual probabilities. (104) The predicted probabilities were generated by the logistic regression model of the TRS. (105) Because the outcome is a binary value (receipt/no receipt of a peri-operative RBCT), locally weighted least squares regression was used to smooth the actual outcome in order for calibration to be assessed over a range of predicted probabilities. (104, 106, 107)

**Simplified Three Point Transfusion Risk Score**

A simplified model was constructed based on the three factors existing in all three TRSs: pre-operative anemia, primary liver malignancy, and major liver resection. The definition of pre-operative anemia was based on that reported in two of the three TRSs, hemoglobin \( \leq 12.5 \) g/dL. Major liver resection was defined as four or more segments resected, based on current recommendations. (122) In order to investigate the statistical validity of these cut off values, alternate definitions were explored by examining the values where \( \chi^2 \) was maximized between patients who received and did not receive a transfusion.

Each was included in a multivariable logistic regression model, with associated odds ratio (OR) and 95% confidence intervals (95% CI) reported. A simplified TRS was calculated where each factor contributed one point, creating a simplified RBCT risk assessment based on the three factors reported as independent predictors of RBCT in each model. This simplified
model, or “Three Point” model, was evaluated in a similar fashion to the previously developed models. All analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary NC).

**Results**

1287 patients who underwent partial hepatectomy were included in this analysis, with 341 (26.5%) of patients receiving a peri-operative RBCT. Patient characteristics are shown in Table 5. Predictors of RBCT in the validation cohorts all differed between transfused and not transfused patients except: pre-operative platelets, liver cirrhosis, cholangiocarcinoma, and primary liver malignancy (Table 6).

**Transfusion Rates**

In Cockbain’s model, lower TRS (0-2) was associated with lower RBCT rates in the derivation cohort compared to the validation cohort (Figure 7A). RBCT rates at scores of 3 and 4 did not differ between the two groups. The transfusion rates in Sima’s cohort showed statistically significant differences with the validation cohort at TRSs of 2 and 4 (Figure 7B). In Pulitano’s model, RBCT rates differed between the derivation and validation cohorts at scores of 0, 1, and 3 (Figure 7C). Differences in RBCT rates at the highest score of 5 in both Cockbain and Pulitano’s TRSs could not be evaluated as no patient in the validation cohort received a TRS of 5.

**Discrimination**

The ROC curves of each TRS in the validation cohort are shown in Figure 8. No statistically significant differences in the AUC scores were detected using DeLong’s test (Table 7). The AUC scores were: Cockbain AUC=0.66 (95% CI, 0.63-0.69), Sima AUC=0.66 (95% CI, 0.63-0.70), and Pulitanó AUC=0.68 (95% CI, 0.64-0.71).

**Calibration**
The predicted and observed probabilities are compared in Figure 9. All four models showed good calibration over the range of TRSs. Each TRS predicted risks of transfusion from 10% up to 70%. Cockbain’s model began to over-predict RBCT risk above a predicted risk of approximately 60%. Sima’s model showed less agreement in intermediate ranges of RBCT predicted risk, between approximately 20% and 50%.

**Development of Three Point Transfusion Risk Score**

Transfused and not transfused patients were found to have differing frequencies of pre-operative anemia and major liver resection, but not primary liver malignancy (Table 6). All were independent predictors of peri-operative RBCT in a multivariable logistic regression model (Table 8). The cut off values of both pre-operative anemia and major liver resection were found to produce the highest $\chi^2$ values between transfused and not transfused patients.

The transfusion rates in the Three Point model yielded four risk categories: low risk (RBCT rate of 14%), moderate risk (27%), high risk (48%) and very high risk (62%) (Figure 10). The discriminative ability of the Three Point Model was AUC=0.66 (95% CI, 0.63-0.69), which did not show a statistically significant difference with the three currently existing, more complex TRSs (Table 7). Calibration across the predicted RBCT risk was good (Figure 9).

**Discussion**

In this study, a multicentre database of patients undergoing hepatectomy was used to externally validate three currently existing TRSs. Some variation existed in transfusion rates between the derivation cohorts of Cockbain, Sima, and Pulitanó and the validation cohort. When examining discriminative ability, no statistically significant differences were seen between the three models, and the AUC of the models ranged from 0.66 to 0.68. All the models showed good calibration across a range of predicted transfusion risk from 10% up to 70%.
Each TRS was developed using pre-operative factors with univariate significance to peri-operative RBCTs for inclusion into a multivariable logistic regression model. These TRS models are not easy to employ, having five to seven factors that led to a scoring of zero to nine, which may not have immediately obvious correlation to a clinical interpretation. Three factors were present in all three models, despite variations in patient populations and institutional practices. This signified a potential set of factors that were more robust for generalizability across different institutions. These three factors: (1) anemia (2) liver disease and (3) extent of resection were then investigated as a simplified TRS. This simple, Three Point TRS did not have reduced performance while improving ease of use and clinical applicability, and easily grouped patients into low, moderate, high and very high risk.

Here, pre-operative anemia was defined as pre-operative hemoglobin of 12.5 g/L or less. While this definition corresponds well with current definitions of mild anemia, a large proportion (28.2%) of patients presented with a hemoglobin value of 12.5 g/dL or less. While many patients experience mild anemia pre-operatively, this cut off of 12.5 g/dL was identified by two groups as an important predictor for peri-operative transfusion. In our cohort, 12.5 g/dL was statistically found to be the optimal cut off value for predicting peri-operative transfusion, suggesting hemoglobin of 12.5 g/dL is an important target for clinicians to optimize patients for hepatectomy in order to reduce risk of peri-operative transfusion. Similarly, major liver resection is heterogeneously defined. Defining major hepatectomy based on the number of segments resected is advantageous as it can be applied to a wide range of patients. Commonly used cut offs for major hepatectomy are three or four segments resected; however, resections of four or greater segments has been shown to be a superior definition when examining post-operative morbidity and mortality. A definition of four or greater segments resected was used here to match current recommendations.
Frequencies of anemia and major liver resection were both found to differ between transfused and not transfused patients; however, primary liver malignancy did not. When these factors were included in a multivariable logistic regression model, all were independent predictors of receipt of RBCT. Rates of anemia were lesser in patients with primary liver malignancies than those without, the majority of who had colorectal liver metastases. Bleeding from the primary tumour and previous surgery or chemotherapy could explain the lower hemoglobin in this group of patients, and the lack of a significant relationship between primary liver malignancy and receipt of RBCT without adjusting for anemia.

An issue with measuring discrimination in each model in the past was the validation of the TRS using too homogenous of a patient cohort (such as single centre) that limited generalizability. This phenomenon is clearly demonstrated when contrasting the AUC of Pulitano’s TRS in external validation (0.68) compared to the AUC of 0.89 reported by Pulitano.(108) This study evaluated the discrimination of the TRS and demonstrated that they consistently had moderate predictive ability when applied to a wider population. The lack of statistically significant differences between the previous models and the Three Point TRS suggest that the increased complexity of the previous models do not improve discriminative ability.

Calibration was not assessed by Cockbain or Pulitano in their derived model. Sima examined scatterplots of predicted and actual probabilities to detect any over or under estimated ranges. Here we employed the same method of comparing the predictive and actual RBCT risk. Good calibration was shown for each model, suggesting the predicted probabilities of patients receiving a RBCT agree closely with the actual probability of RBCT.

Here all TRSs assessing peri-operative RBCT risk in hepatectomy patients were considered for inclusion in this study. Another score developed by Yamamoto et al. examined
intra-operative RBCT risk for hepatocellular carcinoma patients undergoing hepatectomy; however, this TRS was not included as the patient population and outcome were more restrictive. (100)

Multiple strategies exist to reduce intra-operative blood loss and allogeneic RBCTs, but are not needed for all hepatectomy patients. PABD is a potentially appealing strategy for avoiding RBCTs, however is associated with high waste and potentially harmful reduction in pre-operative hemoglobin levels. (66, 81, 83, 84) ANH has shown more promising benefit, but complicates anesthetic care and can also create wastage. (85, 86) Another technique, ICS, may reduce wastage but can be associated with high costs when used for patients who will not require RBCT. (126) Multiple studies have called for pre-operative identification of patients most likely to benefit from these techniques in order to allocate resources accordingly. (80, 86) Some research has been directed at identifying patients likely to benefit from a particular resource; however, a TRS can be more universally applied to assess a number of strategies as well as to provide patients with an idea of their own individual risk of transfusion. (88, 126)

A major strength of this study was the ability to evaluate the existing TRS models in a combined dataset of four specialized regional centres where all sites employed a restrictive RBCT protocol, restricting RBCT to patients without cardiac comorbidity having hemoglobin levels <7 g/dL. This allows for the generalizability to a wider, diverse population to be assessed. The database was largely complete with very little missing data, avoiding issues associated with imputation or exclusion of missing data points. The data values were collected to reflect as closely as possible the information available to surgical teams pre-operatively, including obtaining the size of lesions from pre-operative imaging rather than the final pathology. It therefore better mirrors the prospective evaluation of a patient’s TRS by surgical teams.
This study is limited by its retrospective nature, and does not directly assess the accuracy of prospective use of a TRS in a clinical setting. In addition, the value of this information in targeting resources appropriately is not assessed here, nor is an appropriate risk threshold defined. A previous randomized controlled trial examining the prospective use of a nomogram to direct use of acute normovolemic hemodilution found that while appropriate use of the strategy did not improve overall, use in cases where benefit was expected to be minimal was reduced.\(^{(88)}\)

In conclusion, this study demonstrates the potential of a new simplified Three Point TRS, developed from a validation of existing, more complex, TRS scores. This Three Point TRS considers only pre-operative anemia (hemoglobin ≤12.5 g/dL), primary liver malignancy, and major resection (≥4 segments resected), for a rapid and reliable evaluation of transfusion risk. There is clinical applicability of this score in the clinical planning of a surgical hepatectomy, and may allow for selective application of adjunct strategies and resources to minimize peri-operative RBCT. Future evaluation of this score in a prospective setting will further establish the clinical utility of the Three Point TRS in patients undergoing hepatectomy.
Chapter 4: Discussion

This research evaluated whether ICS can be used cost efficiently in hepatectomy, particularly when directed at patients based on their risk of transfusion. Additionally, we aimed to assess the predictive ability of current TRSs and provide surgeons with a model that is easy to use without sacrificing predictive ability.

Summary of Findings

ICS is an attractive method to capitalize on shed blood during surgery and avoid allogeneic RBCTs. Historically, use of ICS has been avoided in oncologic procedures due to theoretical concerns of transfusing malignant cells and increasing recurrence rates.(20) However; recent clinical and biochemical studies have challenged these beliefs. Use of ICS has not been associated with increased rates of cancer recurrence in multiple disease sites.(89, 91, 93, 112) In addition, biochemical assays have failed to detect malignant cells in blood once filtered using ICS.(92) Current evidence suggests that ICS is safe to use in malignant resections, however, little data exists to inform decision making on where this resource is appropriate to use.

In alternate surgical procedures, ICS reduces risk of RBCTs by nearly 40%.(90) For procedures where likelihood of transfusion is low, the absolute benefit is minimal. This is also true for procedures with minimal blood loss, as a minimum volume of 400-600 mL of blood must be collected in order to allow for filtration and re-transfusion.(92, 114, 115) Because of this, in some surgical procedures ICS has been reported to be costly with little benefit.(113-115) Therefore, it is important to identify patients at risk of RBCT to use this resource appropriately. Optimal use of ICS requires the device be set up prior to incision to maximize the volume of collected blood, requiring decision making regarding use of ICS to occur in the pre-operative setting. To better address this, we used patient risk of RBCT to identify patients or population of
patients who are likely to benefit from ICS, and found that ICS will be a cost minimizing strategy in patients or patient populations with a risk of RBCT of 25% or greater.

Identifying patients or patient populations with a risk of transfusion of or greater than 25% in the pre-operative setting is challenging. Rates of RBCT vary considerably by institution, as do rates by procedure type. (101-103) Knowledge of individual institutional rates of RBCT can help surgeons determine whether ICS use would be cost efficient in their setting. To further reduce use of ICS in procedures where the patient is unlikely to benefit, only individual patients with a risk of RBCT of 25% or greater would be targeted. (115) Predicting patient risk of RBCT in the pre-operative setting is enabled by three currently existing TRSs. (101-103) Each TRS uses only factors known pre-operatively to assess risk of receipt of peri-operative RBCT for patients undergoing hepatectomy. Each score is limited as it was derived only on a single centre, making the applicability beyond this setting unknown. Only one TRS was subject to an independent external validation, where it was found to perform more poorly than on the dataset from which it was derived, but still with moderate predictive ability. (103, 108)

No comparative studies have been performed to compare TRSs and identify an optimal method. Therefore, there is little guidance for surgical teams on which TRS to use. In addition, each TRS contains multiple factors to be assessed in order to compute the TRS. Some of these factors overlap between TRSs, while others are unique to one or two models. In order to address the current limitations of the existing TRSs and promote use in a clinical environment, we assessed and compared the external validity of each TRS. In addition, we examined whether a new, simplified model could maintain similar predictive ability.

Of the three TRSs, all showed moderate discriminative ability with AUCs between 0.66 and 0.68 and no statistically significant differences in the scores were detected. All models achieved good calibration. Calculation of each TRS was relatively complex, with five to seven factors
requiring assessment. There were three general factors required by each model: pre-operative anemia, liver disease, and extent of resection. Use of only these three factors defined as: hemoglobin ≤12.5 g/dL, diagnosis of a primary liver malignancy, and a major liver resection (≥4 segments) created a simplified Three Point TRS. This Three Point TRS is more practical for use in a busy clinical environment without sacrificing predictive ability. In addition, it easily classifies patients into four groups of transfusion risk: low risk (0 points, 14% risk of peri-operative RBCT), moderate risk (1 point, 27% risk), high risk (2 points, 48% risk) and very high risk (3 points, 62% risk). This method for calculating RBCT risk for patients undergoing hepatectomy can be easily integrated into clinical practice, and is an effective way to identify patients at risk of RBCT. This method can be used to direct the use of ICS, and potentially other blood management strategies.

**Implications and Directions for Future Research**

**Decision Model**

A decision model was constructed to mimic the use of ICS in liver resection considering only costs from a health system perspective. Using a societal perspective would incorporate further costs incurred by society as a whole, including impact to patients or family members’ time. Such a perspective would be likely to further favor the use of ICS, as the impact of blood donors’ time would be significant. In addition, this model considered only the costs associated with use or no use of ICS. Units of allogeneic red blood cells are a limited resource, and are reliant on availability of donors, which is one reason that hospitals may wish to encourage ICS beyond costs alone.\(^{(109)}\) In addition, adverse events were not considered, and equivalent outcomes were assumed whether allogeneic or salvaged blood was administered. As the use of allogeneic RBCTs has been associated with poorer short and long term outcomes, use of ICS to limit RBCTs may show potential benefit worth investment. \(^{(26, 27, 35-42, 48, 49, 127)}\) While
recurrence rates have been shown to be similar between patients with and without ICS use during their resection, much of this work has been retrospective in nature and thus subject to bias between selection of patients for ICS use. (91) For a true understanding of the effect of receipt of salvaged blood, a prospective randomized controlled trial is necessary.

**Patient Population and Generalizability**

All the data used for this research was obtained from a database of specialized, tertiary referral hepatopancreatobiliary centres. Because of the retrospective nature, differences in management and decision making were based on clinical or situational factors rather than as designed in a research protocol. This may introduce bias and confounders that even best statistical methods cannot be controlled for. An advantage, however, is that the data represents real world practice and avoids systematic exclusion of patients as seen with prospective designs. In constructing the decision model for ICS use, the true rates and quantities of RBCT were incorporated in the model for nearly all hepatectomies between 2008 and 2012; only 13 patients were excluded based on missing information. In addition, the costs were obtained from institutional billing records. Some data did require supplementation from literature reported values. The costs associated with RBCT are highly variable between institutions; and so we used a comprehensive, activity based cost of RBCT across two North American and two European centres. (32) In addition, as little is known about the use of ICS in surgeries for malignancies, a relative risk of transfusion specific to hepatectomy was not available. Thus, we used a relative risk based on a meta-analysis of 75 randomized controlled trials reporting an overall relative risk of 0.62 (95% CI 0.55-0.70). (90) The relative risk was seen to vary across different types of procedures, from 0.46 in orthopedic procedures up to 0.77 for cardiac procedures, suggesting variability does exist between procedure types.
When examining the predictive ability of TRSs, a comprehensive assessment of external validity was absent from the reported literature and necessary for adoption and use of these TRSs beyond the populations on which they were derived. To address this issue, we used retrospective data from four hepatopancreatobiliary centres compiled by the collaborative HPB CONCEPT team, a collaborative group of surgeons committed to improving care of patients through investigator initiated research. This dataset represents a diverse population of patients, advantageous to assess the generalizability of the TRSs. Although the database is retrospective in nature, careful consideration was used to design the data points as factors that would be pre-operatively known by surgeons. For example, pre-operative imaging was used rather than final pathology to assess factors such as the size of lesions. Such considerations may reduce the predictive ability of the model, but would better reflect use of the model in clinical practice.

**Impact in Directing Blood Conservation Strategies**

We have shown that pre-operative assessment of patient risk of RBCT in hepatectomy is a useful method to identify patients where ICS would be a cost minimizing strategy. This, however, is only a small piece of a comprehensive strategy to reduce RBCTs. Previous research has attempted to predict patients who will benefit from PABD and ANH; however, these prediction models are designed only to assess the impact of the strategy in question.(88, 128) One advantage of a TRS over these nomograms is that it could be theoretically be used to assess the impact of a number of resources.

Ideally in the preoperative setting, surgeons would assign each patient a TRS. From there, they would make an assessment on what resources are appropriate to manage their risk of RBCT. Here, we have shown that a risk of RBCT of 25% or greater would warrant ICS use from a cost perspective, corresponding with a TRS of one or higher. Further evidence is
required to evaluate whether other blood conservation strategies can be targeted based on patient risk of transfusion.

While we have shown reasonable predictive ability in a Three Point TRS, the efficacy of using this TRS to direct resources was not assessed. Previous work developed a nomogram to direct use of ANH, but when prospectively evaluated, the nomogram was not able to improve overall management but did reduce ANH use in patients who were unlikely to benefit from it.\(^{(86, 88)}\) To assess the impact of the TRS, the ability of use of the TRS to avoid transfusions and be cost efficient must be assessed. In addition, evaluation of differences in the short and long term outcomes would be incorporated to identify whether allocation of resources based on this criterion translates to better outcomes for patients.

**Conclusions**

Patient transfusion risk is a useful method to direct blood conservation strategies in hepatectomy. ICS can be used in patients with a transfusion risk of 25% or greater to minimize costs. To do so, transfusion risk must be evaluated in the pre-operative setting. This can be easily performed by considering only whether the patient has anemia (hemoglobin of 12.5 g/dL or less), a primary liver cancer, and whether she/he will be undergoing a major liver resection of four or more segments. Assessing these factors yields four risk categories, of low, medium, high, and very high risk of transfusion. Such assessments should be performed to direct blood conservation resources to appropriate patients and reduce preventable transfusions.
Table 1. Transfusion Risk Scores for Patients undergoing Hepatectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yamamoto et al., 2014</strong></td>
<td></td>
</tr>
<tr>
<td>α-fetoprotein ≥80 ng/mL</td>
<td>1</td>
</tr>
<tr>
<td>Tumour size ≥4 cm</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count &lt;100 x 10⁹/L</td>
<td>2</td>
</tr>
<tr>
<td>Major hepatectomy</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cockbain et al., 2010</strong></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1</td>
</tr>
<tr>
<td>Preoperative biliary drainage</td>
<td>1</td>
</tr>
<tr>
<td>Redo resection</td>
<td>1</td>
</tr>
<tr>
<td>Tumour size &gt;3.5 cm</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin &lt;12.5 g/dL</td>
<td>1</td>
</tr>
<tr>
<td>Extended resection (5+ segments)</td>
<td>1</td>
</tr>
<tr>
<td>Histological diagnosis = Cholangiocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sima et al., 2009</strong></td>
<td></td>
</tr>
<tr>
<td>Number of segments resected</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>1</td>
</tr>
<tr>
<td>4-6</td>
<td>4</td>
</tr>
<tr>
<td>Liver primary malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Extrahepatic organ resection</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin &lt;12 g/L (women) &lt;14 g/L (men)</td>
<td>2</td>
</tr>
<tr>
<td>Platelets &lt;125 x 10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pulitanó et al., 2007</strong></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin ≤12.5 g/dL</td>
<td>1</td>
</tr>
<tr>
<td>Exposure of vena cava</td>
<td>1</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>Associated surgical procedures</td>
<td>1</td>
</tr>
<tr>
<td>Largest tumour &gt;4 cm</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>426 (57.8)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>64 (19-86)</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
</tr>
<tr>
<td>Colorectal metastases, n (%)</td>
<td>484 (65.7)</td>
</tr>
<tr>
<td>Cholangiocarcinoma, n (%)</td>
<td>75 (10.2)</td>
</tr>
<tr>
<td>Hepatoma, n (%)</td>
<td>54 (7.3)</td>
</tr>
<tr>
<td>Neuroendocrine, n (%)</td>
<td>31 (4.2)</td>
</tr>
<tr>
<td>Other metastatic, n (%)</td>
<td>45 (6.1)</td>
</tr>
<tr>
<td>Other primary, n (%)</td>
<td>20 (2.7)</td>
</tr>
<tr>
<td>Other benign, n (%)</td>
<td>28 (4.0)</td>
</tr>
<tr>
<td>Pre-operative anemia</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt;125 g/L, n (%)</td>
<td>210 (28.7)</td>
</tr>
<tr>
<td>Hemoglobin ≥125 g/L, n (%)</td>
<td>521 (71.3)</td>
</tr>
<tr>
<td>Background liver cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Cirrhotic, n (%)</td>
<td>25 (3.4)</td>
</tr>
<tr>
<td>Non-cirrhotic, n (%)</td>
<td>711 (96.7)</td>
</tr>
<tr>
<td>Estimated blood loss (mL), median (IQR)</td>
<td>1000 (500-1500)</td>
</tr>
<tr>
<td>Post-operative allogeneic blood transfusion, n (%)</td>
<td>212 (28.8)</td>
</tr>
<tr>
<td>Transfusion rate in major resections (≥4 segments), n (%)</td>
<td>130 (31.3)</td>
</tr>
<tr>
<td>Transfusion rate in minor resections (&lt;4 segments), n (%)</td>
<td>78 (24.8)</td>
</tr>
<tr>
<td>Quantity of allogeneic RBC units transfused</td>
<td></td>
</tr>
<tr>
<td>No data on quantity transfused, n (%)</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>1u, n (%)</td>
<td>50 (24.0)</td>
</tr>
<tr>
<td>2u, n (%)</td>
<td>74 (35.6)</td>
</tr>
<tr>
<td>3u, n (%)</td>
<td>27 (13.0)</td>
</tr>
<tr>
<td>4u, n (%)</td>
<td>14 (6.7)</td>
</tr>
<tr>
<td>5u, n (%)</td>
<td>10 (4.8)</td>
</tr>
<tr>
<td>Large transfusion (6u-10u), n (%)</td>
<td>26 (12.5)</td>
</tr>
<tr>
<td>Massive transfusion (11u-25u), n (%)</td>
<td>7 (3.4)</td>
</tr>
</tbody>
</table>

Abbreviations: RBC, red blood cell; u, units.
Table 3. Decision Tree Model Costs and Probabilities

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of one allogeneic unit of RBC</td>
<td>761.00(32)</td>
</tr>
<tr>
<td>Cost of 6-10 allogeneic units of RBC</td>
<td>5672.79(32)</td>
</tr>
<tr>
<td>Cost of 11-25 allogeneic units of RBC</td>
<td>12,842.13(32)</td>
</tr>
<tr>
<td>Costs of collecting autologous blood using ICS</td>
<td></td>
</tr>
<tr>
<td>Sorin Xtra and maintenance costs, per case</td>
<td>37.28</td>
</tr>
<tr>
<td>Personnel costs (10 min at $46/hr)</td>
<td>7.67(116)</td>
</tr>
<tr>
<td>Sorin reservoir collection</td>
<td>65.90</td>
</tr>
<tr>
<td>Sorin set collection blood aspiration</td>
<td>21.97</td>
</tr>
<tr>
<td>Saline 0.9%, 3L</td>
<td>4.88</td>
</tr>
<tr>
<td>Heparin, 10,000 U/mL, 5 mL</td>
<td>11.97</td>
</tr>
<tr>
<td>Syringe Tip</td>
<td>0.08</td>
</tr>
<tr>
<td>Costs of filtration and re-transfusion of autologous blood using ICS</td>
<td></td>
</tr>
<tr>
<td>Personnel costs (20 min at $46/hr)</td>
<td>15.34(116)</td>
</tr>
<tr>
<td>Sorin Xtra set bowl</td>
<td>109.84</td>
</tr>
<tr>
<td>Fenwal transfer pack container</td>
<td>4.68</td>
</tr>
<tr>
<td>Filter LipiGard</td>
<td>18.89</td>
</tr>
<tr>
<td>Costs of collection and autotransfusion of blood using ICS</td>
<td>$303.45</td>
</tr>
<tr>
<td>Probability of receiving quantities of allogeneic RBC</td>
<td></td>
</tr>
<tr>
<td>Probability with no ICS of receiving 1u</td>
<td>0.2404</td>
</tr>
<tr>
<td>Probability with no ICS of receiving 2u</td>
<td>0.3558</td>
</tr>
<tr>
<td>Probability with no ICS of receiving 3u</td>
<td>0.1298</td>
</tr>
<tr>
<td>Probability with no ICS of receiving 4u</td>
<td>0.0673</td>
</tr>
<tr>
<td>Probability with no ICS of receiving 5u</td>
<td>0.0481</td>
</tr>
<tr>
<td>Probability receiving a large transfusion (6-10u)</td>
<td>0.125</td>
</tr>
<tr>
<td>Probability of receiving a massive transfusion (11u+)</td>
<td>0.0337</td>
</tr>
<tr>
<td>Probability of receiving only autologous blood OR autologous + allogeneic</td>
<td></td>
</tr>
<tr>
<td>blood when using ICS</td>
<td>0.5928</td>
</tr>
<tr>
<td>Probability with no ICS of receiving allogeneic blood</td>
<td>0.2877</td>
</tr>
<tr>
<td>Relative risk of allogeneic blood transfusion with ICS</td>
<td>0.62(90)</td>
</tr>
</tbody>
</table>

Abbreviations: ICS, intraoperative cell salvage; RBC, allogeneic red blood cells; u, unit; USD, U.S. dollars. All costs were converted from Canadian to US dollars (1.00 CAD = 0.87869 USD, 2014).
<table>
<thead>
<tr>
<th></th>
<th>Cockbain et al., 2010</th>
<th>Sima et al., 2009</th>
<th>Pulitanó et al., 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical history</strong></td>
<td>Coronary artery disease</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Pre-operative biliary drainage</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Prior liver resection</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pre-operate laboratory values</strong></td>
<td>Hemoglobin &lt;12.5 g/dL</td>
<td>Men: hemoglobin &lt;14 g/dL</td>
<td>Hemoglobin ≤12.5 g/dL</td>
</tr>
<tr>
<td><strong>Liver disease</strong></td>
<td>Cholangiocarcinoma</td>
<td>Liver primary malignancy</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td><strong>Burden of disease</strong></td>
<td>Tumour size &gt;3.5 cm</td>
<td>-</td>
<td>Largest tumour &gt;4 cm</td>
</tr>
<tr>
<td><strong>Extent of resection</strong></td>
<td>Extended resection (5+ segments)</td>
<td>2-3 segments resected</td>
<td>Exposure of vena cava</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-6 segments resected</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extrahepatic organ resection</td>
<td>Associated surgical procedures</td>
</tr>
</tbody>
</table>

*Indicates factors present in all three models that were included in a three point simplified transfusion risk score.
**Table 5. Characteristics of Patients Undergoing Hepatectomy at Four Hepatopancreatobiliary Centres (n=1287)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>62 (53-70)</td>
</tr>
<tr>
<td>Pre-operative hemoglobin (g/dL), median (IQR)</td>
<td>13.5 (12.4-14.5)</td>
</tr>
<tr>
<td>Pre-operative platelets (x10^9/L), median (IQR)</td>
<td>225 (182-278)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Colorectal metastases, n (%)</td>
<td>748 (58.1)</td>
</tr>
<tr>
<td>Cholangiocarcinoma, n (%)</td>
<td>120 (9.3)</td>
</tr>
<tr>
<td>Hepatoma, n (%)</td>
<td>127 (9.9)</td>
</tr>
<tr>
<td>Neuroendocrine, n (%)</td>
<td>90 (7.0)</td>
</tr>
<tr>
<td>Other metastatic, n (%)</td>
<td>51 (4.0)</td>
</tr>
<tr>
<td>Other primary, n (%)</td>
<td>9 (0.7)</td>
</tr>
<tr>
<td>Other benign, n (%)</td>
<td>142 (11.0)</td>
</tr>
<tr>
<td><strong>Number of liver tumours</strong></td>
<td></td>
</tr>
<tr>
<td>≤3, n (%)</td>
<td>1076 (83.8)</td>
</tr>
<tr>
<td>4-6, n (%)</td>
<td>127 (9.9)</td>
</tr>
<tr>
<td>7-9, n (%)</td>
<td>33 (2.6)</td>
</tr>
<tr>
<td>≥10, n (%)</td>
<td>48 (3.7)</td>
</tr>
<tr>
<td><strong>Size of largest tumour (cm), median (IQR)</strong></td>
<td>2.7 (1.5-4.8)</td>
</tr>
<tr>
<td><strong>Major liver resection (≥4 segments resected), n (%)</strong></td>
<td>296 (23.0)</td>
</tr>
<tr>
<td>Extrahepatic resection, n (%)</td>
<td>226 (17.6)</td>
</tr>
<tr>
<td>Inflow occlusion, n (%)</td>
<td>301 (23.7)</td>
</tr>
<tr>
<td>Estimated blood loss (mL), median (IQR)</td>
<td>500 (200-1000)</td>
</tr>
<tr>
<td>Procedure time (min), median (IQR)</td>
<td>227 (167-309)</td>
</tr>
<tr>
<td>Peri-operative transfusion, n (%)</td>
<td>341 (26.5)</td>
</tr>
</tbody>
</table>
### Table 6. Patient Characteristics of the Predictors in Reported TRSs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Derivation cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transfused (n=341)</td>
<td>Not transfused (n=946)</td>
</tr>
<tr>
<td><strong>Three Point</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin ≤12.5 g/dL</td>
<td>46.3% (158)</td>
<td>21.6% (204)</td>
</tr>
<tr>
<td>Primary liver malignancy</td>
<td>22.6% (77)</td>
<td>18.9% (179)</td>
</tr>
<tr>
<td>Major resection (24 segments)</td>
<td>50.2% (171)</td>
<td>30.8% (291)</td>
</tr>
<tr>
<td><strong>Cockbain et al., 2010</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>20.0% (20)</td>
<td>11.0% (54)</td>
</tr>
<tr>
<td>Preoperative biliary drainage</td>
<td>15.0% (15)</td>
<td>3.1% (15)</td>
</tr>
<tr>
<td>Redo resection</td>
<td>22.0% (22)</td>
<td>13.5% (66)</td>
</tr>
<tr>
<td>Tumour size &gt;3.5 cm</td>
<td>62.0% (62)</td>
<td>44.4% (217)</td>
</tr>
<tr>
<td>Hemoglobin &lt;12.5 g/dL</td>
<td>47.0% (47)</td>
<td>21.9% (107)</td>
</tr>
<tr>
<td>Extended resection (5+ seg.)</td>
<td>38.0% (38)</td>
<td>15.5% (76)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>22.0% (22)</td>
<td>4.9% (24)</td>
</tr>
<tr>
<td><strong>Sima et al., 2009</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of seg. resected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>21% (119)</td>
<td>36% (229)</td>
</tr>
<tr>
<td>4-6</td>
<td>69% (391)</td>
<td>38% (242)</td>
</tr>
<tr>
<td>Liver primary malignancy</td>
<td>25% (142)</td>
<td>16% (102)</td>
</tr>
<tr>
<td>Extrahepatic organ resection</td>
<td>17% (96)</td>
<td>10% (64)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL, avg ±std dev)</td>
<td>12.3 ±1.8</td>
<td>13.2 ±1.7</td>
</tr>
<tr>
<td>Platelets (x10^9/L, avg ±std dev)</td>
<td>265 ±122</td>
<td>244 ±78</td>
</tr>
<tr>
<td><strong>Pullitanô et al., 2007</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin ≤12.5 g/dL</td>
<td>32.4% (35)</td>
<td>14.2% (30)</td>
</tr>
<tr>
<td>Exposure of vena cava</td>
<td>53.7% (58)</td>
<td>32.5% (69)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>31.5% (34)</td>
<td>22.6% (48)</td>
</tr>
<tr>
<td>Associated surgical procedures</td>
<td>44.4% (48)</td>
<td>23.6% (50)</td>
</tr>
<tr>
<td>Largest tumour &gt;4 cm</td>
<td>62.0% (67)</td>
<td>27.4% (58)</td>
</tr>
</tbody>
</table>

Abbreviations: seg, segments;
Table 7. Comparison of AUCS in TRSs

<table>
<thead>
<tr>
<th></th>
<th>Three Point</th>
<th>Cockbain</th>
<th>Sima</th>
<th>Pulitanó</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC (95% CI)</strong></td>
<td>0.66 (0.63, 0.69)</td>
<td>0.66 (0.63, 0.69)</td>
<td>0.66 (0.63, 0.70)</td>
<td>0.68 (0.64, 0.71)</td>
</tr>
<tr>
<td><strong>DeLong p-value</strong></td>
<td>-</td>
<td>0.83</td>
<td>0.95</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Cockbain</strong></td>
<td>0.83</td>
<td>-</td>
<td>0.83</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Sima</strong></td>
<td>0.95</td>
<td>0.83</td>
<td>-</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Pulitanó</strong></td>
<td>0.37</td>
<td>0.30</td>
<td>0.42</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under receiver operating characteristic curve; TRS, transfusion risk score; 95% CI, 95% confidence interval
### Table 8. Multivariable Logistic Regression Model of the Three Point TRS

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative anemia (hemoglobin ≤12.5 g/dL)</td>
<td>3.17 (2.24-4.16)</td>
</tr>
<tr>
<td>Primary liver malignancy</td>
<td>1.49 (1.08-2.05)</td>
</tr>
<tr>
<td>Major liver resection (≥4 segments)</td>
<td>2.24 (1.72-2.91)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
**Figures**

### Figure 1. Overall Survival of Patients undergoing Hepatectomy for CRLM According to RBCT Status, Where Death within 90 Days Was Included (A) and Excluded (B)

Abbreviations: CRLM, colorectal liver metastases; RBCT, red blood cell transfusion; transfused, received a peri-operative RBCT
Figure 2. Recurrence Free Survival of Patients undergoing Hepatectomy for CRLM according to RBCT Status, Where Death within 90 Days Was Included (A) and Excluded (B)

Abbreviations: CRLM, colorectal liver metastases; RBCT, red blood cell transfusion; transfused, received a peri-operative RBCT
Figure 3. Survival of Patients undergoing Hepatectomy for CRLM, according to the Number of RBCT Units Received, Where Death within 90 Days Was Included (A) and Excluded (B)

Abbreviations: CRLM, colorectal liver metastases; RBC, red blood cells; RBCT, red blood cell transfusion;
Figure 4. Decision Model for ICS Adoption and Non-Adoption in Hepatectomy

Abbreviations: ICS, intraoperative cell salvage
Figure 5 Probabilistic Sensitivity Analysis at Varying Patient Risk of RBCT

Abbreviations: ICS, intraoperative cell salvage; RBCT, red blood cell transfusion
Figure 6 One Way Sensitivity Analyses for the Incremental Costs of Using ICS

Abbreviations: ICS, intraoperative cell salvage; RBC, allogeneic red blood cells; USD, US dollars.
Figure 7. Transfusion Rate Across TRSs in the Derivation and Validation Cohorts of (A) Cockbain et al., 2010 (B) Sima et al., 2009 and (C) Pulitanó et al., 2007

*Indicates statistical significance where p≤0.05
Abbreviations: TRS, transfusion risk score
Figure 8. Receiver Operating Curves of Transfusion Risk Scores
Figure 9. Calibration Plots of Actual versus Predicted Probabilities of RBCT Using the TRSs of (A) Cockbain et al., 2010 (B) Sima et al., 2009 (C) Pulitano et al., 2007 and (D) Three Point

Abbreviations: RBCT, red blood cell transfusions; TRS, transfusion risk score
Figure 10. RBCT Risk Categories Using a Three Point TRS

Abbreviations: RBCT, red blood cell transfusion; transfused, received a peri-operative red blood cell transfusion; TRS, transfusion risk score
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