Transfusion Criteria for Fresh Frozen Plasma in Liver Resection

A 3 + 3 Cohort Expansion Study

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Objective: To establish transfusion criteria for use of fresh frozen plasma (FFP) in liver resection.

Background: Fresh frozen plasma has been transfused in liver resection without adequate supporting evidence, leading to unnecessary use.

Design: Prospective study using a phase 1 dose-escalation, 3 + 3 cohort expansion design, modified for FFP transfusion. We designated a serum albumin level of 3.0 g/dL (step 1) as the starting limit for no transfusion and reduced the level in 0.2-g/dL steps. Advancement to the next step was permitted when the albumin level equaled the target value for the previous step in 3 patients. If the albumin value on postoperative day 2 fell below the target value, 100 mL of albumin, 25%, was transfused on that day and on postoperative day 3. The study continued until high-grade postoperative complications occurred without transfusion. If 1 of 3 patients developed Clavien-Dindo grade II or higher complications, 3 more patients (3 + 3 cohort) were added to the same step.

Setting: Hepatobiliary pancreatic surgery center of a university hospital.

Patients: Patients with hepatocellular carcinoma who had had Child-Pugh class A liver function and an intraoperative blood loss of less than 1000 mL.

Intervention: Transfusion or no transfusion of FFP.

Main Outcome Measure: Reduction of transfusion rate in liver resection.

Results: Of the 213 consecutive patients with liver cancer enrolled, 172 patients (80.8%) fulfilled the inclusion criteria. Step progression proceeded until step 5 (albumin level, 2.2 g/dL) without high-grade complications, but step 2 (albumin level, 2.8 g/dL) required 63 patients to complete because 1 patient developed grade II complications (massive ascites). Step progression was broken off at step 5 in the 172nd patient because the postoperative day 2 albumin value did not fall below the step 4 level (2.4 g/dL), defined as the goal limit. The overall operative morbidity rate was 27.9%; the mortality rate was 0%. The FFP transfusion rate was significantly reduced from 48.6% in a previous series involving 222 patients (unpublished historical data from our institution) to 0.6% (1 of 172 patients) in the present study (P < .001). The postoperative hospital stay in the present study was significantly shorter than that in our previous series (13 vs 16 days; P = .01). Total medical costs were significantly reduced from a median of $21 061 (range, 10 032-59 410) to $17 267 (11 823-35 785; P = .04).

Conclusion: In liver resection, FFP transfusion is not necessary in patients with serum albumin levels higher than 2.4 g/dL on postoperative day 2.


In high-volume medical centers, liver resection for malignant neoplasms has been performed with acceptable blood loss (median, 607 mL; range, 509-750 mL) and satisfactory operative morbidity (25%; range, 16%-44%) and mortality (1.3%; range, 0%-4.7%). Minimizing intraoperative blood loss, avoiding blood transfusion, and strict postoperative management have contributed to these excellent outcomes. Fresh frozen plasma (FFP) has been transfused for supplementation of coagulation factors and maintenance of colloid osmotic balance by supplementation of albumin. Perioperative management with the use of FFP transfusion has contributed to decreased morbidity and mortality. No deaths were reported in a recent series.

See Invited Critique at end of article

However, FFP transfusion is now considered only in specific circumstances, and most high-volume medical centers use very
limited amounts, with no apparent effect on outcomes.\textsuperscript{13,14} The indication for FFP transfusion and the reduction in the volume are attributed to the use of hospital-specific criteria developed empirically; an accurate categorization of patients with no need for perioperative FFP transfusion is unavailable.\textsuperscript{1-4} All currently available criteria have been defined retrospectively and generally include an international normalized ratio (INR) less than 1.5\textsuperscript{15-18} or maintaining postoperative serum albumin levels higher than 3.0 g/dL.\textsuperscript{(to convert to grams per liter, multiply by 10).\textsuperscript{3,12}}

To accurately categorize patients with no need for perioperative FFP transfusion, we performed a prospective study in patients who underwent elective liver resection for cancer. Based on our perioperative management, we used the postoperative serum albumin level as the most straightforward indicator of the need for FFP transfusion\textsuperscript{13,10,20} and then examined how far the level could be decreased without causing adverse events. Our study protocol was derived from a prospective dose-escalation design (ie, a 3 cohort expansion design),\textsuperscript{21} often used to set maximum dosage limits in phase 1 trials of anticancer drugs.

### METHODS

**INCLUSION CRITERIA**

The eligibility criteria included liver function defined as Child-Pugh class A, curative hepatic resection for malignant neoplasms, an intraoperative blood loss of less than 1000 mL without blood or FFP transfusions, adequate bone marrow and renal reserves (white blood cells, >3000/μL [to convert to 10⁶ per liter, multiply by 0.001]; platelets, >50×10⁹/μL [to convert to 10⁶ per liter, multiply by 1.0]; and serum creatinine, <1.5 mg/dL [to convert to micromoles per liter, multiply by 88.4]; and age between 15 and 80 years. Exclusion criteria were preoperative serum albumin levels less than 3.0 g/dL and postoperative occurrence of unstable cardiovascular or renal function, or other serious medical conditions that could not be treated effectively without albumin administration.

An English-language summary of the protocol is available at the Clinical Trials Registry managed by the University Hospital Medical Information Network in Japan (http://www.umin.ac.jp/ctr/index.htm: UMIN000002898). This study was approved by the Nihon University Itabashi Hospital ethics committee, and written informed consent was obtained from all patients.

**LIVER RESECTION**

The indications for surgical resection and the operative procedures were in accordance with the criteria of Makuuchi et al.\textsuperscript{24} Anatomic resection of the Couinaud segment was the first-line operative procedure if permitted by the patient’s functional liver reserve. Minor hepatectomy was defined as limited resection or resection of up to 2 Couinaud segments, and major hepatectomy consisted of more than 2 segmentectomies, left or right hepatectomy, or extended hemihepatectomy.\textsuperscript{25}

### STEP PROGRESSION PROFILE

This prospective study was based on the 3 + 3 cohort expansion design.\textsuperscript{21} The concept of the dose-escalation model is to reach the safety limit in the fewest number of patients. In the present study, the starting target value for the serum albumin level on postoperative day (POD) 2 was 3.0 g/dL (step 1), which was defined according to our FFP transfusion criteria\textsuperscript{3,12}.\textsuperscript{21} (Figure 1). The target level was decreased in 0.2-g/dL steps thereafter (eg, 2.8 g/dL for step 2 and 2.6 g/dL for step 3). When the serum albumin level on POD2 equaled the target step value in 3 patients, the next step was begun. If the serum albumin value on POD2 was below the target step value, the patient was given 100 mL of albumin, 23% (Buminate; Baxter Healthcare Corporation, Westlake Village, California), on POD2 and POD3. No further transfusions were given unless complications occurred.

Progression to the next step was allowed until postoperative complications developed without transfusion or the serum albumin level reached the lowest limit. The complication grade was defined according to the Clavien-Dindo classification, which includes therapeutic consequences and severity of complications.\textsuperscript{23} For each complication, the severity was defined on a scale of I to V. The need for blood transfusion was categorized as grade II. If 1 of 3 patients developed grade II complications, 3 more patients were added to the same step. If grade II or III complications occurred a second time during the same step or grade IV or V complications developed, step advancement was terminated. The lowest limit was defined as the step in which no patient reached the target value. The step progression was discontinued when the serum albumin level did not reach the target step value in any patient after the same number of patients as that in the previous step had been enrolled. The POD2 serum INR and serum albumin values in the step progression protocol were recorded to compare the trends of these variables. Postoperative complications were assessed by a single liver surgeon (Y.K.) who was not involved in subsequent surgical procedures or postoperative treatments.

![Figure 1. Step progression profile. To convert albumin to grams per liter, multiply by 10.](image-url)
Liver Disease; POD2, postoperative day 2.

Inflow blood-occlusion technique. A closed irrigation drain was placed in each cut surface of the liver.

Total surgical costs per patient were compared between the present study and our previous series, on the basis of the Japanese National Health Insurance system. The costs included all hospital fees (eg, operation, drugs, and nursing care) but excluded physicians’ fees.

### STATISTICAL ANALYSIS

The χ² test, paired t test, and Mann-Whitney test were used to compare nominal and continuous variables. Multiple comparisons of trends in laboratory indices of liver function were made by 1-way repeated-measures analysis of variance. Significance was defined as P ≤ .05. All analyses were performed using a statistical software package (JMP version 8.0; SAS Institute, Inc, Cary, North Carolina).

### RESULTS

### RISK ANALYSIS OF THE COMPLICATIONS

Risk factors for postoperative complications were analyzed among 11 perioperative variables in our previous series of patients (2002-2006; 222 patients) who met the same eligibility criteria as those in the present study (Table 1). Among 3 independent factors, we used only the POD2 albumin value (odds ratio, 2.91; 95% CI, 1.58-92.1; P = .02) as an indicator of the need for postoperative intervention.

### ELIGIBILITY CRITERIA

Between January 1, 2007, and June 30, 2008, we enrolled 213 consecutive patients with liver cancer who were scheduled to undergo liver resection (Figure 1). Forty-one patients were excluded; the remaining 172 patients (80.8%) were included. No patient who met the eligibility criteria received intraoperative FFP transfusion.

### STEP PROGRESSION PROFILE

The step progression proceeded from step 1 to step 5 (Figure 1). Step 1 required 15 patients: the serum albumin level on POD2 equaled the target value of 3.0 g/dL in the 5th, 12th, and 15th patients (Figure 2A). Step 2 required 63 patients because a grade II complication (total amount of ascites, 15 137 mL during 2 weeks) developed in the 29th patient. This patient was given additional FFP (7440 mL), followed by a predefined dose of 200 mL of albumin. Step 2 therefore required 6 patients with the target value of 2.8 g/dL to pass and was completed in the 63rd patient. Step 3 had a target serum albumin level of 2.6 g/dL and required 34 patients to complete; 3 patients achieved that level. Step 4 was completed after 3 patients reached the target albumin level (2.4 g/dL) and none of the 30 patients had high-grade complications. Step progression was broken at step 5 in the 172nd patient because the serum albumin level on POD2 did not fall to below 2.4 g/dL in 60 consecutive patients (steps 4 and 5 combined).

Overall, only 1 patient (the 29th patient) needed FFP transfusion to treat postoperative intractable ascites. A total of 20 patients (11.6%) received albumin, 25%, solution according to the protocol, and the median serum albumin level rose to 0.2 g/dL (range, 0.1-0.5 g/dL), which corresponded to the value of 1 step. We rechecked serum albumin levels after albumin administration; the level in all but 1 patient rose above the threshold value at each cutoff value. Only the fourth patient did not reach levels above the value in step 1.

We also determined the INR on POD2 (Figure 2B). The median INR was 1.15 (range, 0.88-1.46). The INR was not above 1.50 in any patient. The INR in the patient who needed FFP transfusion because of ascites was 1.4. Similar trends in INR and albumin levels were confirmed.

### Table 1. Analysis of Postoperative Complications in 222 Patients (2002-2006)^

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complications (n=69)</th>
<th>No Complications (n=153)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67 (52-78)</td>
<td>68 (39-80)</td>
<td>.87</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9 (3.0-5.1)</td>
<td>3.8 (3.0-4.9)</td>
<td>.68</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>0.64 (0.26-2.09)</td>
<td>0.57 (0.27-1.66)</td>
<td>.19</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>INR</td>
<td>0.95 (0.88-1.14)</td>
<td>0.96 (0.83-1.13)</td>
<td>.89</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>ICG-R15, min</td>
<td>10.6 (3.8-36.2)</td>
<td>9.1 (2.2-31.3)</td>
<td>.03</td>
<td>1.06 (1.01-13.3)</td>
<td>.04</td>
</tr>
<tr>
<td>Blood loss, g</td>
<td>548 (5-990)</td>
<td>526 (5-845)</td>
<td>.70</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Operation time, min</td>
<td>322 (195-967)</td>
<td>301 (142-756)</td>
<td>.08</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>POD2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>2.8 (2.4-3.4)</td>
<td>3.0 (2.4-4.0)</td>
<td>.099</td>
<td>2.91 (1.58-92.1)</td>
<td>.02</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>0.96 (0.33-3.27)</td>
<td>0.79 (0.35-2.67)</td>
<td>&lt;.001</td>
<td>9.59 (3.04-125.5)</td>
<td>.002</td>
</tr>
<tr>
<td>INR</td>
<td>1.08 (0.93-1.32)</td>
<td>1.06 (0.85-1.34)</td>
<td>.62</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>MELD score</td>
<td>6 (6-12)</td>
<td>6 (6-11)</td>
<td>.58</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations: ellipses, not applicable; ICG-R15, indocyanine green retention rate at 15 minutes; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; POD2, postoperative day 2.

SL conversion factors: To convert albumin to grams per liter, multiply by 10; bilirubin to micromoles per liter, multiply by 17.104.

Data were significant in the univariate analysis were entered into the multivariate analysis.
SURGICAL OUTCOMES

The albumin levels and INR in 172 patients reached nadirs just after the operation and then gradually returned to preoperative levels (Figure 3). The overall incidence of complications according to the Clavien-Dindo classification was 27.9% (48 of 172) (Table 2). There were 47 grade I complications and only 1 grade II complication; no grade III, IV, or V complications occurred during any step. The frequency of complications accord-
ing to the Clavien-Dindo classification ranged from 23.3% to 33.3%, and there were no significant differences between any step ($P = .68$). Atelectasis, wound infection, and pleural effusion were frequent complications. There were no significant differences in the types of complications ($P = .38$). The duration of hospital stay also did not differ significantly between any step ($P = .61$).

### COMPARISON OF 2 PERIODS

Comparing the results between 2 periods, intraoperative blood loss was significantly higher in the previous series (419 vs 536 mL; $P = .04$) (Table 3). Only 1 of the 172 patients (0.6%) in the present study received additional FFP transfusions (a total of 7440 mL from POD2) because of massive ascites. In our previous series ($N = 222$), 108 patients (48.6%) received a total of 172 160 mL of FFP. Of the total administered volume of FFP, 45.4% was transfused to 108 patients during or just after the operation, whereas 10.1% was transfused on POD3 or subsequently. The median hospital stay in the present study was significantly shorter than in the previous series (13 vs 16 days; $P = .01$). The median total surgical costs were also significantly lower in the present study ($17 267 vs $21 061; $P = .04$), representing an 18% reduction compared with the previous series.

### Table 3. Comparison of Outcomes Between 2 Periods

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Surgical procedure, No. (%)a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>28 (16.3)</td>
<td>39 (17.6)</td>
<td>.49</td>
</tr>
<tr>
<td>Minor</td>
<td>144 (83.7)</td>
<td>183 (82.4)</td>
<td>.49</td>
</tr>
<tr>
<td>Blood loss, median (range), mL</td>
<td>419 (5-920)</td>
<td>536 (5-990)</td>
<td>.04</td>
</tr>
<tr>
<td>FFP transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients</td>
<td>1 (0.6)</td>
<td>108 (48.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total amount, mL</td>
<td>7440</td>
<td>172 160</td>
<td></td>
</tr>
<tr>
<td>Proportion, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POD0</td>
<td>0</td>
<td>45.4</td>
<td></td>
</tr>
<tr>
<td>POD1</td>
<td>0</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>POD2</td>
<td>18.3</td>
<td>20.7</td>
<td></td>
</tr>
<tr>
<td>$\geq$POD3</td>
<td>81.7</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Hospital stay, median (range), d</td>
<td>13 (7-79)</td>
<td>16 (7-93)</td>
<td>.01</td>
</tr>
<tr>
<td>Surgical cost, median (range), $</td>
<td>17 267</td>
<td>21 061</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: ellipses, not calculated; FFP, fresh frozen plasma; POD, postoperative day.

aMajor liver resection, more than 2 segments; minor, up to 2 segments.

This prospective study showed that the lower safety limit of the serum albumin level allowing FFP transfusion to be avoided was 2.4 g/dL in patients undergoing liver resection. There were neither high-grade complications nor deaths without FFP in eligible patients who had Child-Pugh class A liver function and an intraoperative blood loss of less than 1000 mL. We successfully reduced the transfusion rate from 48.7% in our previous series of patients who met the same eligibility criteria to 0.6% in the present series.

Owing to recent advances in liver operations, most centers now use very limited volumes of FFP transfusion in patients who receive liver resection; however, to our knowledge, no previous study has prospectively determined the cutoff value. Patients with no need for perioperative FFP transfusion should be accurately identified and categorized. The objective of FFP transfusion is not only to correct coagulation abnormalities but also to control intractable ascites, which characteristically occurs after liver operations. Makuuchi et al achieved zero operative mortality in more than 1000 liver resections by adhering to a policy of transfusing FFP to maintain total serum protein levels at 6.0 g/dL and serum albumin levels at 3.0 g/dL. Thus, we used the postoperative serum albumin level as an indicator of the need for FFP transfusion in this step-escalation design. In all patients in the present study, the trend in the INR was
similar to that in the albumin level. The INR did not exceed 1.50 in any patient.

In our previous series of 222 patients, 69.2% of FFP was transfused on POD0 and POD1 to compensate for the decrease in the serum albumin level caused by intraoperative blood loss. A similar trend was seen by Martin et al., who used a total of 405 U of FFP (median, 4 U [range, 1-23]) in 260 patients on the basis of the prothrombin values. In their study, 77% of the patients received transfusions within POD2. However, our results suggest that early postoperative use of FFP can be avoided in patients who meet the eligibility criteria that we used. In the present study, patients received albumin, 25%, solution according to the step-progression protocol; all of these patients had serum albumin values higher than 2.4 g/dL. Our results indicate that such patients do not require albumin transfusions.

In clinical oncology, the concept underlying the step-escalation design is to attain the maximum tolerated dosage without reaching dose-limiting toxic effects in the minimum number of patients. The 3 + 3 cohort design contributes to reducing the number of participants treated at biologically inactive doses and decreases the number of patients per step. To our knowledge, this approach has not been used previously to establish criteria for transfusion in operations. Oncologic trials classify toxic effects according to the 0 to 5 grading scales of the National Cancer Institute's Common Toxicity Criteria (http://ctep.cancer.gov/). We used the Clavien-Dindo classification to define a complication grade-based stopping rule. This modification and criteria for the use of FFP transfusion and to contribute to avoiding the unnecessary use of FFP in liver resection.

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Another Bastion of Empiricism Falls?

Adding science to the use of blood and blood products in the military and civilian trauma settings has been an active area of investigation for years. The appropriate use of FFP in the setting of massive blood transfusion requirements is a topic often studied. Interest in these topics has led to the evolution of “transfusion medicine” until it has become a distinct subspecialty. Nevertheless, the appropriate use of FFP after liver resection has not been previously well studied except to document the lack of standards and the significant variability in practice. Patients undergoing resection often have varying degrees of underlying liver disease, making it difficult to anticipate the impact of surgery and the possibility of synthetic dysfunction in the hepatic remnant. Despite great interest and effort, to date, no device, measure, or formula has risen to common use that can reliably predict outcomes after major liver resection. As a result, the (unnecessary) use of FFP after something as common as liver resection has remained distinctly inexact and completely empirical—until now, perhaps.

In a novel approach, Yamazaki et al have taken the 3 + 3 cohort expansion design common in cancer research and applied it to the setting of FFP use after liver resection. By applying this prospective method, they have arrived at a conclusion and given us a discrete threshold for the use of FFP. This new guideline will avoid needless use of FFP, reducing risk and expense. Most important, just perhaps, they have removed another stronghold of empiricism—the practice of medicine that disregards scientific theory and relies solely on practical experience. One down and quite a few more to go.

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