Advantage of autologous blood transfusion in surgery for hepatocellular carcinoma

Yoshito Tomimaru, Hidetoshi Eguchi, Shigeru Marubashi, Hiroshi Wada, Shogo Kobayashi, Masahiro Tanemura, Koji Umeshita, Yuichiro Doki, Masaki Mori, Hiroaki Nagano

Yoshito Tomimaru, Hidetoshi Eguchi, Shigeru Marubashi, Hiroshi Wada, Shogo Kobayashi, Masahiro Tanemura, Koji Umeshita, Yuichiro Doki, Masaki Mori, Hiroaki Nagano, Department of Surgery, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita 565-0871, Osaka, Japan
Koji Umeshita, Division of Health Sciences, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita 565-0871, Osaka, Japan
Author contributions: Tomimaru Y was responsible for the review of the literature and initial preparation of the paper; Eguchi H, Marubashi S, Wada H, Kobayashi S, Tanemura M, and Umeshita K supported the preparation; Doki Y, Mori M, and Nagano H prepared the final version of the manuscript.
Correspondence to: Hiroaki Nagano, MD, PhD, Department of Surgery, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka E-2, Suita 565-0871, Osaka, Japan. hnagano@gesurg.med.osaka-u.ac.jp
Telephone: +81-6-6879-3251 Fax: +81-6-6879-3259
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Abstract

AIM: To evaluate the significance of autologous blood transfusion (AT) in reducing homologous blood transfusion (HT) in surgery for hepatocellular carcinoma (HCC).

METHODS: The proportion of patients who received HT was compared between two groups determined by the time of AT introduction; period A (1991-1994, n = 93) and period B (1995-2000, n = 201). Multivariate logistic regression analysis was performed in order to identify independent significant predictors of the need for HT. We also investigated the impact of AT and HT on long-term postoperative outcome after curative surgery for HCC.

RESULTS: The proportion of patients with HT was significantly lower in period B than period A (18.9% vs 60.2%, \( P < 0.0001 \)). Multivariate logistic regression analysis identified AT administration as a significant independent predictor of the need for HT (\( P < 0.0001 \)). Disease-free survival in patients with AT was comparable to that without any transfusion. Multivariate analysis identified HT administration as an independent significant factor for poorer disease-free survival (\( P = 0.0380 \)).

CONCLUSION: AT administration significantly decreased the need for HT. Considering the postoperative survival disadvantage of HT, AT administration could improve the long-term outcome of HCC patients.

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Key words: Hepatocellular carcinoma; Surgery; Autologous blood transfusion; Homologous blood transfusion

Peer reviewer: Dr. Assy Nimer, MD, Assistant Professor, Liver Unit, Ziv Medical Centre, BOX 1008, Safed 13100, Israel

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INTRODUCTION

Surgical resection is a safe and effective treatment for hepatocellular carcinoma (HCC). Because HCC usually develops in patients with liver cirrhosis, most of such patients present with bleeding tendencies related to...
chronic liver dysfunction\[1-3\]. Therefore, surgery for HCC frequently requires intraoperative transfusion. Homologous blood transfusion (HT) is necessary for patients with excessive intraoperative bleeding, though this is still associated with risks of infections and/or immunological complications\[4\]-\[8\]. Moreover, evidence suggests that HT may be adversely associated with tumor recurrence and poor postoperative survival in various kinds of cancers\[8\]-\[13\]. Autologous transfusion (AT), which represents collection and reinfusion of the patient’s own blood or blood components before surgery, and has been developed as a strategy to reduce the need for HT, is currently used for patients scheduled for surgery for various diseases including HCC\[11\]-\[17\]. It has been the policy in our hospital since 1995 to prepare for AT for patients scheduled for HCC surgery. To date, several investigators have examined the significance of AT in terms of reducing the need for HT and of postoperative outcome, but only a few were conducted with proper statistical analyses to identify the significance of AT\[16\]-\[17\].

In the present study, we reviewed the frequency of HT and AT administration in patients undergoing surgery for HCC, and statistically analyzed the significant factors that could predict the need for HT. We also compared the difference between the effects of AT and HT on long-term postoperative outcome after curative surgery for HCC.

MATERIALS AND METHODS

The present study included 294 patients with HCC who underwent hepatic resection at the Department of Surgery, Osaka University Hospital between January 1991 and December 2000. In 93 patients between 1991 and 1994 (period A), AT was not administered, and, when blood was needed, HT was administered. Between 1995 and 2000 (period B), AT was carried out preoperatively in the remaining 201 patients provided: (1) they agreed to the storage; (2) their hemoglobin (Hb) level was $\geq 11.0\ g/dL$ before storage; and (3) they were free of severe cardiopulmonary and/or cerebrovascular diseases, or infection. Autologous blood was collected 1 to 3 times, with 200-400 mL of blood at a time. The blood was stored in a liquid state without freezing. Iron supplements were given daily to the patients who deposited the autologous blood in the post-storage period. In addition, if the total volume of the collected blood was $\geq 800\ mL$, recombinant human erythropoietin was administered. All through the study period, during hepatic resection, blood transfusion was carried out when the Hb level fell to $< 8.0\ g/dL$ in patients with normal cardiopulmonary function or $< 9.0\ g/dL$ in patients with severe cardiopulmonary or cerebrovascular diseases. In patients who had previously deposited autologous blood, autologous blood was first used prior to homologous blood. In this study, patients who required HT were defined as the HT group, irrespective of prior AT, and the remaining patients without HT were defined as the non-HT group.

Furthermore, patients in whom only AT was performed were defined as the AT group, and patients without AT or HT were as defined as the non-transfusion group.

Hospital records were collected retrospectively to gather clinical information including clinical factors, tumor-related factors and surgery-related factors. In patients with autologous blood storage, preoperative Hb was indicated as Hb before the storage. The surgical procedure was selected based on the extent of the tumor and residual liver function. The indication for surgery and selection of surgical procedure were not different between period A and period B. The histological grade of differentiation of HCC was determined according to the Edmondson-Steiner classification, and was based on the areas of the tumor with the highest grade\[14\]. Data were expressed as mean ± standard deviation. Differences between groups were assessed by the chi-square test, Fisher’s exact test or the Mann-Whitney $U$ test. Survival rates were calculated according to the Kaplan-Meier method, and compared using the log-rank test. Multivariate logistic regression analysis was performed for the selection of significant variables. Statistical analysis was performed using StatView (version 5.0; SAS Institute Inc., Cary, NC). A $P$ value $< 0.05$ was considered significant. The study protocol was approved by the Human Ethics Review Committee of Osaka University Hospital and a signed consent form was obtained from each patient.

RESULTS

Table 1 shows the clinicopathological characteristics of patients in period A ($n = 93$) and in period B ($n = 201$). The clinical features, tumor-related features, and surgery-related factors were not significantly different between patients of the 2 groups. HT was administered in 56 of the 93 patients (60.2%) in period A. In period B, HT was administered in 38 patients (18.9%) (HT group), AT in 134 patients (66.7%), and neither AT nor HT in 45 patients (22.4%) (non-transfusion group). In 134 AT patients, the amount of transfused autologous blood was 200 mL in 3 patients, 400 mL in 63 patients, 600 mL in 2 patients, 800 mL in 62 patients, 1000 mL in 1 patient, and 1200 mL in 3 patients. Among the 134 patients with AT, only AT was administered in 118 patients (58.7%) (AT group), and both AT and HT in the remaining 16 patients (8.0%). Figure 1 shows the distribution of patients according to blood transfusion. Thus, the proportion of patients who received HT was significantly lower in period B than in period A ($P < 0.0001$). With regard to disease-free survival examined only in patients with curative surgery for HCC, there were no significant differences between period A and period B; the 1-, 3-, 5-, and 10-year disease-free survival rates were 73.9%, 39.5%, 24.7%, and 7.2% for patients in period A, and 65.9%, 34.8%, 21.9%, and 7.2% for patients in period B ($P = 0.5688$), respectively. The 1-, 3-, 5- and 10-year overall survival rates were 85.7%, 75.6%, 63.1%, and 28.5% for patients in period A, and 92.9%, 70.6%,
In order to identify the factors that can predict the need for HT, various clinical parameters, tumor-related factors, and surgery-related factors were compared between the non-HT group and the HT group (Table 2). The preoperative Hb level was not significantly different between the 2 groups (13.5 ± 1.6 g/dL vs 13.2 ± 1.7 g/dL, P = 0.1708). The proportion of patients who received AT was significantly lower in the HT group than the non-HT group [59.0% (118/200) vs 17.0% (16/94), P < 0.0001]. The maximum tumor size was significantly larger in the HT group than in the non-HT group (4.9 ± 3.7 cm vs 3.6 ± 2.4 cm, P = 0.0003). As for surgery-related factors, there were significant differences in surgical procedure (P = 0.0035), operation time (P < 0.0001), resected liver volume (P < 0.0001), and intraoperative blood loss (P < 0.0001), suggesting that surgery in the HT group was major compared to that in the non-HT group.

To identify significant factors that could predict the need for HT, multivariate logistic regression analysis was performed (Table 3). The analysis was carried out using the 6 significant factors identified in the comparison of the non-HT group and the HT group. The analysis identified AT administration, intraoperative blood loss, and resected liver volume as significant independent predictors for the need of HT (P < 0.0001, P < 0.0001, P = 0.0362, respectively). Long-term postoperative outcome after surgery for HCC was examined. In this analysis, patients were limited to those with curative resection, which was defined as complete removal of all macroscopically evident tumors [non-HT group: 193 patients (non-transfusion group: 78 patients; AT group: 115 patients), HT group: 83 patients]. Among the 276 patients, 37 patients (13.4%) were followed-up for more than 10 years. The clinicopathological features of the groups are shown in Table 4. First, we compared the long-term postoperative outcome between the non-transfusion group and the AT group. The preoperative Hb level was significantly higher in the AT group than in the non-

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Data are expressed as number of patients and mean ± standard deviation. HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin.

58.2%, and 40.3% for patients in period B (P = 0.3202).

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Table 1  Clinicopathological characteristics of patients of periods A and B with hepatocellular carcinoma

|                          | Period A (1991-1994) (n = 93) | Period B (1995-2000) (n = 201) | P-value |
|--------------------------|-------------------------------|---------------------------------|---------|
| Clinical factors         |                               |                                 |         |
| Gender (male/female)     | 81/12                         | 161/40                          | 0.144   |
| Age (yr)                 | 61 ± 9                        | 62 ± 9                          | 0.102   |
| HBs-Ag (±)               | 73/20                         | 169/32                          | 0.243   |
| Anti-HCV Ab (±/unknown)  | 29/62/2                       | 71/125/5                        | 0.471   |
| Child-Pugh classification| 79/14/20                      | 160/41/20                       | 0.275   |
| Preoperative Hb (g/dL)   | 13.6 ± 1.5                    | 13.3 ± 1.6                      | 0.213   |
| Tumor-related factors    |                               |                                 |         |
| Number of tumors         | 70/23                         | 146/55                          | 0.635   |
| Maximum tumor size (cm)  | 3.8 ± 2.7                     | 4.1 ± 3.1                       | 0.450   |
| Vascular invasion (±)    | 83/10                         | 172/29                          | 0.388   |
| Histological grade (Ⅰ/Ⅱ/Ⅲ/IV/unknown) | 40/41/12 | 89/92/20 | 0.975 |
| Intraoperative blood loss (mL) | 2190 ± 5689 | 1621 ± 2209 | 0.219 |

Table 2  Clinicopathological characteristics of patients with hepatocellular carcinoma according to homologous blood transfusion

|                          | Non-HT group (n = 200) | HT group (n = 94) | P-value |
|--------------------------|------------------------|-------------------|---------|
| Clinical factors         |                        |                   |         |
| Gender (male/female)     | 162/38                 | 80/14             | 0.390   |
| Age (yr)                 | 62 ± 9                 | 60 ± 9            | 0.084   |
| HBs-Ag (±)               | 168/32                 | 74/20             | 0.269   |
| Anti-HCV Ab (±/unknown)  | 65/130/5               | 35/57/2           | 0.437   |
| Child-Pugh classification| 3/32                   | 72/22             | 0.157   |
| Preoperative Hb (g/dL)   | 13.5 ± 1.6             | 13.2 ± 1.7        | 0.171   |
| AT administration (±)    | 82/118                 | 78/16             | < 0.0001|
| Tumor-related factors    |                        |                   |         |
| Number of tumors         | 149/51                 | 67/27             | 0.559   |
| Maximum tumor size (cm)  | 3.6 ± 2.4              | 4.9 ± 3.7         | 0.000   |
| Vascular invasion (±)    | 177/23                 | 78/16             | 0.195   |
| Histological grade (1, II/III, IV/unknown) | 91/88/21 | 38/45/11 | 0.446 |
| Surgery-related factors  |                        |                   |         |
| Procedure (nonanatomical/anatomical) | 111/89 | 35/59   | 0.004   |
| Operation time (min)     | 264 ± 130              | 356 ± 166         | < 0.0001|
| Resected liver volume (g) | 159 ± 196             | 336 ± 490         | < 0.0001|
| Intraoperative blood loss (mL) | 993 ± 707       | 3522 ± 6104       | < 0.0001|

1Data are expressed as number of patients and mean ± standard deviation. HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin.

In order to identify the factors that can predict the need for HT, various clinical parameters, tumor-related factors, and surgery-related factors were compared between the non-HT group and the HT group (Table 2). The preoperative Hb level was not significantly different between the 2 groups (13.5 ± 1.6 g/dL vs 13.2 ± 1.7 g/dL, P = 0.1708). The proportion of patients who received AT was significantly lower in the HT group than the non-HT group [59.0% (118/200) vs 17.0% (16/94), P < 0.0001]. The maximum tumor size was significantly larger in the HT group than in the non-HT group (4.9 ± 3.7 cm vs 3.6 ± 2.4 cm, P = 0.0003). As for surgery-related factors, there were significant differences in surgical procedure (P = 0.0035), operation time (P < 0.0001), resected liver volume (P < 0.0001), and intraoperative blood loss (P < 0.0001), suggesting that surgery in the HT group was major compared to that in the non-HT group.

To identify significant factors that could predict the need for HT, multivariate logistic regression analysis was performed (Table 3). The analysis was carried out using the 6 significant factors identified in the comparison of the non-HT group and the HT group. The analysis identified AT administration, intraoperative blood loss, and resected liver volume as significant independent predictors for the need of HT (P < 0.0001, P < 0.0001, P = 0.0362, respectively). Long-term postoperative outcome after surgery for HCC was examined. In this analysis, patients were limited to those with curative resection, which was defined as complete removal of all macroscopically evident tumors [non-HT group: 193 patients (non-transfusion group: 78 patients; AT group: 115 patients), HT group: 83 patients]. Among the 276 patients, 37 patients (13.4%) were followed-up for more than 10 years. The clinicopathological features of the groups are shown in Table 4. First, we compared the long-term postoperative outcome between the non-transfusion group and the AT group. The preoperative Hb level was significantly higher in the AT group than in the non-
transfusion group (14.1 ± 1.1 g/dL vs 12.8 ± 1.8 g/dL, P < 0.001). Tumor-related factors were similar in the 2 groups. There were no significant differences in the disease-free survival rates between the AT group (1-, 3-, 5-, and 10-year: 70.6%, 37.1%, 22.3%, and 11.2%, respectively) and the non-transfusion group (73.1%, 41.3%, 30.7%, and 9.6%, respectively) (P = 0.3874) (Table 1). In this regard, the present study demonstrated a reduction of HT administration in surgery for HCC after the introduction of AT. Our results are in agreement with those of previous reports which emphasized the significance of AT in reducing the need for HT in surgery for HCC[16,17]. However, in these previous reports, only 20-30 patients were included in the AT group. Furthermore, although the Hb level immediately before surgery was reported in the AT group, the Hb level before storage was not indicated, suggesting a different clinical background of patients who received HT and those of other groups. On the other hand, in the present study, despite its retrospective design, the clinicopathological background, including the Hb level, was similar in the 2 groups as shown in Table 1. In this regard, the present study is significant as it identified the benefits of AT in the reduction of HT administration.

In the present study, we analyzed the data for significant predictors of HT use. The results showed that AT administration was an independent significant predictor of the need for HT, and support the significance of AT in reducing the need for HT. In the analysis, preoperative Hb, which is reported to be significantly associated with the need for HT[10,23], was not an independent significant factor. While the reason for this difference in the results

**Table 3** Results of multivariate logistic regression analysis for the need for homologous blood transfusion

| Procedure     | OR     | 95% CI  | P-value |
|---------------|--------|---------|---------|
| Non-HT group  |        |         |         |
| AT administration | ±      | 28.571  | 9.615-83.333 | <0.0001 |
| Maximum tumor size (cm) | <5/≥5 | 1.126  | 0.500-2.538 | 0.774   |
| Operation time (min) | <300/≥300 | 1.016  | 0.449-2.202 | 0.967   |
| Resected liver volume (g) | <200/≥200 | 2.532  | 1.062-6.061 | 0.036   |
| Intraoperative blood loss (mL) | <2000/≥2000 | 30.303 | 9.346-100.000 | <0.0001 |

**Table 4** Clinicopathological characteristics of patients who underwent curative surgery for hepatocellular carcinoma

| Clinical factors | Non-HT group (n = 193) | HT group (n = 83) | P-value | Non-transfusion group (n = 78) | Non-HT group (n = 115) | P-value |
|------------------|------------------------|------------------|---------|-------------------------------|-----------------------|---------|
| Gender (male/female) | 156/37 | 70/13 | 0.488 | 63/15 | 93/22 | 0.986 |
| Age (yr) | 62 ± 8 | 61 ± 9 | 0.115 | 62 ± 8 | 61 ± 9 | 0.878 |
| HBs-Ag (±) | 163/30 | 67/16 | 0.445 | Nov-67 | 96/19 | 0.649 |
| Anti-HCV Ab (±/unknown) | 62/127 | 31/51/1 | 0.426 | 21/34/3 | 41/73/1 | 0.254 |
| Child-Pugh classification (A/B) | 161/32 | 65/18 | 0.262 | 66/12 | 95/20 | 0.833 |
| Preoperative Hb (g/dL) | 13.5 ± 1.5 | 13.4 ± 1.6 | 0.425 | 12.8 ± 1.8 | 14.1 ± 1.1 | <0.0001 |
| Tumor-related factors | | | | | | |
| Number of tumors (single/multiple) | 147/46 | 64/19 | 0.866 | 62/16 | 85/30 | 0.372 |
| Maximum tumor size (cm) | 3.5 ± 2.4 | 4.8 ± 3.7 | 0.000 | 3.3 ± 2.2 | 3.6 ± 2.4 | 0.287 |
| Vascular invasion (±) | 172/21 | 70/13 | 0.268 | 73/5 | 99/16 | 0.101 |
| Histological grade (Ⅰ, Ⅱ/Ⅲ, N/unknown) | 89/83/21 | 33/41/9 | 0.304 | 36/34/8 | 53/49/13 | 0.412 |

1Data are expressed as number of patients and mean ± standard deviation. HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin; AT: Autologous transfusion; HT: Homologous transfusion.

**DISCUSSION**

The results of the present study demonstrated a reduction in HT administration in surgery for HCC after the introduction of AT. Our results are in agreement with those of previous reports which emphasized the significance of AT in reducing the need for HT in surgery for HCC[16,17]. However, in these previous reports, only 20-30 patients were included in the AT group. Furthermore, although the Hb level immediately before surgery was reported in the AT group, the Hb level before storage was not indicated, suggesting a different clinical background of patients who received HT and those of other groups. On the other hand, in the present study, despite its retrospective design, the clinicopathological background, including the Hb level, was similar in the 2 groups as shown in Table 1. In this regard, the present study is significant as it identified the benefits of AT in the reduction of HT administration.

In the present study, we analyzed the data for significant predictors of HT use. The results showed that AT administration was an independent significant predictor of the need for HT, and support the significance of AT in reducing the need for HT. In the analysis, preoperative Hb, which is reported to be significantly associated with the need for HT[10,23], was not an independent significant factor. While the reason for this difference in the results
remains unclear, it could be due to the effect of recombinant human erythropoietin administered after the storage of autologous blood. Alternatively, it is possible that, since the subjects of the above previous studies did not receive AT, the significance of preoperative Hb is overestimated. Thus, the present study is significant in terms of identifying the effect of AT in reducing HT using appropriate statistical analysis.

We also investigated the effects of AT and HT on postoperative outcome after curative surgery for HCC. The study revealed that the disease-free survival rates were comparable between the non-transfusion group and the AT group when the clinical background was similar. Furthermore, the disease-free survival rates of the HT group were significantly worse than those of the non-HT group, based on the results of univariate analysis. Since there was a significant difference in the maximum tumor size between the 2 groups, which suggests the possibility of different tumor biology and recurrences between the HT group and the non-HT group, the survival rate was compared in subgroups based on tumor size, and showed significant differences in the pa-

Figure 2  Disease-free survival after curative surgery for hepatocellular carcinoma. A: There were no significant differences between the non-transfusion group (solid line) and the Autologous transfusion (AT) group (dotted line) \( (P=0.3874) \); B: The cumulative disease-free survival in the non-Homologous transfusion (HT) group (solid line) was significantly better than in the HT group (dotted line) \( (P=0.0305) \); C: The disease-free survival in the non-HT group (solid line) was significantly better in than the HT group (dotted line) in patients with maximum tumor size of \( \leq 5.0 \) cm \( (P=0.0452) \); D: No significant differences were noted between the non-HT group (solid line) and the HT group (dotted line) in patients with the maximum tumor size > 5.0 cm \( (P=0.7391) \).

Table 5  Statistical analysis of disease-free survival of patients with curative resection for hepatocellular carcinoma

| Clinical factors                        | Univariate | Multivariate |
|----------------------------------------|------------|-------------|
| Gender (male/female)                   | 0.840      |             |
| Age (yr) \( (\leq 63/> 63) \)          | 0.402      |             |
| HBs-Ag (t)                             | 0.279      |             |
| Anti-HCV Ab (t)                        | 0.045      | 1.401       |
| Child-Pugh classification (A/B)        | 0.079      |             |
| Preoperative Hb (g/dL)                 | 0.824      |             |
| (\( \leq 12/> 12 \))                   |             |             |
| Transfusion (non-HT group/HT group)    | 0.031      | 1.372       |
| (non-HT group/HT group)                | 1.018-1.849| 0.038       |
| Tumor-related factors                  |            |             |
| Number of tumors (single/multiple)     | 0.000      | 1.819       |
| Maximum tumor size (cm) \( (\leq 5/> 5) \) | 0.001      | 1.07        |
| Vascular invasion (t)                  | <0.0001    | 2.473       |
| Histological grade \( (I, II, III, IV) \) | 0.017      | 1.188       |

OR: Odds ratio; CI: Confidence interval; HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin; HT: Homologous transfusion.
Some evidences suggest that homologous blood transfusion (HT) may be adversely associated with tumor recurrence and poor survival in various kinds of cancers, and autologous blood transfusion (AT) is currently used for patients scheduled for surgery. To date, several investigators have examined the significance of AT in terms of reducing the need for HT and postoperative outcome, but few were conducted with proper statistical analyses to identify the significance of AT in surgery for hepatocellular carcinoma (HCC).

**Research frontiers**

The authors compared the proportion of patients who received HT between 2 groups determined by the time of AT introduction; period A (1991-1994, n = 93) and period B (1995-2000, n = 201), and performed multivariate logistic regression analysis for identification of independent significant predictors of the need for HT. Furthermore, they investigated the impact of AT and HT on long-term postoperative outcome after curative surgery for HCC.

**Innovations and breakthroughs**

The present study showed that the proportion of patients having HT was decreased after AT introduction, that AT administration was a significant independent predictor of the need for HT, and identified HT administration as an independent significant factor for poorer disease-free survival.

**Applications**

Considering the results of the present study, it could be suggested that AT administration could improve the long-term outcome of patients with HCC.

**Peer review**

This is a large series of patients treated in several ways with respect to the need for blood transfusion during their surgery for HCC. Unfortunately the authors have a mix of numbers that they have used in different ways to make the conclusion they wanted to make.

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**COMMENTS**

**Background**

Some evidences suggest that homologous blood transfusion (HT) may be adversely associated with tumor recurrence and poor survival in various kinds of cancers, and autologous blood transfusion (AT) is currently used for patients scheduled for surgery. To date, several investigators have examined the significance of AT in terms of reducing the need for HT and postoperative outcome, but few were conducted with proper statistical analyses to identify the significance of AT in surgery for hepatocellular carcinoma (HCC).
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