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Perioperative transfusion in pancreatoduodenectomy

The double-edged sword of pancreatic surgeons

Hyeong Min Park, MD, Sang-Jae Park, MD, PhD*, Jae Ryong Shim, MD, Eung Chang Lee, MD, Seung Duk Lee, MD, PhD, Sung-Sik Han, MD, PhD, Seoung Hoon Kim, MD, PhD

Abstract

We designed the study to clarify the prognostic significance of perioperative (preoperative, intraoperative, and postoperative) red blood cell (RBC) transfusion following pancreaticoduodenectomy (PD) for periampullary cancers.

This study retrospectively analyzed 244 periampullary cancer patients (pancreatic cancer, 124 patients; bile duct cancer, 63 patients; and ampullary cancer, 57 patients) treated by PD from June 2001 to June 2010 at the National Cancer Center, Korea (NCC2017-0106).

A total of 112 (46%) of 244 patients had received transfusion (preoperative, 5%; intraoperative, 17%; and postoperative, 37%). The 5-year survival rate of patients without perioperative transfusion was 36%, whereas that of patients with a transfusion was 25% ($P = .04$). Perioperative transfusion and intraoperative transfusion were found to be independent poor prognostic factors [relative risk (RR): 1.52 and 1.95, respectively]. The independent factors associated with perioperative transfusion were being female, operation time >420 minutes, portal vein (PV) resection, and preoperative serum hemoglobin (Hb) < 12 mg/dL. As the amount of perioperative transfusion increased, overall survival (OS) decreased.

Perioperative transfusion, especially intraoperative transfusion was an independent prognostic factor for survival after PD. Therefore, for patients with periampullary cancer, intraoperative bleeding and operation time should be minimized and preoperative anemia corrected.

Abbreviations: ASA = American Society of Anesthesia, Hb = hemoglobin, HR = hazard ratio, LN = lymph node, OS = overall survival, PD = pancreaticoduodenectomy, PPPD = pylorus preserving pancreaticoduodenectomy, PV = portal vein, RBC = red blood cell, RR = relative risk, TRIM = transfusion-related immune modulation.

Keywords: blood transfusion, pancreatoduodenectomy, periampullary cancer, Whipple operation

1. Introduction

For the treatment of periampullary cancer, only surgical removal offers the chance of long-term survival and cure.[1,2] Although perioperative mortality has decreased dramatically in the past decades, along with advances in surgical techniques, surgical instruments, and intensive care facilities with increased experience, patients undergoing pancreaticoduodenectomy (PD) or pylorus preserving pancreaticoduodenectomy (PPPD) for the treatment of periampullary cancer often require perioperative blood transfusion.[3,4] Most studies on PD or PPPD for periampullary disease report a red blood cell (RBC) transfusion rate between 30% and 70%.[5–7] In our previous study, approximately 60% of patients who underwent PD for periampullary cancer received intraoperative transfusion.[8] Some studies reported the effect of transfusion on survival of periampullary cancer patients after resection. Sutton et al[9] argued that intraoperative and postoperative transfusion are independent factors associated with decreased disease-free survival in patients who underwent PD for pancreatic adenocarcinoma. Park et al[8] reported the independent prognostic significance of intraoperative transfusion for patients with ampullary cancer after surgery. Yao et al[10] also concluded that intraoperative RBC transfusion adversely influenced survival in patients with ampullary cancer after PD, consistent with the results of the aforementioned study. Furthermore, many clinicians accept transfusion-related immune modulation (TRIM) as strong evidence of an association between perioperative allogenic RBC transfusion and its effect on recurrence after curative tumor resection.[11,12] In the study by Cata et al,[11] perioperative transfusion produced alteration in the antiinflammatory/proinflammatory milieu, with a net result of immunosuppression, especially in old red cells rather than in leukocytes or fresh frozen fractions. Miki et al[12] reported that exaggerated systemic induction of interleukin-6 after curative resection of

Editor: Shefali Agrawal.

This work was supported by National Cancer Center Research Grant 1510201-3.

Presented to the World congress of IASGO 2016 of the International Association of Surgeons, Gastroenterologists and Oncologists, Seoul, Korea, September 2016.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Center for Liver Cancer, National Cancer Center, Gyeonggi-do, South Korea.

* Correspondence: Sang-Jae Park, Center for Liver Cancer, National Cancer Center, 323, Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, South Korea (e-mail: spark@ncc.re.kr).

Medicine (2017) 96:49(e9019)

Received: 11 October 2017 / Received in final form: 9 November 2017 / Accepted: 10 November 2017

http://dx.doi.org/10.1097/MD.0000000000009019

colorectal cancer was associated with a poor prognosis. However, it remains uncertain whether transfusion really affects the long-term outcome of periampullary cancer following PD or PPPD. Moreover, few studies have investigated the effects of transfusion subgroups (preoperative, intraoperative, and postoperative transfusion) on prognosis after PD or PPPD. Therefore, we analyzed data in order to clarify the prognostic significance of perioperative (preoperative, intraoperative, and postoperative) RBC transfusion following PD for periampullary cancers.

2. Methods

For this retrospective study, we reviewed the medical records of 342 patients who underwent curative PD or PPPD for periampullary cancer at the National Cancer Center, Korea between June 2001 and June 2010 in order to assess the impact of perioperative blood transfusion on prognosis. Patients who underwent PD or PPPD for other cancers (n = 48), duodenal cancer (n = 14), and benign disease (n = 36) were excluded. Other cancers included neuroendocrine tumor (n = 27) and other organ-originating cancers (n = 21). Finally, 244 patients with pathologically confirmed periampullary adenocarcinoma were enrolled in this study. The series included 124 pancreatic head cancers, 63 bile duct cancers, and 57 ampullary cancers. There were 148 men and 96 women with a median age of 63 years (range: 42–87 years). A conventional Whipple operation was performed in 52 patients and PPPD in 192 patients. The median follow-up interval was 22 months (range: 0–161 months). Follow-up was obtained via medical records, letters, or telephone contact up to July 2015.

In our institution, indications for transfusion include significant perioperative blood loss, serum hemoglobin (Hb) concentration of <7 g/dL, or serum Hb level of 7 to 10 g/dL, combined with any sign or symptom of acute bleeding.

Preoperative transfusion was defined as any allogenic transfusion within a week preoperatively. Postoperative transfusion was defined as transfusion within 30 days of surgery. Intraoperative transfusion included all transfusions initiated during the operation, even if completed after surgery. The only transfusion products checked in this study were whole blood and packed RBCs.

Analytic variables for possible prognostic factors were perioperative transfusion combined with age, gender, preoperative Hb level, preoperative bilirubin level, tumor location, operation time, type of operation, histological differentiation, tumor size, depth of invasion, lymph node (LN) metastasis, microvascular invasion, lymphatic invasion, perineural invasion, margin status, American Society of Anesthesia (ASA) classification, and whether or not portal vein (PV) resection was performed. Further analysis was performed by replacing the factor of presence of transfusion with the amount of transfusion (none, 1–2 packs, 3–5 packs, or ≥6 packs). Approval was obtained from the institutional ethical committee (*Institutional Review Board*, National Cancer Center, Korea) before starting the study (NCC2017-0106).

2.1. Statistical analysis

Overall survival (OS) was analyzed using the Kaplan–Meier method, and the survival difference between transfused and nontransfused groups was compared using a log-rank test. The analytic variables of the transfused patients were compared with the nontransfused patients using a Chi-square test. To investigate the combined effects of different variables on survival, Cox proportional hazards regression model was used. For all tests, a *P*-value of less than .05 was considered significant. The prognostic significance of perioperative transfusion for overall periampullary cancer, pancreatic head cancer, bile duct cancer, and ampullary cancer was evaluated.

3. Results

3.1. Significance of transfusion on the prognosis of periampullary cancer

Perioperative transfusion was administered to 112 (45.9%) of 244 patients who underwent PD or PPPD for periampullary cancer. Based on the transfusion period, the preoperative transfusion rate was 4.9% (12/244), the intraoperative transfusion rate was 16.8% (41/244), and the postoperative transfusion rate 36.5% (89/244). The median and mean amounts of RBCs transfused were 2.0 and 4.8 units (range 1–39 units), respectively. OS after PD or PPPD in periampullary cancer patients is shown in Fig. 1A. The actuarial 2-year/5-year survival rates were 48.7%/

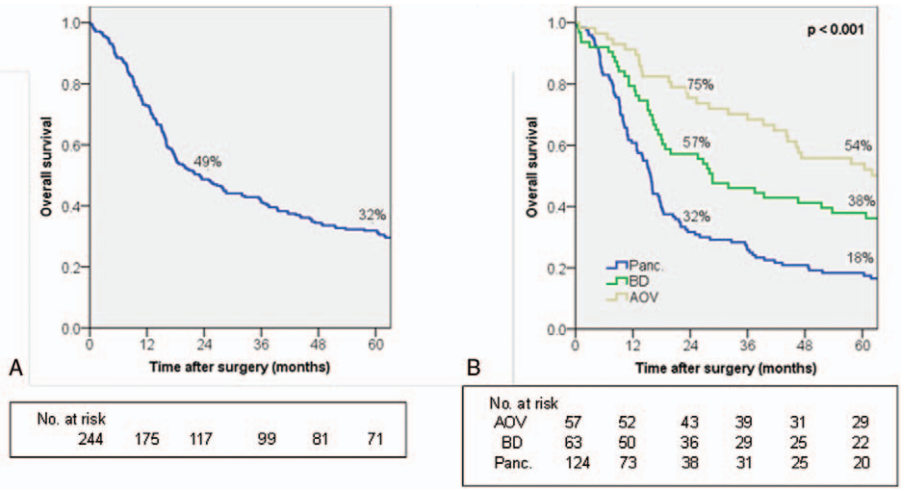

Figure 1. (A) Overall survival after PD or PPPD with curative intent for periampullary cancer. (B) Overall survival of periampullary cancer subgroups after PD or PPPD with curative intent. $P < .001$ (log rank test).

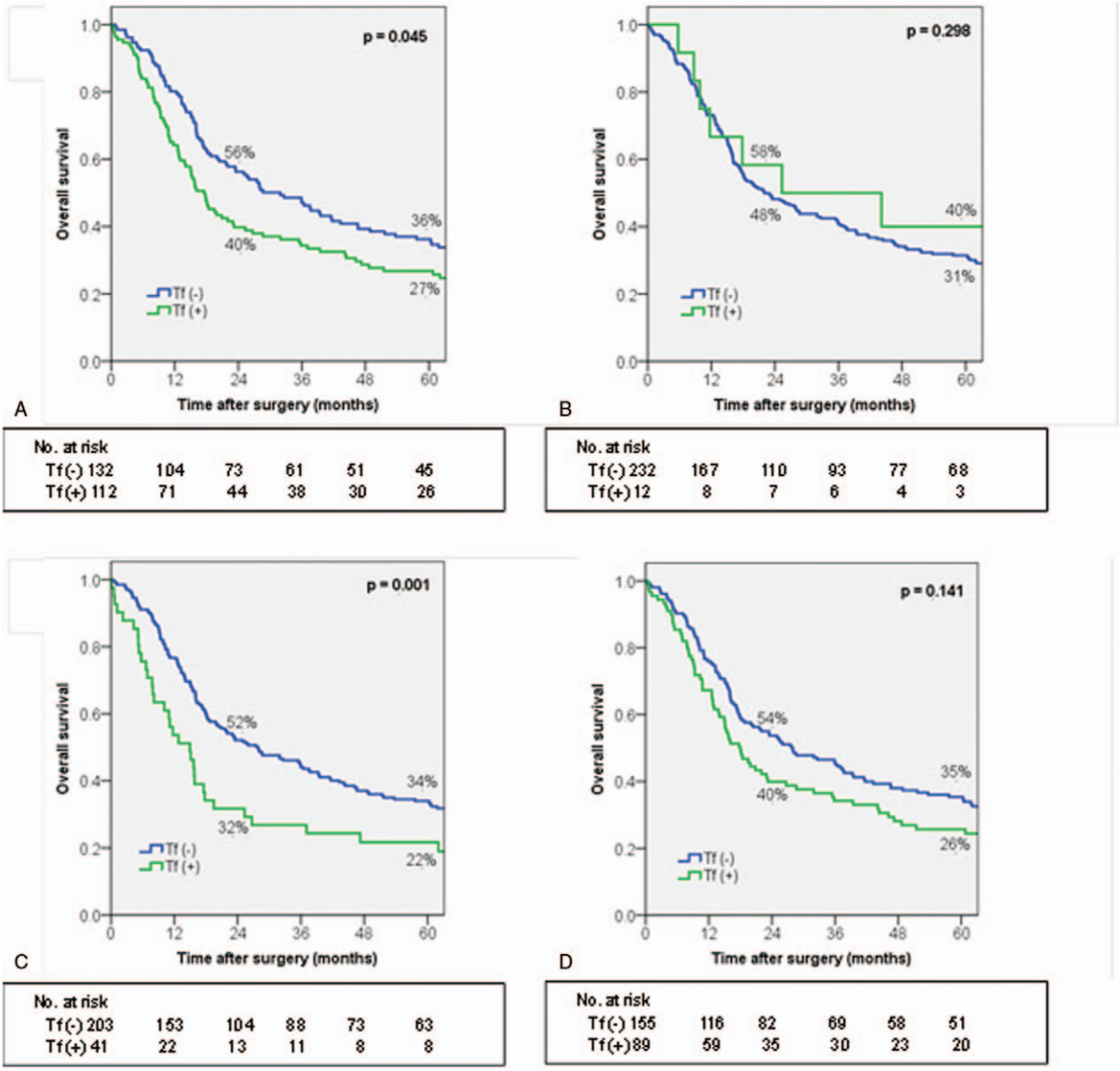

Figure 2. Overall survival after PD or PPPD with curative intent for periampullary cancer according to whether (A) perioperative transfusion or (B) preoperative transfusion or (C) intraoperative transfusion or (D) postoperative transfusion. (A) $P = .045$, (B) $P = .298$, (C) $P = .001$, (D) $P = .141$ (log rank test).

31.9%, and those of the nontransfused patients were 56.3%/36.2%, compared to 39.8%/26.8% for transfused patients ($P = .04$, log-rank test). Preoperative transfusion ($P = .29$, log-rank test) and postoperative transfusion ($P = .14$, log-rank test) showed no significant differences in survival; however, the actuarial 2-year/5-year survival rates of patients without intraoperative transfusion were 52.1%/34.0%, compared with 31.7%/21.7% for patients with intraoperative transfusion ($P < .001$, log-rank test) (Fig. 2).

Although postoperative transfusion showed no significance for prognosis after PD or PPPD, the postoperative transfusion rate was higher compared to the intraoperative or preoperative transfusion rates. Moreover, there was a tendency for receipt of postoperative transfusion to be associated with inferior OS compared to no postoperative transfusion (Fig. 2D). Therefore, we divided the postoperative transfusion group into an early transfusion subgroup (transfused within 3 days after PD) and a late transfusion subgroup (transfused from the third day after PD). In the subgroup analyses, postoperative transfusion did not reach statistical significance for OS after PD or PPPD (data not shown). Age, T-stage, LN metastasis, tumor size, tumor location, cell differentiation, microvascular invasion, lymphatic invasion, perineural invasion, margin status, perioperative transfusion, intraoperative transfusion, and PV resection showed significant differences on univariate analysis for OS after PD or PPPD for periampullary cancer (Table S1, http://links.lww.com/MD/B998). Following multivariate analysis, age, LN metastasis, cell differentiation, microvascular invasion, margin status, perioperative transfusion, and intraoperative transfusion were found to be independent prognostic factors for those with periampullary cancer (Table S1, http://links.lww.com/MD/B998).

Because there was a marked difference in OS rates according to the periampullary cancer subgroups (Fig. 1B), the prognostic significance of perioperative transfusion for pancreatic cancer, bile duct cancer, and ampullary cancer, respectively, was

Table 1

Significant factors associated with perioperative transfusion in patients with periampullary cancer.

Factor	Tf. (−) (n = 132)	Tf. (+) (n = 112)	*P*	Multivariate analysis HR	*P*
Sex			.002		.01
Male	92 (62%)	56 (38%)			
Female	40 (42%)	56 (58%)		2.21 [1.19–4.11]	
Op. time, minute			<.001		<.001
<420	70 (74%)	25 (26%)			
≥420	62 (42%)	87 (58%)		4.97 [2.63–9.39]	
PV resection			.02		.01
Yes	18 (38%)	29 (62%)		2.64 [1.28–5.42]	
No	114 (58%)	83 (42%)			
Preop. Hb, mg/dL			<.001		<.001
≥ 12	80 (65%)	44 (35%)			
≥10, <12	48 (49%)	49 (51%)		12.13 [3.50–42.02]	<.001
<10	4 (17%)	19 (83%)		1.83 [0.97–3.44]	.06

Hb = hemoglobin, HR = hazard ratio, Op = operation, Preop. = preoperative, PV = portal vein, Tf. = transfusion.

investigated. However, perioperative transfusion did not show significant differences in OS after PD or PPPD.

3.2. Factors associated with transfusion

The independent factors associated with perioperative transfusion were being female [*P* = .01, hazard ratio (HR): 2.21], operation time over 420 minutes (*P* < .001, HR: 4.97), PV resection (*P* = .01, HR: 2.64), and preoperative serum Hb less than 12 mg/dL (*P* < .001, HR: 12.13) (Table 1). In addition, operation time over 420 minutes (*P* = .001, HR: 4.61) and PD (*P* = .01, HR 2.64) showed significant associations with intraoperative transfusion (Table 2).

3.3. The amount of transfusion and prognosis of periampullary cancer

As the amount of perioperative transfused RBCs increased, the OS rate significantly decreased (*P* = .04, log rank test) (Fig. 3A). Perioperative transfusion of more than six packs was an independent risk factor for OS (*P* < .001, HR: 2.99) of periampullary cancer following PD or PPPD.

The amount of intraoperative transfusion showed significance for OS (*P* = .001, log rank test) (Fig. 3C). However, only intraoperative transfusion of less than 3 packs showed a significance for OS (*P* < .001, HR: 2.05) on multivariate analysis for prognosis of periampullary cancer following PD or PPPD.

The amount of preoperative or postoperative transfusion did not reach statistical significance for OS of patients with periampullary cancer following PD or PPPD (Fig. 3B and D).

4. Discussion

Allogenic transfusion is essential for patients with excessive bleeding or cardiogenic problems, and for critically ill patients. This is because transfusion can improve oxygen supply and minimize hypoxic damage of organs. However, this is different for patients with oncological problems, in whom surgery is planned. In addition, it is difficult to ignore the side effects of transfusion. Therefore, it is important to maintain a balance between the application and suspension of transfusion.[13,14]

The relationship between transfusion and prognosis after PD or PPPD for periampullary cancer remains controversial. Some authors report a negative effect of transfusion on prognosis after surgery, while others report no correlation between transfusion and postoperative outcome.[15–18] Because of the low survival rate of periampullary cancer following PPPD, transfusion may not be considered important. TRIM is the widely accepted hypothesis regarding the impact of RBC transfusion for the prognosis of cancer after curative resection.[11,12] TRIM is based on immunosuppression as a cause of the early recurrence of cancer. In accordance with this concept, in this study, patients who received intraoperative RBC transfusions had a significantly lower OS rate. Furthermore, intraoperative RBC transfusion was

Table 2

Significant factors associated with intraoperative transfusion in patients with periampullary cancer.

Factor	Tf. (−) (n = 132)	Tf. (+) (n = 112)	*P*	Multivariate analysis HR	*P*
Op. time, minute			<.001		.001
<420	89 (94%)	6 (6%)			
≥420	114 (77%)	35 (23%)		4.61 [1.84–11.56]	
Op. type			.01		.01
PD	37 (71%)	15 (29%)		2.64 [1.24–5.62]	
PPPD	166 (87%)	26 (13%)			

HR = hazard ratio, Op = operation, PD = pancreatoduodenectomy, PPPD = pylorus preserving pancreatoduodenectomy, Tf. = transfusion.

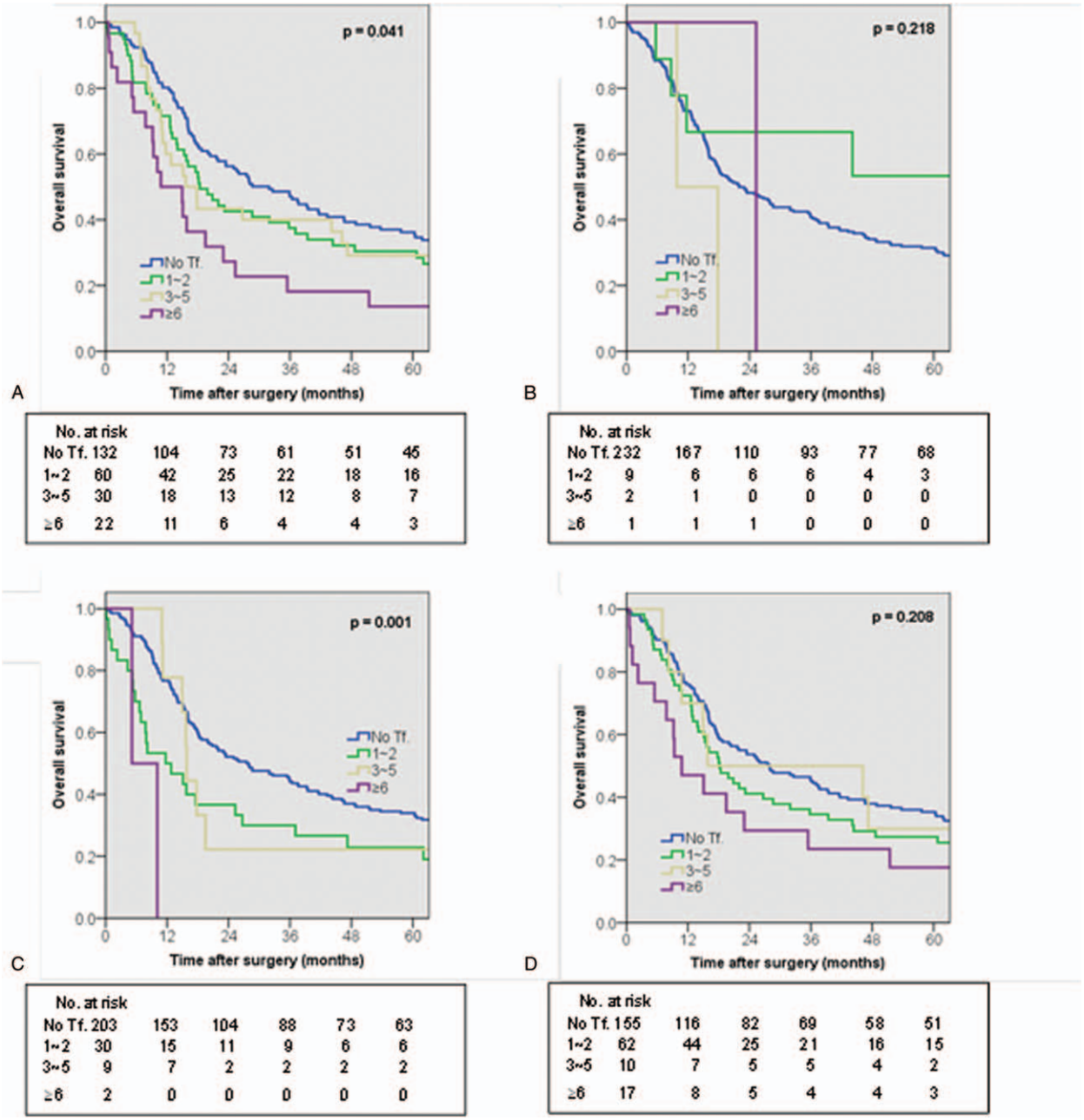

Figure 3. Overall survival after PD or PPPD with curative intent for periampullary cancer according to the amount of (A) perioperative transfusion or (B) preoperative transfusion or (C) intraoperative transfusion or (D) postoperative transfusion. (A) $P = .041$, (B) $P = .218$, (C) $P = .001$, (D) $P = .208$ (log rank test).

an independent risk factor for OS in patients with periampullary cancer following PD or PPPD. Moreover, Ahmad et al[19] argued that higher transfusion requirements were associated with a higher readmission rate after PD. Shiba et al[20] showed a significant impact of fresh-frozen plasma transfusion on the prognosis of pancreatic cancer after pancreatic resection.

Our study has some limitations. First, as with all retrospective studies, this investigation may have a selection bias regarding the starting point and the amount of the RBC transfusion. This retrospective study also lacked a causal association between transfusion and postoperative prognosis. In addition, the number of patients was small, despite the fact that the study was conducted over a period of more than 10 years; this is because periampullary cancer is a rare disease. Therefore, statistical analysis remains a challenge. The long period of the study may have weakened consistency because, during that time, surgical techniques and perioperative management may have progressed. We could not directly reveal an association between TRIM and early cancer recurrence, because it was difficult to apply the accurate length of disease-free survival (DFS). However, the low OS of patients with intraoperative transfusion and its significance may represent an indirect expression of TRIM.

When we divided the overall 10-year study period into 3 periods, the RBC transfusion rate and amount of RBC transfused decreased over time, whereas the median OS length

increased (data not shown). These results are in support of the TRIM hypothesis, which is the basis concept behind this study. Singer et al[21] reported their efforts to eliminate transfusion in patients undergoing PD artificially and showed improved outcome with decreased transfusion rates and amounts. Ross et al[22] reported significantly increased postoperative complications in a transfused group and almost half the intraoperative transfusions did not meet their predetermined transfusion criteria.

Despite the several limitations of this study, it is meaningful that intraoperative RBC transfusion showed significance on both univariate and multivariate analyses for OS of patients with periampullary cancer following PD or PPPD. However, preoperative transfusion and postoperative transfusion did not show the statistical significance for postoperative prognosis. Through the result of this study, we can assume that the time of perioperative transfusion is more important in regards to the effect on the OS following PD or PPPD than transfusion itself. Because the immunological modulation of patients during surgery may be the most sensitive and weakest factor for early cancer recurrence, intraoperative transfusion could show a significant adverse effect on the prognosis of periampullary cancer. Therefore, efforts to reduce intraoperative bleeding are important. Although postoperative transfusion did not show significance on OS in patients who underwent PD or PPPD for periampullary cancer, we did subgroup analysis between early and late postoperative transfusion subgroups because there was a tendency that postoperative transfusion showed superior OS compared to no transfusion. The lack of difference in OS between the 2 postoperative transfusion subgroups supports the hypothesis that immunological modulation of patients during surgery may be the most sensitive and weakest factor for early cancer recurrence. Some authors have suggested modified surgical techniques during PD; that is, early inferior pancreaticoduodenal artery ligation, which minimizes blood loss through inflow control. Although they were unable to show significant improvement in prognosis after PD, the estimated intraoperative blood loss and transfusion rate were significantly decreased.[23,24] Calleja et al[25] reported that preoperative ferric carboxymaltose treatment in patients with colon cancer significantly reduced RBC transfusion requirements and length of hospital stay. In addition, Tomimaru et al[26] showed that autologous intraoperative blood transfusion could replace allogenic transfusion by comparing postoperative prognosis in hepatocellular carcinoma between autologous and homologous blood transfusion groups. Strict application of transfusion protocols to each patient undergoing cancer surgery may also contribute to a reduction in blood transfusion. Surgeons can apply and control all of the aforementioned methods in order to reduce the need for transfusion.

In the present study, it was unclear why perioperative transfusion and intraoperative transfusion were independent prognostic factors for survival after PD. However, among the perioperative transfusion subgroups, only intraoperative transfusion was associated with the OS after PD or PPPD. It means that the time of transfusion has an effect on the postoperative outcome more than transfusion itself. Therefore, for patients with periampullary cancer, in order to reduce perioperative transfusion (especially intraoperative transfusion), and improve long-term outcomes, intraoperative bleeding or operation time should be minimized and preoperative anemia should be corrected.

Acknowledgments

The authors thank SE Lee and EK Hong at the Center for Liver Cancer, National Cancer Center, Korea for their valuable contribution to the data processing.

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