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# Perioperative Red Blood Cell Transfusion Is Associated with Poor Long-term Survival in Pancreatic Adenocarcinoma

TOMOYUKI ABE[1], HIRONOBU AMANO[1,2], KEIJI HANADA[3], TOMOYUKI MINAMI[3], SHUJI YONEHARA[4], MINORU HATTORI[5], TSUYOSHI KOBAYASHI[2], TOSHIKATSU FUKUDA[6], MASAHIRO NAKAHARA[1], HIDEKI OHDAN[2] and TOSHIO NORIYUKI[1,2]

[1]*Department of Surgery, Onomichi General Hospital, Onomichi, Japan;*
[2]*Department of Gastroenterological and Transplant Surgery, Applied Life Sciences, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan;*
[3]*Department of Gastroenterology, Onomichi General Hospital, Onomichi, Japan;*
[4]*Department of Pathology, Onomichi General Hospital, Onomichi, Japan;*
[5]*Advanced Medical Skill Training Center, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan;*
[6]*Department of Surgery, Medical Corporation Japan Railway Hiroshima Hospital, Hiroshima, Japan*

**Abstract.** *Background/Aim: Perioperative red blood cell transfusion (RBCT) can negatively affect the host's immune system. We investigated the effects of perioperative RBCT on long-term survival among patients with pancreatic ductal adenocarcinoma (PDAC). Patients and Methods: We retrospectively evaluated 148 patients with PDAC who underwent surgery with curative intent (33 who received RBCTs and 115 who did not). Significant prognostic variables on univariate analysis were subjected to multivariate analyses using a Cox proportional hazard regression model. Results: Both groups exhibited significant differences in age, preoperative haemoglobin levels, carbohydrate antigen 19-9 levels, maximum tumour size, tumour staging, operative time, intraoperative blood loss, major vascular resection, and the proportion of pancreaticoduodenectomies performed. Patients who underwent RBCTs exhibited significantly poorer overall survival ($p<0.001$) and recurrence-free survival ($p<0.001$) compared to patients who did not. Conclusion: Perioperative RBCT was associated with poorer long-term survival among patients with PDAC who underwent surgery with curative intent.*

*Correspondence to:* Hironobu Amano, Department of Surgery, Onomichi General Hospital, Hirahara 1-10-23, Onomichi, Hiroshima, 722-8508 Japan. Tel: +81 848228111, Fax: +81 848233214, e-mail: amanojack@star.odn.ne.jp

*Key Words:* Blood transfusion, pancreatic adenocarcinoma, transfusion-related immune modulation.

Pancreatic ductal adenocarcinoma (PDAC) is a life-threatening malignancy. Only surgery can provide long-term survival, with a 5-year survival rate of 15-40% in most studies (1-4). Improved systemic chemotherapy for PDAC has reduced the mortality rate (5, 6), although the long-term survival rates remain dismal. Previous studies have reported that risk factors for poor long-term survival include a large tumour diameter, lymph node metastasis, perineural invasion, and adjuvant therapy (2, 7-9).

Several studies have revealed that cancer-related anaemia and perioperative blood transfusions negatively affect long-term outcomes after surgical resection for various cancer types (10-16). Preoperative anaemia is also associated with tumour hypoxia, which increases resistance to chemotherapy and radiotherapy; cancer-related anaemia may be responsible for poor local tumour control, which leads to poor long-term survival (17). It is also possible that perioperative suppression of the host's immune system plays an important role in controlling cancer progression, that can be affected by natural killer cell activity, suppression of monocyte phagocytosis, and increased suppressor T-cell activity (18, 19). However, because some studies have reported that perioperative red blood cell transfusions (RBCT) does not influence long-term outcomes (20-23), the hypothesis that RBCT adversely affects outcomes after tumour resection remains controversial. Therefore, this study aimed to investigate the effects of perioperative RBCT on disease recurrence and survival among patients who underwent resection with curative intent for PDAC.

## Patients and Methods

*Patients*. This retrospective study identified 148 consecutive inpatients who underwent surgery at the Onomichi General Hospital's Department of Surgery between January 2004 and December 2015. The study's design was approved by the local institutional review board, and all patients provided informed consent for their treatment (OJH-201509). The surgery type was selected based on the tumour's location. Pancreaticoduodenectomy using the subtotal stomach preservation method was normally performed for cases of pancreatic head cancer. In cases of pancreatic body and tail cancer, open distal pancreatectomy was performed with lymphadenectomy. Major vascular resection was defined as portal vein resection and reconstruction. We excluded patients who died within 30 days after surgery to eliminate the effects of short-term postoperative outcomes.

Perioperative RBCT was defined as the transfusion of red blood cell concentrate. We did not consider other blood products in our analyses (*e.g.* fresh frozen plasma, platelets, albumin, and coagulation factors). Tumour-node-metastasis (TNM) staging was performed according to the American Joint Committee on Cancer criteria (24). Propensity score analysis was used to overcome selection bias (related to the different distributions of patient and tumour characteristics, such as TNM classification and preoperative general condition) and to facilitate the comparison of patients who did and did not receive RBCTs.

*Complications and morbidity*. Complications were defined according to the methods of Dindo *et al*. (25). We focused on postoperative complications that were grade IIIa or higher. Postoperative mortality was defined as any death that occurred within 30 days after surgery.

*Follow-up strategy*. All patients were followed until death. All patients underwent annual follow-ups using abdominal ultrasonography and laboratory testing for tumour markers (carbohydrate antigen 19-9 [CA19-9] and carcinoembryonic antigen). Dynamic computed tomography (CT) was performed every 6 months. If a definitive diagnosis of recurrence could not be made based on tumour marker data, ultrasound-guided biopsy imaging (CT, magnetic resonance imaging, endoscopic ultrasonography, or fluorodeoxyglucose-positron emission tomography) was performed.

*Statistical analyses*. Survival data were calculated from the date of surgery. Overall survival (OS) and recurrence-free survival (RFS) rates were analysed using the Kaplan-Meier method and the log-rank test. Multivariate analyses for OS and RFS were performed using a Cox regression model. Propensity score analysis was performed using inverse probability of treatment weighting (IPTW) to overcome bias related to the different distributions of the covariates among patients who did and did not receive RBCTs. C statistics and the Hosmer-Lemeshow test were used to determine that the model was well calibrated (Hosmer-Lemeshow test; $p$=0.219) and had good discrimination (C statistic=0.918; 95% confidence interval [CI]: 0.868-0.968, $p$<0.001). After the IPTW processing, differences in OS and RFS between the two groups were retested using Cox regression analyses and multiple logistic regression analyses. Two-tailed $p$-values of <0.05 were considered to be statistically significant. All analyses were performed using SPSS software (version 22; IBM Corp., Armonk, NY).

## Results

This study included 148 patients (77 men and 71 women) with a histological diagnosis of PDAC; their clinicopathological characteristics are shown in Table I. The median age was 73 years (range: 39-86 years). Seventy-eight patients (52.7%) underwent pancreaticoduodenectomy, 61 patients (41.2%) underwent distal pancreatectomy, and 9 patients (6.1%) underwent total pancreatectomy. Thirty-four patients (22.8%) required major portal vein resection. The median preoperative haemoglobin level was 12.8 g/dl (range: 9.1-16.4 g/dL), the median operating time was 430 min (range: 129-826 min), and the median estimated blood loss was 620 mL (range: 30-6,588 ml). One-hundred and fifteen patients (77.8%) did not require perioperative RBCTs, and 33 patients (22.2%) received RBCTs (31 intraoperative RBCTs and 2 postoperative RBCTs). A pathological TNM stage of 1-2 was observed in 74 patients (50.0%), and a stage of 3-4 was observed in 74 patients (50.0%). Lymph node metastasis was detected in 97 patients (65.5%) and perineural invasion was detected in 91 patients (61.5%). We recorded one in-hospital death (secondary to progressive pulmonary failure) in the RBCT group. Both groups exhibited similar proportions of postoperative complications (Clavien-Dindo grade ≥IIIa; $p$=0.641). The median follow-up time was 17 months (range: 0.4-139.2 months).

*Comparison of patients who did and did not receive RBCT*. The patients who did not receive RBCTs were younger ($p$=0.029) and had higher preoperative haemoglobin levels ($p$<0.001), lower CA19-9 levels ($p$<0.001), smaller tumours ($p$<0.001), and lower TNM stage ($p$=0.001). Patients who did not receive RBCTs also had shorter operative times ($p$<0.001), less intraoperative blood loss ($p$<0.001), fewer instances of major vein resection ($p$<0.001), and a lower proportion of pancreaticoduodenectomy ($p$<0.001). Moreover, patients who did not receive RBCTs exhibited higher rates of negative surgical margins ($p$=0.029) and were more likely to receive adjuvant chemotherapy ($p$=0.017).

*Risk factors for poor survival after resection with curative intent*. The crude unweighted analyses revealed that patients who received RBCTs experienced significantly poorer OS compared with patients who did not receive RBCTs ($p$<0.001; Figure 1, Table II). Patients who received RBCTs exhibited 3-year and 5-year OS rates of 4.5% and 0%, respectively, compared with rates of 45.7% and 28.1% among patients who did not receive RBCTs, respectively. Patients who received RBCTs also exhibited significantly poorer RFS compared with patients who did not receive RBCTs ($p$<0.001; Figure 2, Table III). Multivariate Cox regression analyses revealed that RBCT was an independent risk factor for poorer OS (HR: 4.198, 95%CI: 2.232-7.897,

Table I. *The patients' clinicopathological characteristics according to perioperative transfusion status.*

| Variables | All patients (n=148) | No RBCT (n=115) | RBCT (n=33) | *p*-Value |
|---|---|---|---|---|
| Male sex, n (%) | 77 (52.0%) | 61 (53.0%) | 16 (48.5%) | 0.695 |
| Age, years (median (range)) | **73 (39-86)** | **72 (39-86)** | **76 (53-85)** | **0.029** |
| BMI, kg/m2 (median (range)) | 21.6 (16.3-33.5) | 22.1 (16.7-33.5) | 20.7 (16.3-32.9) | 0.191 |
| ASA grade III-IV, n (%) | 16 (10.7%) | 10 (8.7%) | 6 (17.6%) | 0.198 |
| Pre-op Hb, g/dL (median (range)) | **12.8 (9.1-16.4)** | **13.1 (9.2-16.4)** | **11.6 (9.1-16.3)** | **<0.001** |
| T-Bil, mg/dL (median (range)) | 0.63 (0.19-13.8) | 0.62 (0.19-13.8) | 0.64 (0.25-11.5) | 0.534 |
| PT, % (median (range)) | 87.0 (33.0-148.0) | 87.0 (37.0-125.0) | 88.0 (33.0-148.0) | 0.635 |
| CRP, mg/dL (median (range)) | 0.11 (0.01-17.48) | 0.10 (0.01-17.48) | 0.20 (0-10.4) | 0.088 |
| CEA, ng/mL (median (range)) | 3.2 (0.5-106.3) | 3.3 (0.5-30.4) | 3.0 (1.0-106.3) | 0.857 |
| CA19-9, U/mL (median (range)) | **98.6 (1.0-29,042.4)** | **65.4 (1.0-23,848.0)** | **372.1 (16.4-29,042.4)** | **<0.001** |
| Tumor size, mm (median (range)) | **30.0 (1-145)** | **25.0 (1-75)** | **35 (15-145)** | **<0.001** |
| Tumor staging (3, 4) | **74 (50.0%)** | **49 (42.6%)** | **25 (75.8%)** | **0.001** |
| N1 lymph node staging, n (%) | 97 (65.5%) | 73 (63.5%) | 24 (72.7%) | 0.408 |
| Perineural invasion, n (%) | 91 (61.5%) | 69 (60.0%) | 22 (66.7%) | 0.547 |
| Histological grading (Well), n (%) | 77 (52.0%) | 56 (48.7%) | 21 (63.6%) | 0.111 |
| PRBCs transfused, n | 33 | 0 | 33 | – |
| Intraoperative transfusion | 31 | 0 | 31 | |
| Postoperative transfusion | 2 | 0 | 2 | |
| Length of hospital stay, days (range) | 22 (5-227) | 21.0 (5.0-227.0) | 23.0 (14.0-141.0) | 0.052 |
| Postoperative complications, n (%) | 32 (21.6%) | 24 (20.9%) | 8 (24.2%) | 0.641 |
| Grade B/C pancreatic fistula, n (%) | 24 (16.1%) | 19 (16.5%) | 5 (14.7%) | >0.999 |
| Operative time, min (median (range)) | **425 (129-826)** | **369 (129-727)** | **546 (195-826)** | **<0.001** |
| Intraoperative blood loss, mL (median (range)) | **617.5 (30.0-6,588.0)** | **489.0 (30.0-1711.0)** | **1,305.0 (120.0-6588.0)** | **<0.001** |
| Adjuvant chemotherapy, n (%) | **106 (71.1%)** | **88 (76.5%)** | **18 (52.9%)** | **0.017** |
| Major vein resection, n (%) | **34 (22.8%)** | **18 (15.7%)** | **16 (47.1%)** | **<0.001** |
| Pancreaticoduodenectomy, n (%) | **78 (52.7%)** | **54 (47.0%)** | **24 (72.7%)** | **<0.001** |
| R1 resection margin, n (%) | **24 (16.2%)** | **14 (12.2%)** | **10 (30.3%)** | **0.029** |

Bolded variables are statistically significant ($p<0.05$). ASA: American Society of Anesthesiologists; BMI: body mass index; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; Hb: haemoglobin; Pre-op: preoperative; PRBC: packed red-blood cells; RBCT: red blood cell transfusion; PT: prothrombin time; T-Bil: total bilirubin.

$p<0.001$) and RFS (hazard ratio: 1.905, 95% CI: 1.024-3.543, $p=0.042$).

*IPTW analysis*. After the IPTW process, we confirmed that patients who received RBCTs exhibited significantly poorer weighted OS and RFS rates compared to patients who did not receive RBCTs ($p<0.001$ for both groups; Table IV).

## Discussion

This study revealed that perioperative RBCT was strongly associated with poor OS and RFS rates among patients who underwent resection with curative intent for PDAC. To the best of our knowledge, this is the first study to find that RBCT was strongly related to tumour progression and recurrence using IPTW analysis. Several investigators have reported that perioperative RBCT suppresses the host's immune system, which promotes PDAC recurrence and decreases OS after resection with curative intent (10, 14, 22, 26-28). In this study, patients who received RBCTs were more likely to be older, have preoperative anaemia, have advanced tumour stage, require a longer operation, and experience greater intraoperative blood loss compared to patients who did not receive RBCTs; these characteristics may be related to poorer long-term outcomes. Unfortunately, randomized controlled trials cannot be performed in this setting, which motivated us to perform a cohort study with IPTW and regression analyses to balance the underlying differences in the covariates between patients who did and did not receive RBCTs. These weighted analyses confirmed that perioperative RBCT was strongly associated with poorer OS and RFS outcomes after resection for PDAC.

Previous studies have found that postoperative blood transfusions (not intraoperative blood transfusions) negatively affected long-term outcomes after surgical resection for gastrointestinal malignancies (29, 30). However, other studies have found no association between blood transfusions and prognosis, especially in cases of hepatocellular carcinoma (20, 21). In this study, most patients who received a transfusion (31/33) received

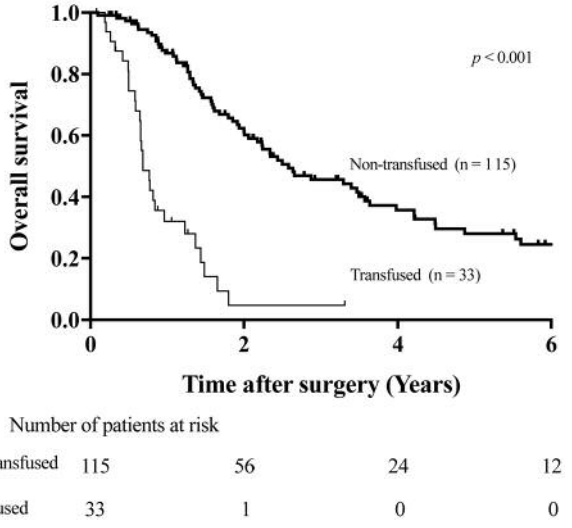


Figure 1. *Patients with pancreatic adenocarcinoma who received a perioperative red blood cell transfusion experienced significantly poorer overall survival rates compared to patients who did not receive such a transfusion (p<0.001).*

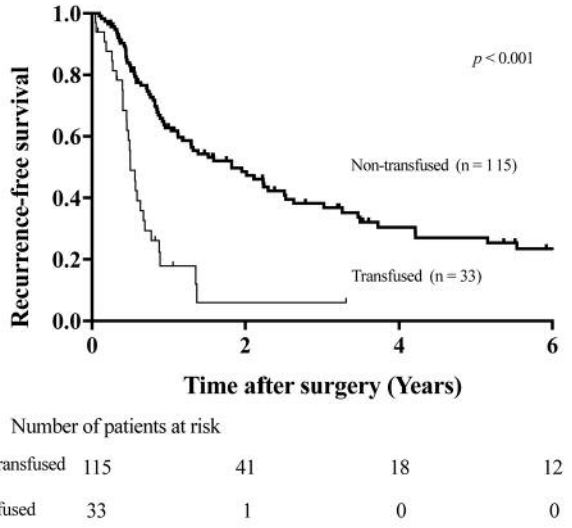


Figure 2. *Patients with pancreatic adenocarcinoma who received a perioperative red blood cell transfusion experienced significantly poorer recurrence-free survival rates compared to patients who did not receive such a transfusion (p<0.001).*

intraoperative blood transfusions, and only 2 patients received postoperative blood transfusions. Similar to previous studies, we found that perioperative RBCT was significantly associated with poor long-term outcomes in cases of PDAC (22). Furthermore, Kneuertz *et al*. (14) found that patients who received more than 2 postoperative units of blood experienced the shortest median OS; in our study, a median of 4 units (range=2-30 units) were used for each RBCT. Thus, avoiding unnecessary RBCTs may be useful for improving the long-term prognosis in these cases, and it may be appropriate to apply blood-conserving techniques in patients with preoperative anaemia or those who require major vein resection. Moreover, the use of recombinant human erythropoietin, folic acid, vitamin B12, and cell-salvage devices could help to minimize the need for intraoperative and postoperative transfusions, although further studies are needed to evaluate these approaches.

The current hypothesis regarding transfusion-related immunomodulation is that it promotes the escape of circulating tumour cells from tumoricidal immune cells, and this immune suppression is a logical explanation for poor RFS in patients who receive RBCTs. The early progression of circulating tumour cells might also predict tumour recurrence (31), and iron overload secondary to blood transfusion may have adverse effects on postoperative outcomes in cases of PDAC. Furthermore, there is increasing evidence that excess iron in the body may accelerate the progression of liver fibrosis and tumour recurrence. Our data support these theories because patients who received RBCT experienced shorter recurrence intervals after resection compared with patients who did not receive RBCTs. Therefore, it is critical to prevent unnecessary RBCTs during the perioperative period, as well as preoperatively evaluate biomarkers related to immune activity, such as cytotoxic T-lymphocytes. The criteria for neoadjuvant chemotherapy and adjuvant chemotherapy are derived from pathological and radiological data, with several biomarkers and microRNA being reported as useful predictive markers (32, 33). Given the deteriorated immune activity in patients with PDAC, a combination of neoadjuvant systemic chemotherapy and surgical resection may be key to improving long-term prognosis by considering the effective biomarkers, especially for patients with immunodeficiency or a high risk for recurrence.

Our study had several potential limitations. First, even the use of IPTW analysis cannot eliminate the risk of hidden bias; propensity score analysis only has a limited ability to reduce the significant bias that can be introduced in retrospective analyses. Patients who received RBCTs seemed to be older, have more advanced disease, and have a higher rate of pancreaticoduodenectomy. Even after propensity-matched analysis, in which these biases were diminished as much as possible, the imbalance of patient numbers between the two groups made it difficult to draw statistically significant conclusions. Second, we used a single-centre non-randomized design with a small sample size, and these factors are prone

Table II. *Univariate and multivariate analyses of factors that were associated with overall survival after resection with curative intent for patients with pancreatic adenocarcinoma (N=148).*

| Variables | | Univariate analyses | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | N (%) | 3-year survival | 5-year survival | *p*-Value | HR | 95% CI | *p*-Value |
| Gender | | | | | | | |
| Male | 77 (52.0%) | 36.5% | 27.2% | 0.756 | | | |
| female | 71 (48.0%) | 36.7% | 18.1% | | | | |
| Age (years) | | | | | | | |
| <70 | 61 (41.2%) | 55.3% | 33.0% | **0.003** | 1 | | 0.054 |
| ≥70 | 87 (58.8%) | 26.0% | 15.6% | | 1.656 | 0.991-2.765 | |
| ASA | | | | | | | |
| I-II | 132 (89.2%) | 36.9% | 24.2% | 0.252 | | | |
| III-IV | 16 (10.8%) | 33.5% | 13.4% | | | | |
| Preoperative Hb (g/dl) | | | | | | | |
| <11 | 19 (12.8%) | 6.9% | – | **<0.001** | 1 | | 0.961 |
| ≥11 | 129 (87.2%) | 41.5% | 26.3% | | 0.978 | 0.409-2.399 | |
| CEA (ng/ml) | | | | | | | |
| <5.0 | 108 (73.0%) | 40.9% | 26.2% | **0.014** | 1 | | 0.575 |
| ≥5.0 | 38 (25.7%) | 24.3% | 10.1% | | 1.153 | 0.700-1.898 | |
| CA19-9 (U/ml) | | | | | | | |
| <38.0 | 56 (37.8%) | 52.2% | 39.0% | **<0.001** | 1 | | 0.387 |
| ≥38.0 | 91 (61.5%) | 27.4% | 13.0% | | 1.251 | 0.753-2.078 | |
| NLR | | | | | | | |
| <3.0 | 112 (75.7%) | 42.6% | 28.3% | **0.009** | 1 | | 0.225 |
| ≥3.0 | 36 (24.3%) | 21.1% | 11.5% | | 1.381 | 0.820-2.325 | |
| mGPS | | | | | | | |
| 0 | 123 (83.1%) | 41.1% | 25.9% | **0.006** | 1 | | 0.983 |
| 1, 2 | 25 (16.9%) | 18.2% | 9.1% | | 0.992 | 0.486-2.027 | |
| Tumor size (mm) | | | | | | | |
| <30 | 73 (49.3%) | 51.4% | 39.0% | **<0.001** | 1 | | **0.044** |
| ≥30 | 74 (50.0%) | 23.3% | 7.0% | | 1.632 | 1.012-2.630 | |
| Tumor staging | | | | | | | |
| 1-2 | 74 (50.0%) | 47.2% | 32.8% | **0.002** | 1 | | **0.045** |
| 3-4 | 74 (50.0%) | 26.3% | 12.5% | | 1.724 | 1.011-2.939 | |
| Lymph node metastasis | | | | | | | |
| None | 49 (33.1%) | 56.5% | 44.7% | **<0.001** | 1 | | **0.041** |
| Present | 99 (66.9%) | 26.7% | 9.2% | | 1.818 | 1.025-3.223 | |
| Intraoperative blood loss (ml) | | | | | | | |
| <620 | 74 (50.0%) | 43.8% | 26.9% | **0.009** | 1 | | 0.452 |
| ≥620 | 74 (50.0%) | 29.8% | 18.6% | | 1.229 | 0.717-2.106 | |
| RBCT | | | | | | | |
| No | 115 (77.7%) | 45.7% | 28.1% | **<0.001** | 1 | | **<0.001** |
| Yes | 33 (22.3%) | 4.5% | – | | 4.198 | 2.232-7.897 | |
| Operative time (min) | | | | | | | |
| <425 | 74 (50.0%) | 43.3% | 28.7% | **0.025** | 1 | | 0.33 |
| ≥425 | 74 (50.0%) | 30.5% | 15.9% | | 0.75 | 0.421-1.337 | |
| Adjuvant chemotherapy | | | | | | | |
| No | 42 (28.4%) | 38.0% | 21.1% | 0.378 | | | |
| Yes | 106 (71.6%) | 36.7% | 23.4% | | | | |
| Postoperative complications | | | | | | | |
| <Clavien-Dindo Grade 3a | 116 (78.4%) | 35.6% | 25.0% | 0.226 | | | |
| ≥Clavien-Dindo Grade 3a | 32 (21.6%) | 41.5% | 14.8% | | | | |

Bolded variables are statistically significant ($p<0.05$). ASA: American Society of Anesthesiologists; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio; Hb: haemoglobin; mGPS: modified Glasgow Prognostic Score; NLR: neutrophil-to-lymphocyte ratio; PT: prothrombin time; RBCT: red blood cell transfusion.

Table III. *Univariate and multivariate analyses of factors that were associated with recurrence-free survival after resection with curative intent for patients with pancreatic adenocarcinoma (N=148).*

| Variables | | Univariate analyses | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | N (%) | 3-year survival | 5-year survival | *p*-Value | HR | 95% CI | *p*-Value |
| Gender | | | | | | | |
| Male | 77 (52.0%) | 30.7% | 28.0% | 0.615 | | | |
| Female | 71 (48.0%) | 32.5% | 16.4% | | | | |
| Age (years) | | | | | | | |
| <70 | 61 (41.2%) | 42.3% | 33.0% | **0.01** | 1 | | 0.118 |
| ≥70 | 87 (58.8%) | 24.2% | 15.2% | | 1.469 | 0.907-2.381 | |
| ASA | | | | | | | |
| I-II | 132 (89.2%) | 33.0% | 23.6% | 0.207 | | | |
| III-IV | 16 (10.8%) | 20.6% | 13.8% | | | | |
| Preoperative Hb (g/dl) | | | | | | | |
| <11 | 19 (12.8%) | 7.3% | – | **<0.001** | 1 | | 0.818 |
| ≥11 | 129 (87.2%) | 34.7% | 25.8% | | 0.913 | 0.421-1.987 | |
| CEA (ng/ml) | | | | | | | |
| <5.0 | 108 (73.0%) | 36.2% | 24.1% | **0.017** | 1 | | 0.285 |
| ≥5.0 | 38 (25.7%) | 15.7% | – | | 1.302 | 0.802-2.113 | |
| CA19-9 (U/ml) | | | | | | | |
| <38.0 | 56 (37.8%) | 47.1% | 36.4% | **<0.001** | 1 | | 0.214 |
| ≥38.0 | 91 (61.5%) | 21.7% | 13.8% | | 1.375 | 0.832-2.271 | |
| NLR | | | | | | | |
| <3.0 | 112 (75.7%) | 36.5% | 27.5% | **0.003** | 1 | | 0.144 |
| ≥3.0 | 36 (24.3%) | 17.5% | 8.8% | | 1.450 | 0.881-2.386 | |
| mGPS | | | | | | | |
| 0 | 123 (83.1%) | 33.5% | 25.4% | **0.018** | 1 | | 0.663 |
| 1-2 | 25 (16.9%) | 14.6% | 9.7% | | 0.864 | 0.447-1.668 | |
| Tumour size (mm) | | | | | | | |
| <30 | 73 (49.3%) | 51.1% | 38.6% | **<0.001** | 1 | | 0.084 |
| ≥30 | 74 (50.0%) | 12.0% | 6.0% | | 1.543 | 0.943-2.524 | |
| Unknown | 1 (0.7) | | | | | | |
| Tumour staging | | | | | | | |
| 1-2 | 74 (50.0%) | 46.5% | 31.7% | **<0.001** | 1 | | **0.035** |
| 3-4 | 74 (50.0%) | 14.4% | 12.0% | | 1.723 | 1.039-2.858 | |
| Lymph node metastasis | | | | | | | |
| None | 49 (33.1%) | 53.6% | 44.3% | **<0.001** | 1 | | **0.032** |
| Present | 99 (66.9%) | 19.7% | 8.1% | | 1.851 | 1.054-3.252 | |
| Intraoperative blood loss (ml) | | | | | | | |
| <620 | 74 (50.0%) | 39.8% | 27.1% | **0.006** | 1 | | 0.191 |
| ≥620 | 74 (50.0%) | 22.7% | 17.6% | | 1.422 | 0.839-2.410 | |
| RBCT | | | | | | | |
| No | 115 (77.7%) | 38.2% | 27.1% | **<0.001** | 1 | 1.024-3.543 | **0.042** |
| Yes | 33 (22.3%) | 6.0% | – | | 1.905 | | |
| Operative time (min) | | | | | | | |
| <425 | 74 (50.0%) | 40.2% | 29.2% | **0.012** | 1 | | 0.191 |
| ≥425 | 74 (50.0%) | 22.0% | 16.1% | | 1.422 | 0.839-2.410 | |
| Adjuvant chemotherapy | | | | | | | |
| No | 42 (28.4%) | 39.1% | 24.4% | 0.797 | | | |
| Yes | 106 (71.6%) | 28.9% | 22.0% | | | | |
| Postoperative complications | | | | | | | |
| <Clavien-Dindo Grade 3a | 116 (78.4%) | 33.4% | 23.6% | 0.252 | | | |
| ≥Clavien-Dindo Grade 3a | 32 (21.6%) | 24.7% | 19.8% | | | | |

Bolded variables are statistically significant ($p<0.05$). ASA: American Society of Anesthesiologists; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; HR: hazard ratio; Hb: haemoglobin; mGPS; modified Glasgow Prognostic Score; NLR: neutrophil-to-lymphocyte ratio; PT: prothrombin time; RBCT: red blood cell transfusion.

Table IV. *Predicted overall and recurrence-free survival rates using red blood cell transfusion status after inverse probability of treatment weighting analysis.*

| End-point | IPTW | | |
|---|---|---|---|
| | HR | 95% CI | *p*-Value |
| Overall survival | 8.55 | 4.87-15.02 | <0.001 |
| Recurrence-free survival | 4.31 | 2.57-7.22 | <0.001 |

CI: Confidence interval; HR: hazard ratio; IPTW: inverse probability of treatment weighting.

to bias. However, it is ethically impossible to perform a randomized trial by withholding RBCTs during surgery.

In conclusion, perioperative RBCT was independently associated with a poor prognosis after surgery with curative intent for patients with PDAC. IPTW and multivariable Cox regression analyses confirmed that RBCT was significantly associated with poorer OS and RFS rates. Therefore, we recommend that surgeons attempt to control intraoperative bleeding and avoid unnecessary perioperative RBCTs.

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## Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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