ORIGINAL ARTICLE

Perioperative blood transfusion is not associated with overall survival or time to recurrence after resection of perihilar cholangiocarcinoma

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Abstract

Background: Perioperative blood transfusions have been associated with worse oncological outcome in several types of cancer. The objective of this study was to assess the effect of perioperative blood transfusions on time to recurrence and overall survival (OS) in patients who underwent curative-intent resection of perihilar cholangiocarcinoma (PHC).

Methods: This retrospective cohort study included consecutive patients with resected PHC between 1992 and 2013 in a specialized center. Patients with 90-day mortality after surgery were excluded. Patients who did and did not receive perioperative blood transfusions were compared using univariable Kaplan–Meier analysis and multivariable Cox regression.

Results: Of 145 included patients, 80 (55.2%) received perioperative blood transfusions. The median OS was 49 months for patients without and 41 months for patients with blood transfusions (P = 0.46). In risk-adjusted multivariable Cox regression analysis, blood transfusion was not associated with OS (HR 1.00, 95% CI 0.59–1.68, P = 0.99) or time to recurrence (HR 1.00, 95% CI 0.57–1.78, P = 0.99). In addition, no differences in effect were found between different types of blood products transfused.

Conclusion: Blood transfusion was not associated with survival or time to recurrence after curative resection of PHC in this series. The alleged association is presumably related to the circumstances necessitating blood transfusions.

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Introduction

Perihilar cholangiocarcinoma (PHC) is the most common type of cholangiocarcinoma,[1] and originates at or near the biliary confluence. Surgical resection is the only potentially curative treatment for PHC, yielding a median overall survival of 19 to 39 months.[2,3]

Complete excision of PHC requires extended liver resection, which may cause significant blood loss. Perioperative blood transfusions with packed red blood cells (pRBC) are used to compensate for critical blood loss, but have been associated with increased risk of tumor recurrence and decreased long-term outcome in several tumor types, including colorectal, prostate, lung, and head and neck cancer.[4–11] The effect of blood transfusions on prognosis is attributed to a distinct pathology of immunosuppression, known as transfusion-related immune modulation (TRIM). Blood transfusion seems to provoke an immune deviation[12] and changes in the anti-inflammatory/pro-inflammatory environment.[13–15] These substantial alterations form a complex and dynamic interplay creating a pro-tumor environment, which has been suggested to facilitate growth of residual cancer cells at the resection margin, transformation of micro-metastases into clinical metastases, or both.

Despite multiple studies showing an association between perioperative blood transfusion and prognosis, it is unclear whether this effect is caused by clinical circumstances requiring transfusions or is due to the blood transfusion itself.[16,17]

Conflicting results have been reported after resection of cholangiocarcinoma.[18–23] Some studies included both proximal and distal cholangiocarcinoma, but these should be regarded as distinct tumor entities with different prognosis, as the latter involves the pancreatic head.[24,25] The aim of this study was to assess the effect of perioperative blood transfusions on overall survival (OS) and time to recurrence in patients who recovered after resection of PHC, thus excluding patients who died from post-operative complications. As a secondary analysis, we also assessed the individual effects of different transfusion products.[5]

Methods

A retrospective database was used, identifying 167 consecutive patients who underwent a curative-intent resection of PHC at a single center (Academic Medical Center, Amsterdam, The Netherlands) between 1992 and 2013. All patients who died within 90 days after resection (n = 22; 13.2%) were excluded. These patients most likely died from perioperative complications, which is a potential confounder when assessing the effect of transfusion on long-term outcome.[26] PHC was defined as a pathologically confirmed biliary malignancy originating at the biliary confluence, right or left hepatic duct, or common hepatic duct.[24] Patient selection and perioperative management have been described previously.[27] Briefly, patients underwent routine preoperative biliary drainage, and preoperative low-dose radiotherapy (3 × 3.5 Gy) to prevent seeding metastases. An extrahepatic bile duct resection without liver resection was performed in patients with Bismuth type I tumors. For Bismuth type 2, 3 and 4 tumors, resection encompassed excision of the liver hilum en bloc with (extended) hemihepatectomy, excision of the portal vein bifurcation when involved, and complete lymphadenectomy of the hepatoduodenal ligament. Caudate lobectomy was performed in most patients since the late 90s.

Data collection and definitions

Perioperative transfusion was defined as administration of one or more blood products within seven days before or after surgery. Blood transfusions were further classified into the different blood products administered, consisting of pRBC, fresh-frozen plasma (FFP) or platelets. Overall survival was measured from the date of surgery to the date of death. Patients were censored when alive at January 1st, 2014. Since survival status was synchronized with the Dutch municipal register, no patients were lost to follow-up of overall survival. Time to recurrence was measured from the time of surgery to the time of the first recurrence on imaging. No adjuvant chemotherapy was administered after initial curative resection. Clinical follow-up was performed routinely every three months in the first year after surgery and every six months in the following five years. Laboratory tests and follow-up CT scans were performed in the first six months to detect early recurrence, and in later course when indicated. Patients who had no observed recurrence were censored at the time of the last follow-up (not necessarily with imaging) prior to January 2014. Major complications were graded according to the Clavien–Dindo classification[28]; severe morbidity included grade III and IV complications (grade V, post-operative death, was excluded from the analysis).

Statistical analysis

Continuous data are expressed as mean (±standard deviation) or median (±interquartile range (IQR)) as applicable. For comparing continuous variables a t-test or Mann–Whitney U test was used; for comparing proportions, Fisher's exact test or Chi square test was used. Firstly, characteristics between patients with and without a blood transfusion were compared, including patient demographics, comorbidities, preoperative status and treatment, and perioperative details. Survival was analyzed using a Kaplan–Meier survival plot, and compared with a log rank test. All models in Cox multivariable survival analysis were adjusted for age, sex and known prognostic factors including resection margin, lymph node stage, tumor differentiation,[29] and major complications.[30] The same prognostic factors were used in the analysis assessing the impact of different blood products of OS.

Statistical analysis was performed using SPSS (version 20, SPSS Inc., Chicago, IL). Two sided P-values < 0.05 were considered significant.

Results

Patient characteristics

Of 145 patients included, 80 (55.2%) received a perioperative blood transfusion: 26 patients (17.9%) received one or two blood units, and 54 patients (37.2%) received more than two blood units (total range, 1–47). Evaluation of different time spans shows a decrease in administered blood transfusions; 1992–1999 20 (62.5%), 2000–2006 25 (67.6%), 2007–2014 35 (46.1%). Table 1 details baseline and intra-operative characteristics of patients with and without perioperative transfusion. Patients receiving blood products were younger, more often jaundiced at presentation, and more often suffered from preoperative cholangitis. Also, the disease was more extensive in patients who had received perioperative blood transfusion, as evidenced by a higher Bismuth classification and Blumgart stage on preoperative imaging, and use of more extended resections and portal vein reconstruction. Patients with a perioperative blood transfusion more often had a major post-operative complication.

Overall survival

The median OS in the study cohort was 47 months (95% confidence interval [CI] 39–55). The median follow-up among survivors was 47 months (range 4–244). At last follow-up, 83 patients (57.2%) had died. Median OS of patients receiving a blood transfusion was 41 months compared to 49 months in

Table 1 Baseline and intra-operative characteristics of patients with and without perioperative transfusion for perihilar cholangiocarcinoma. Variables are expressed as numbers (count) and percentages, unless stated otherwise

Variable	Total (N = 145)	No transfusion N = 65	Transfusion N = 80	P-value[a]
Age (years), mean (sd)	63 ± 11.1	66 ± 10.7	59 ± 10.7	0.001
Sex				0.108
Female	56	21 (37.5)	35 (62.5)	
Male	89	44 (49.4)	45 (50.6)	
ASA classification				0.389
1–2	126	54 (42.9)	72 (57.1)	
3	16	8 (50.0)	8 (50.0)	
Jaundice at presentation				0.050
No	30	18 (60.0)	12 (40.0)	
Yes	112	46 (41.1)	66 (58.9)	
Preoperative biliary drainage				0.074
No	19	11 (57.9)	8 (42.1)	
Percutaneous	5	1 (20.0)	4 (80.0)	
Endoscopic	89	44 (49.4)	45 (50.6)	
Both	32	9 (28.1)	23 (71.9)	
Preoperative cholangitis				0.012
No	105	55 (52.4)	50 (47.6)	
Yes	27	7 (25.9)	20 (74.1)	
Preoperative total bilirubin (μmol/L), median (IQR)	14 ± 8	11 ± 10	19 ± 28	0.488
Preoperative hemoglobin, mean (sd)	7.9 ± 1.1	8.0 ± 1.0	7.8 ± 1.1	0.197
Blumgart classification				0.002
1	70	40 (57.1)	30 (42.9)	
2	29	7 (24.1)	22 (75.9)	
3	22	6 (27.3)	16 (72.7)	
Bismuth classification				<0.001
Left or right duct only	16	13 (81.2)	3 (18.8)	
1/2	41	29 (70.7)	12 (29.3)	
3A/B	69	17 (24.6)	52 (75.4)	
4	19	6 (31.6)	13 (68.4)	
Type of resection				0.001
No major hepatectomy	43	29 (67.4)	14 (32.6)	
(Ext.) left hepatectomy	54	23 (42.6)	31 (57.4)	
(Ext.) right hepatectomy	48	13 (27.1)	35 (72.9)	
Caudate lobe resection				0.129
No	65	33 (50.8)	32 (49.2)	
Yes	80	32 (40.0)	48 (60.0)	
PV reconstruction				0.023
No	118	58 (49.2)	60 (50.8)	
Yes	27	7 (25.9)	20 (74.1)	
Blood loss (100 ml), mean (sd)	22.8 ± 15.4	12.5 ± 6.9	31.8 ± 15.1	<0.001
Major post-operative complications (Clavien grade 3 or 4)				0.002
No	94	51 (54.3)	43 (45.7)	
Yes	50	14 (28.0)	36 (72.0)	

(*continued on next column*)

Table 1 (*continued*)

N, number of patients.

patients without blood transfusions, which was not significant in univariable analysis (P = 0.46; Fig. 1a). To further explore a potential dose-dependent association, patients were stratified for the number of blood products transfused (none, 1 or 2, or ≥3). A trend towards worse OS was observed, but the effect remained non-significant (P = 0.23; Fig. 1b). Patients with three or more transfusions had a median OS of 39 months compared to a median OS of 41 months in patients who received one or two blood products. Multivariable analysis was performed to assess the association between one or more units transfused versus no units transfused. Risk-adjustment revealed significant associations between OS and known prognostic factors, including lymph node involvement, R1 resection, and tumor differentiation, but no association with blood transfusion (Table 2).

Time to recurrence

Recurrence status was unknown in 12 patients who were lost to follow-up of recurrences (8.3%). Among the other 133 patients, tumor recurrence was detected in 72 patients (54.1%) during follow up. Initial recurrences were classified according to the 7th edition of the AJCC staging system[24] as local recurrence in 20 patients (15.0%), distant recurrence in 39 patients (29.3%), or both in 13 patients (9.8%). The median time to recurrence in all patients was 39 months; the median time to recurrence was 39 months among patients receiving a blood transfusion, and 44 months among patients without blood transfusions (P = 0.91; Fig. 2a). Similar to OS, stratification for the number of blood products (none, 1–2, or ≥3) revealed a trend in time to recurrence, but the effect was non-significant (P = 0.25; Fig. 2b). Interestingly, patients with one or two units transfused had a

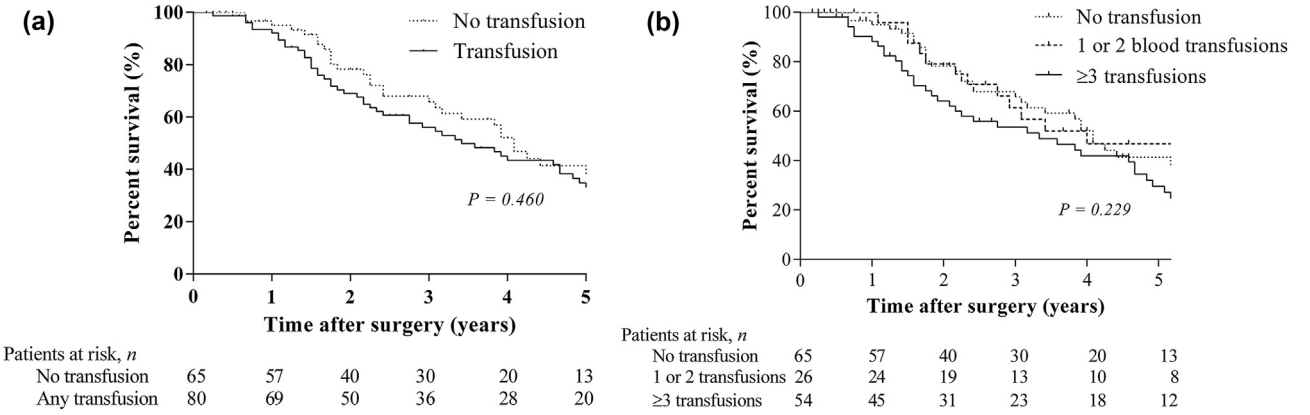

Figure 1 Kaplan-Meier curves for overall survival

Table 2 Prognostic factors for overall survival

	Variable	Est. median survival (months)	Cox regression			
			Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Blood transfusion	No	49	Reference	0.461	Reference	0.993
	Yes	41	1.18 (0.76–1.83)		1.00 (0.59–1.68)	
Age	Per year	NA	1.00 (0.98–1.02)	0.651	0.99 (0.96–1.01)	0.150
Sex	Female	47	Reference	0.474	Reference	0.854
	Male	47	1.18 (0.75–1.84)		1.05 (0.63–1.74)	
Type of resection	No major hepatectomy	41	Reference	0.516	Reference	0.890
	Major hepatectomy	48	0.86 (0.55–1.35)		1.04 (0.61–1.76)	
Portal vein reconstruction	No	46	Reference	0.057	Reference	0.028
	Yes	NA[a]	0.51 (0.25–1.02)		0.43 (0.20–0.91)	
Margin	R0	49	Reference	0.099	Reference	0.015
	R1	38	1.46 (0.93–2.28)		1.93 (1.14–3.28)	
Lymph node metastases	N0	49	Reference	0.001	Reference	0.001
	N1	27	2.27 (1.38–3.73)		2.49 (1.17–4.28)	
Tumor differentiation	Well	68	Reference	0.009	Reference	0.014
	Moderate/poor	38	2.21 (1.22–4.02)		2.15 (1.17–3.96)	
Major complications	No	49	Reference	0.185	Reference	0.218
	Yes	29	1.36 (0.86–2.15)		1.37 (0.83–2.28)	

HR, hazard ratio; **CI**, confidence interval; **NA**, not available.
[a] The median survival in patients with PV reconstruction is not available, this is because more than half of the patients is alive. The median has not been reached.

non-significant longer time to recurrence compared to patients with no transfusions (median 61 versus 44 months, respectively). Time to recurrence was shortest in patients with three or more units transfused (median 33 months). Finally, the association between one or more transfused units (versus no units transfused) was assessed in multivariable analysis. Again, risk-adjustment revealed significant associations of time to recurrence with known prognostic factors, including lymph node involvement, tumor differentiation and major complications but no association with one or more units transfused. (Table 3)

Red blood cells, platelets concentrates and fresh-frozen plasma

Seventy-seven patients received pRBC (53.1%), 47 patients received FFP (32.4%) and 9 patients received platelet concentrates in (6.2%). Univariable analysis showed that FFP had a

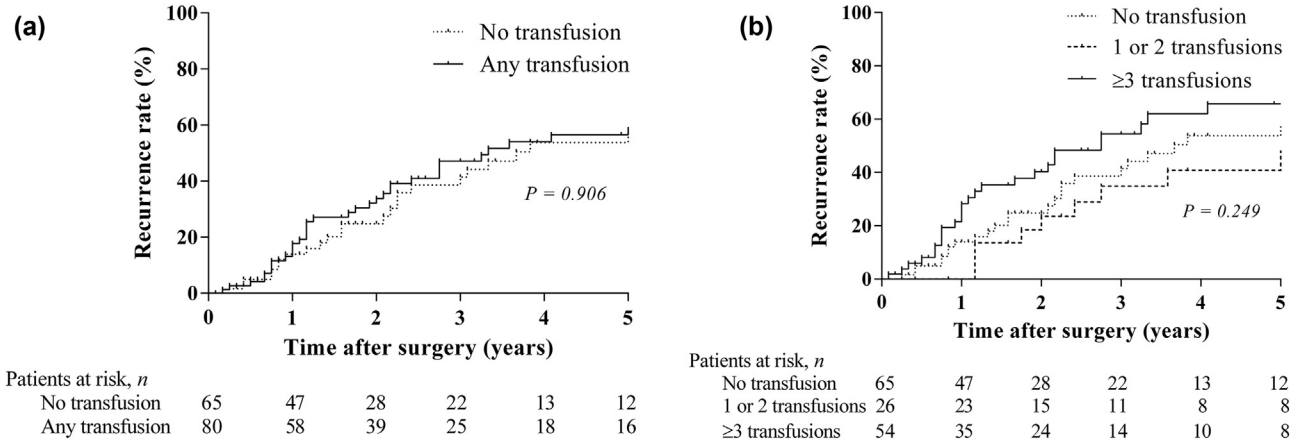

Figure 2 Kaplan-Meier curves for time to recurrence

Table 3 Prognostic factors for time to recurrence

	Variable	Est. median time to recurrence (months)	Cox regression			
			Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Blood transfusion	No	44	Reference	0.906	Reference	0.989
	Yes	39	0.97 (0.59–1.59)		1.00 (0.57–1.78)	
Age	Per year	NA	0.99 (0.97–1.02)	0.528	1.00 (0.97–1.02)	0.636
Sex	Female	61	Reference	0.313	Reference	0.710
	Male	39	1.30 (0.78–2.16)		1.12 (0.62–2.02)	
Type of resection	No major hepatectomy	36	Reference	0.263	Reference	0.656
	Major hepatectomy	44	0.75 (0.46–1.24)		0.88 (0.49–1.57)	
Portal vein reconstruction	No	40	Reference	0.610	Reference	0.354
	Yes	NA[a]	0.61 (0.30–1.24)		0.69 (0.31–1.52)	
Margin	R0	44	Reference	0.703	Reference	0.392
	R1	33	1.11 (0.65–1.90)		1.31 (0.71–2.41)	
Lymph node metastasis	N0	68	Reference	<0.001	Reference	<0.001
	N1	16	3.63 (2.13–6.20)		3.85 (2.13–6.96)	
Tumor differentiation	Well		Reference	0.012	Reference	0.011
	Moderate/poor	33	2.49 (1.22–5.06)		2.56 (1.24–5.31)	
Major complications	No	46	Reference	0.118	Reference	0.071
	Yes	27	1.51 (0.90–2.51)		1.67 (0.96–2.91)	

HR, hazard ratio; **CI**, confidence interval; **NA**, not available.
[a] The median survival in patients with PV reconstruction is not available, this is because more than half of the patients is alive. The median has not been reached.

non-significant adverse effect on OS (HR 1.36, 95% CI 0.87–2.12). After risk-adjustment in multivariable analysis, none of the three had a significant effect on OS. (Table 4)

Discussion

We set out to assess the effect of perioperative blood transfusions on long-term outcomes after resection of perihilar cholangiocarcinoma in a single center, specialized in biliary tract surgery. After appropriate risk-adjustment, no effect of blood transfusion was found on tumor recurrence or overall survival.

Blood transfusions have been associated with worse oncological outcomes in several types of cancer,[9,16,17,31,32] including multiple studies in cholangiocarcinoma.[21,22,33] These studies attributed this association to transfusion-related immune modulation (TRIM), which is characterized by an increase in T helper

Table 4 Blood product-specific effect on overall survival

	No. (%)	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Packed red blood cells	77 (53.1%)	1.18 (0.76–1.82)	0.470	0.88 (0.54–1.44)	0.601
Fresh-frozen plasma	47 (32.4%)	1.36 (0.87–2.12)	0.172	1.05 (0.66–1.68)	0.874
Platelet concentrates	9 (6.2%)	0.64 (0.23–1.75)	0.383	0.69 (0.25–1.95)	0.694

HR, hazard ratio; **CI**, confidence interval.

Table 5 Overview of recent studies assessing the effect blood transfusion on overall survival after resection of cholangiocarcinoma

Author, reference, publication year	N	Type of cholangio-carcinoma	Univariable analysis		Multivariable analysis	
			HR or RR (95% CI)	P-value	HR or RR (95% CI)	P-value
Studies with significant association						
Young *et al*. 2011[21]	83	Perihilar	NA	0.01	2.00 (1.09–3.69)	0.03
Nagino *et al*. 2013[22]	574	Perihilar	NA	0.002	1.35 (1.06–1.72)	0.02
Studies with non-significant association						
Muller *et al*. 2014[41]	128	Any extrahepatic (hilar or distal)	2.05 (1.19–3.51)	0.01	1.14 (0.52–2.48)	0.75
Chauhan *et al*. 2011[18]	51	Hilar	NA	0.37	–	
Furusuwa *et al*. 2014[19]	144	Hilar	NA	0.02	1.49 (0.90–2.47)	0.12
Li *et al*. 2014[23]	58[a]	Intrahepatic	NA	0.05	1.98 (1.05–3.72)	0.44
Present study	145	Perihilar	1.18 (0.76–1.83)	0.46	1.00 (0.59–1.68)	0.99

N, number of patients in the study; **HR**, hazard ratio; **RR**, relative risk; **NA**, not available.
[a] Perioperative blood transfusion cut off was 600 mL.

type 2 (Th2) and regulatory T-cells. Th2 cytokines promote matrix metalloproteinase expression, invasiveness and metastasis of tumor cells.[13] This in turn leads to down-regulation of the secretion of T helper type 1 cytokines, which normally suppress tumor growth and initiate changes to the inflammatory environment.[12] Recent experimental evidence supports these findings.[34–37] Taking this into account, in combination with other side effects such as transfusion-related acute lung injury (TRALI), current guidelines recommend a cautious policy to use perioperative blood transfusions only when it is highly required.[38]

The alleged association between blood transfusion and overall survival were not corroborated in more recent studies. Several studies found no effect of blood transfusion on overall survival,[39,40] including several studies in cholangiocarcinoma (Table 5). Amongst others,[18,19,23,41] Muller *et al.* found no effect of blood transfusions in a propensity-matched analysis of patients undergoing resection of distal or proximal extrahepatic cholangiocarcinoma.[41] The present study adds weight to that observation by analyzing a large homogenous cohort restricted to patients undergoing resection of perihilar cholangiocarcinoma, which is associated with a higher risk of blood loss because of the extended liver resections required to achieve complete removal of the tumor. Moreover, we excluded all patients who died within 90 days after surgery, thereby eliminating a potential confounding bias of perioperative complications and truly focusing the analysis on long-term outcome. We found no association with time to tumor recurrence and no association with overall survival, neither in unadjusted nor in risk-adjusted analysis.

In the abovementioned studies, the presumed effect of blood transfusion on long-term outcomes disappeared when the analysis was adjusted for the circumstances that require the blood transfusion. Additionally, one study showed no effect of blood transfusion in a large cohort of veterans undergoing surgery when the analysis was adjusted for perioperative complications.[26] Other studies have suggested that anemia-induced hypoxia is the actual contributor to tumor recurrence instead of the blood transfusion.[42–44] This theory was supported by the long-term results of a clinical trial comparing allogeneic versus autologous blood transfusion in colorectal cancer surgery.[45] Counter-intuitively, this study showed worse overall and disease free survival after autologous transfusion, which was attributed to the induction of iatrogenic anemia before surgery. Furthermore, recent evidence demonstrates that a higher hemoglobin level mediates the response to radiation through delivery of oxygen to the tumor.[46] These studies fit into a generally changing attitude towards perioperative blood transfusion: the assumption that perioperative blood transfusion is safe in terms of long-term outcome, and can be helpful when it is clinically required. A meta-analysis could provide a higher level of evidence to shed more light on this discussion. In that perspective, publication of

negative studies is equally important as publishing positive studies, in order to prevent publication bias.

In our study, a relatively large amount of patients (55%) received blood transfusion, reflecting a liberal transfusion policy during the study period. Some studies reported less frequent use of blood transfusions during resection of PHC,[41,47] whereas other studies reported transfusion rates similar to the present study.[18,19,39] The applied transfusion policy is apparently justified since no association of blood transfusion with survival has been found.

Up to now, little is reported about the association between survival and fresh-frozen plasma or platelet concentrates,[5,48] as literature mainly focuses on the effect of packed red blood cells.[49,50] An interesting finding of our study is that the distinction between blood products has no influence on the outcome. Comparable results were reported for example by Tomimaru *et al.*, who found that FFP transfusion did not affect cancer prognosis following hepatic resection for HCC.[51] McGrath *et al.* concluded that platelet transfusions in cardiac surgery have no effect on morbidity after cardiac surgery.[52]

Several studies have shown a dose-dependent relationship, with three or more units of transfused blood almost doubling the risk observed with one or two units.[9,17,53,54] Although, the principal analysis found no effect of blood transfusions on long-term outcomes, we cannot exclude a potential effect of massive blood transfusion, which could still cause immune modulation and alterations to the inflammatory response. Moreover, blood transfusion remains a costly therapy and unnecessary blood transfusions should be avoided. Transfusions can still cause alloimmunization, transmission of viral diseases, graft-versus-host disease, and an increased post-operative infection rate.[4,6,7,55] It is important to make an individualized decision on the use of blood transfusion in every patient undergoing cancer surgery, in conjunction with other precautionary measures.[5]

This retrospective study has several limitations. The cohort stretched over a long time period (1992–2013), which may have introduced heterogeneity related to changes in perioperative care. On the other hand, this approach enabled us to analyze the effect of blood transfusion in the largest cohort of resected PHC to date. Nevertheless, it remains a relatively small sample size with which a type II error cannot be ruled out. Furthermore, no information was available on the storage time of pRBC's, which may also affect outcome. Limiting the study to perihilar cholangiocarcinoma improved homogeneity, as distal and intrahepatic cholangiocarcinoma are regarded as different tumor entities with their own specific treatment and prognosis. Although, we performed risk-adjustment for a variety of observed confounding factors, potential bias due to unknown or unobserved confounders cannot be excluded.

In conclusion, perioperative blood transfusion was not associated with overall survival or time to recurrence in this large single-center cohort of patients who recovered from resection of perihilar cholangiocarcinoma. Therefore, the use of blood transfusion during or after surgery for perihilar cholangiocarcinoma seems safe in terms of long-term outcome. The alleged association of perioperative blood transfusions with worse outcomes after curative resection of PHC is presumably due to the circumstances necessitating blood transfusions instead of the blood transfusion per se.

Funding sources

None.

Conflicts of interest

None declared.

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