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The Effect of Perioperative Blood Transfusion on Long-Term Survival Outcomes Following Surgery for Pancreatic Ductal Adenocarcinoma: A Systematic Review

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Abstract

Objective: Evaluate survival outcomes associated with perioperative allogeneic red blood cell transfusion (RBCT) in patients with pancreatic ductal adenocarcinoma undergoing surgery.

Methods: PubMed, Embase, Cochrane, and Web of Science were queried for English-language articles until May 28, 2020. Studies evaluating long-term outcomes of RBCT compared with no transfusion in adults with pancreatic ductal adenocarcinoma undergoing pancreatectomy were included. E-value sensitivity analysis assessed potential for unmeasured confounders to overcome these findings.

Results: Of 4379 citations, five retrospective cohort studies were included. Three studies reported shorter recurrence-free survival by 1–5 months with RBCT. Two studies found shorter disease-specific survival by 5–13 months with RBCT. Overall survival was reduced by 5–7 months with RBCT in three studies. All multivariable findings associated with RBCT could be readily overcome unmeasured confounding on sensitivity analysis. Confounding in baseline characteristics resulted in high risk of bias.

Conclusions: Imprecision, unmeasured confounding, small effect sizes, and overall low quality of the available literature result in uncertainty regarding the effect of transfusion on recurrence-free survival, disease-specific survival, and overall survival in patients undergoing surgery for pancreatic cancer. Randomized trials are needed to determine if there is a causal relationship between transfusion and survival following pancreatic resection.

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Keywords

pancreatic cancer; pancreatectomy; transfusion; survival; mortality; systematic review

Introduction

Allogeneic blood transfusions are frequently needed for patients undergoing pancreatic resection but there is concern that they may worsen oncologic outcomes because of immune suppression. Although guidelines recommend conservative use of blood transfusions, the use of blood products is still common during cancer surgery, and triggers for transfusion vary widely among clinicians.[1–5] The immune effects of allogeneic blood transfusions in cancer surgery were raised as a concern in the early 1980s.[6,7] A Cochrane systematic review and meta-analysis of perioperative blood transfusion on colon cancer recurrence reported an association between blood transfusion and earlier recurrence, but the studies examined were heterogeneous, retrospective, lack matched analyses, and were confounded, calling into question the validity of the conclusions.[8]

Patients undergoing surgery for pancreatic ductal adenocarcinoma (PDAC) are at risk for large volume blood loss resulting in the need for blood transfusion because of the deep-seated anatomical location of the pancreas, potential adjacency of the tumor with major surrounding vessels, and surgeons' goals to achieve negative margins resulting in extensive resections. Given the poor overall survival for PDAC, it is important to understand how blood transfusion during pancreatic resection might influence long-term outcomes.[9]

There are few literature reviews assessing the effect of perioperative blood transfusion on long-term survival outcomes following surgery for pancreatic cancer. Previous reviews examined studies that had substantial heterogeneity and pooled disparate survival outcomes resulting in uncertainty regarding the influence of blood transfusion on pancreatic cancer outcomes.[10] The purpose of this systematic review is to evaluate long-term survival outcomes in patients who received perioperative blood transfusions for pancreas cancer surgery examining higher-quality and homogeneous studies.

MATERIALS AND METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards.[11]

Literature Search

In collaboration with a medical librarian (B.M.), we searched for English-language articles in PubMed, Embase, Cochrane (all databases), and Web of Science up to May 28, 2020. Search terms relating to "blood transfusion," "pancreatic cancer," and "pancreas surgery" were used (see Supplemental Table 1, which shows expanded search terms).

Study Selection and Data Collection

A primary reviewer (L.Y.) independently performed the title and abstract screen, full-text review, data extraction, and risk of bias assessment. All stages of review were appraised by a second reviewer (E.H.L), and all disagreements were resolved with discussion. Primary literature evaluating long-term outcomes of perioperative allogeneic whole blood or packed red blood cell transfusion compared with no transfusion in adults with primary PDAC perioperatively for pancreatectomy were included. Studies only reporting short-term outcomes were excluded. Only studies that evaluated blood transfusion as the primary intervention were included to limit the number of lower quality studies. Case reports, case series, abstracts, editorials, reviews or meta-analyses, trial listings, and non-human studies were excluded. Studies of the topics of transplant, benign disease, or non-pancreas cancer, including liver cancer, cholangiocarcinoma, ampullary cancer, or duodenal cancer, were excluded. Studies on pancreatic neuroendocrine tumors were also excluded, as the survival outlook for this disease process is significantly different from PDAC. Studies of multiple cancer types were excluded if there was no subgroup analysis for pancreas. Studies assessing autotransfusions, non-red blood cell, or non-whole blood transfusions (eg,. fresh frozen plasma, platelets) were excluded.

We extracted data on the following: study design, sample size, patient and tumor characteristics, intraoperative characteristics, short-term (<90-day) postoperative outcomes, and long-term (>90-day) survival outcomes. Patient and tumor characteristics included age, ethnicity, sex, body mass index, American Society of Anesthesiologists score, co-morbidities, tumor histology, size, grade, stage, presence of lymphovascular invasion or perineural invasion, receipt of neoadjuvant therapy, and preoperative laboratory values, such as hemoglobin, albumin, bilirubin, international normalized ratio, and cancer antigen (CA) 19–9. Intraoperative characteristics included operating room (OR) time, estimated blood loss (EBL), intraoperative transfusions, intraoperative complications, surgical approach, procedure, combined procedures, major vein resection, and resection margin.

Short-term postoperative outcomes included length of stay, readmissions, reoperations, emergency department visits, postoperative transfusions, postoperative complications, and mortality.

Long-term outcomes included length of follow-up, receipt of adjuvant therapy, recurrence-free survival (RFS), disease-specific survival (DSS), and overall survival (OS).

Risk of Bias and Certainty of Evidence

The risk of bias in each observational study was assessed with the Cochrane Risk of Bias In Non-randomized Studies-of Interventions.[12] The studies generally had low selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias because of missing data, and bias in measurement of outcomes. Study-specific differences in the selection of the reported result were deemed to have moderate bias when *P* values, clinically relevant data, and pooled transfusion outcomes were not reported.

We used the criteria of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group to summarize the findings and assess overall certainty of the evidence.[13]

Statistical Analysis

Univariable and multivariable findings were extracted directly from the study source. Pooled totals were back-calculated when only subgroup data was available. Risk differences and 95% confidence intervals were calculated from reported counts and sample sizes to estimate significance when *P* values were not reported.

E-value sensitivity analysis was performed to determine the effect of unmeasured confounding on the multivariable findings for each study.[14] Study-specific cumulative outcome incidences, point estimates, 95% confidence intervals, and *P* values from outcomes that underwent multivariable analyses were used in performing the sensitivity analysis.

Stata was used to perform I^2 analysis to assess study heterogeneity using the natural log of the effect sizes and standard errors for the RFS outcome.[15] A funnel plot was created to evaluate publication bias using a random effects model of the natural log of the study effect sizes and standard errors.

RESULTS

Literature Search

A total of 4379 studies were found across four databases, with 2861 studies remaining after duplicates were removed. An additional 1110 records were excluded prior to screening. Of the 1751 titles and abstracts screened, 36 full-text articles were reviewed for eligibility, and five studies were included in the final analysis.[16–20] Thirty-one full-text articles were excluded for the following reasons: lack of long-term data (n = 17), mixed populations of multiple cancers without subgroup analyses for pancreatic cancer (n = 8), non-PDAC (n = 1), non-pancreas cancer (n = 1), lack of comparison of transfusion (n = 1), review (n = 1), case series (n = 1), and overlapping data sets from the same institution (n = 1) (Figure 1).

Study and Patient Characteristics

All five studies included in the qualitative analysis were retrospective, however two studies utilized data from prospectively collected databases (Table 1).[19,20] Three studies were based in the United States,[18–20] and two were from institutions in Japan and South Korea.[16,17] Four studies used data from single institutions, while one study analyzed patients from multiple institutions.[19] Four studies reported on PDAC,[16–19] and one study analyzed “exocrine neoplasms of the pancreas,”[20] which were interpreted to be PDAC. Three studies examined only patients that underwent either standard or pylorus-preserving pancreaticoduodenectomies,[18–20] while the remaining two studies included a mix of Whipple procedure and other pancreatectomy.[16,17] All included studies evaluated the effect of packed red blood cell transfusion compared with no transfusion. Two of the six studies performed propensity matching using inverse probability of treatment weighting and greedy matching,[16,19] however neither study reported any matched descriptive data. One of these

studies matched for only the RFS outcome.[19] The studies varied in size from 148 to 697 patients, with a total of 1646 patients included in the analysis.

There were a number of differences between the non-transfused and transfused cohorts in patient, tumor, and surgical characteristics in all studies. Overall, most of the patients were at least in their seventh decade of life, with the study by Abe et al reporting average ages in the 70s.[16] In three studies, patients who received blood transfusions were significantly older than their non-transfusion counterparts,[16,19,20] and there were significantly more baseline co-morbidities in the transfusion cohort in two studies.[18,19] In three of the four studies reported preoperative labs, there were significant differences in baseline laboratory values between each cohort, such as hemoglobin, CA 19–9, total bilirubin, international normalized ratio, and albumin.[16,18,20] The remaining study reported on only preoperative CA 19–9, which was not significantly different between the groups ($P = 0.058$).[17] Of the three studies that reported on preoperative hemoglobin levels or anemia, all patients who eventually received transfusion had significantly lower hemoglobin levels.[16,18,20]

Of the three studies that reported tumor size, two reported significantly larger tumors in the transfused cohort.[16,19] Three of the four studies that reported operative duration had significantly longer times in the transfused group;[16,18,19] the remaining study did not find a statistically significant difference between groups ($P = 0.064$).[17] All five studies demonstrated a significantly greater intraoperative EBL in the transfused cohort.

Due to the heterogeneity in clinical outcomes of the observational studies, a meta-analysis was not conducted.

Postoperative Outcomes

Length of stay was longer in the transfused cohort in two studies (see Supplemental Table 2, which shows the full evidence table).[16,18] One study reported increased 90-day readmission and reoperation rates associated with transfusion,[19] and three of five studies reported increased short-term total complication rates for patients who received blood transfusions.[18–20]

The median RFS was shorter for patients who received blood transfusions in all three studies that reported this outcome, ranging from one to five months (Table 2).[17–19] On multivariable analysis, three of four studies reported a significant association between blood transfusion and reduced RFS (Table 3).[16,18,19] In the matched study by Sutton et al, RFS was similar when comparing 1–2U of blood transfused to no transfusion, but it was significantly shorter when comparing >2U transfusions to 1–2U ($P = 0.014$) or no transfusions ($P < 0.001$).[19] In the same study's multivariable analysis assessing the subgroups of patients who received intra- or post-operative transfusions of 1–2U or > 2U of blood, intraoperative transfusion of 1–2U did not significantly affect RFS (hazard ratio [HR], 0.7; 95% confidence interval [CI], 0.46–1.06; $P = 0.081$), while intraoperative transfusions >2U and postoperative transfusions yielded hazard ratios of nearly two (HR, 2.09; 95% CI, 1.32–3.29; $P = 0.002$). In the matched study by Abe et al, a multivariable analysis found that blood transfusion decreased RFS with a hazard ratio of 4.31; 95% CI, 2.57–7.22; $P < 0.001$.[16]

Of the six included studies, two reported DSS,[17,20] while three studies reported OS.[16,18,19] Disease-specific survival was shorter for patients who received a blood transfusion in both studies that reported this outcome by a range of five to 13 months on univariable analysis (Table 2). In the study by Yeh et al, a subgroup analysis was performed based on the timing of the transfusion intra- or post-operatively.[20] Patients who received transfusions intraoperatively did not differ in DSS compared with those who were not transfused (23 vs 24 mo, $P = 0.655$), however patients who received postoperative transfusions had significantly shorter survival than those who were not transfused (17 vs 26 mo, $P < 0.001$). On multivariable analysis, Kim et al demonstrated a significant association between blood transfusion and decreased DSS (HR, 1.94; 95% CI, 1.23–3.07; $P = 0.004$),[17] whereas no significant difference was found by Yeh et al (HR, 1.7; 95% CI, 1.0–2.4; $P = 0.051$) (Table 3).[20]

Overall survival was shorter in the transfused group by five to seven months in three studies (Table 2).[16,18,19] Two studies detected a dose response on univariable analysis, which demonstrated shorter survival with >2U transfused compared with 1–2U.[18,19] On multivariable analysis, all three studies showed a significant association between blood transfusion and decreased OS (Table 3).[16,18,19] Of note, one study found a significant association between shorter OS and postoperative blood transfusion > 2U but did not reach significance when 1–2U were transfused (HR, 1.35; 95% CI, 0.99–1.85; $P = 0.056$).[19]

E-value Sensitivity Analysis

E-value sensitivity analyses were performed to assess the robustness of the association between blood transfusion during and after pancreatectomy for pancreatic cancer and RFS, DSS, and OS (Table 3). E-values assess the potential for unmeasured or uncontrolled confounders to overcome the results of observational study findings.[21] The “E-value” measure is defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association and is related to the evidence for causality in observational studies that are potentially subject to confounding.

Table 3 lists the studies, multivariable findings, and corresponding E-value sensitivity analyses for each survival outcome. Based on the sensitivity analysis, all multivariable findings that were significantly associated with blood transfusion, including those that were matched, could be easily be overcome by unmeasured confounding, as demonstrated by the overlap of the study-specific point estimates, calculated E-values, and their confidence intervals. All five studies were at-risk for having their findings negated by unmeasured confounding if those confounders could be identified.

Risk of Bias

The observational studies had a high risk of bias, as each study was confounded because of differences in the preoperative and operative characteristics between cohorts (see Supplemental Table 3, which shows the full risk of bias assessment). The quality of the two studies that matched those who received blood transfusions to the control cohort could not be assessed, because only unmatched data was reported.[16,19]

There was significant asymmetry of the funnel plot suggesting publication bias for the RFS outcome, but the interpretation of this plot was limited because there were so few studies (see Supplemental Figure 1, which illustrates the funnel plot for publication bias). One study did not report the RFS outcome and was not included in the I^2 analysis and the funnel plot.[20] The remaining four studies had substantial variation in their effect sizes and standard errors, resulting in an I^2 of 91.5% (Table 4).[16–19] There were two outliers in the funnel plot: Abe et al had the largest effect size and standard error of all studies and fell far outside the 95% CI contours[16]; Sutton et al, which reported multiple subgroups, also fell outside of the 95% CI contours of the plot based on the postoperative transfusion >2U subgroup.[19]

DISCUSSION

This systematic review evaluated the association between the administration of perioperative red blood cell transfusion compared with no transfusion on long-term survival outcomes in adults with PDAC who underwent pancreatectomy in five observational studies (n = 1646) (Table 5). There is very low certainty of evidence that RFS, DSS, and OS are reduced in patients who receive blood transfusions compared with those who do not. The certainty of evidence for these outcomes was downgraded because of the lack of prospective data, study limitations of the retrospective studies, imprecision, and potential for unmeasured confounding based on sensitivity analysis. The RFS and DSS outcomes were subject to inconsistency between the univariate and multivariable findings. In addition, significant heterogeneity and publication bias further downgraded the certainty of evidence, although the interpretation was limited due to the paucity of eligible studies. Although an association was found between blood transfusion and decreased survival, the small effect size and low quality of the studies suggest that the relationship between transfusion and survival remains uncertain.

A previous systematic review and meta-analysis included 23 studies concluding that blood transfusions reduced long-term survival in patients following pancreatic cancer surgery. [10] However, the review had many limitations. Multiple disparate disease processes, such as PDAC, ampullary carcinoma, and cholangiocarcinoma, were combined, as were different types of survival outcomes, such as OS and DSS, resulting in substantial heterogeneity between the combined studies, precluding the ability to interpret any meta-analysis. In our analysis, OS and DSS were considered separately, because they are inherently different measures of survival.[22] In our study, only articles describing the assessment of primary cancers of the pancreas were included to ensure a homogenous group of studies was evaluated that were comparable.

There were limitations of the articles summarized in the current systematic review. One major source of bias was substantial differences in baseline patient, tumor, and operative characteristics in these studies. The transfused cohorts were older, had more co-morbidities, lower preoperative hemoglobin levels, larger tumors, longer operative durations, and greater EBL, which are all important contributing factors for perioperative blood transfusion and may also be independently associated with poorer survival following pancreatectomy. The transfused cohorts in these studies were essentially a different population from the non-transfused group, and these studies are subject to both measured and unmeasured

confounding likely relating to patient factors such as frailty or tumor extent which, based on the E-value sensitivity analysis, could have their results negated if weak unmeasured confounders were identified.

While there were generally consistent multivariable findings that patients who receive perioperative blood transfusion appear to have worse short- and long-term outcomes, the current review could not establish whether receipt of blood transfusion is causally related to worsened cancer survival. Worsened survival in transfused patients could result because of the correlation of more operative blood loss with larger, more invasive tumors and a more compromised baseline status of the patients. A previous study found that that five-year survival rates increased in pancreatic cancer surgery patients over a 18-year study period as operative techniques improved and blood loss decreased, with worse survival associated with EBL >400 mL (HR, 2.17; 95% CI, 1.48–3.17; $P < 0.001$).[23] Given that all included studies had significantly increased EBL in the transfused cohorts, and EBL may be related to performing surgery on more complicated cancers, the worsened survival associated with blood transfusion may not be associated with blood transfusions themselves.

There are limitations of the current review. First, all eligible studies were retrospective, observational, and subject to measured and unmeasured confounding with no available prospective or randomized data. Second, while two studies performed propensity matching, neither reported their matched characteristics.[16,19] Third, pre-specified selection criteria to include only higher quality studies were employed. However, due to the paucity of included studies and their relatively small sample sizes, our conclusions are inherently imprecise, and measures of heterogeneity were difficult to interpret because of the small number of studies.

In summary, this systematic review of five observational studies found a weak association between perioperative blood transfusion in patients undergoing pancreatectomy for pancreatic cancer with worsened RFS, OS, and DSS. However, this association could easily be reversed if unmeasured confounders were identified that were related to the decision to transfuse and mortality outcomes. Prospective, randomized trials with consideration of baseline patient characteristics and operative complexity (eg, tumor size, EBL, vascular resection, resection margins) are needed to determine if blood transfusion is causally related to cancer mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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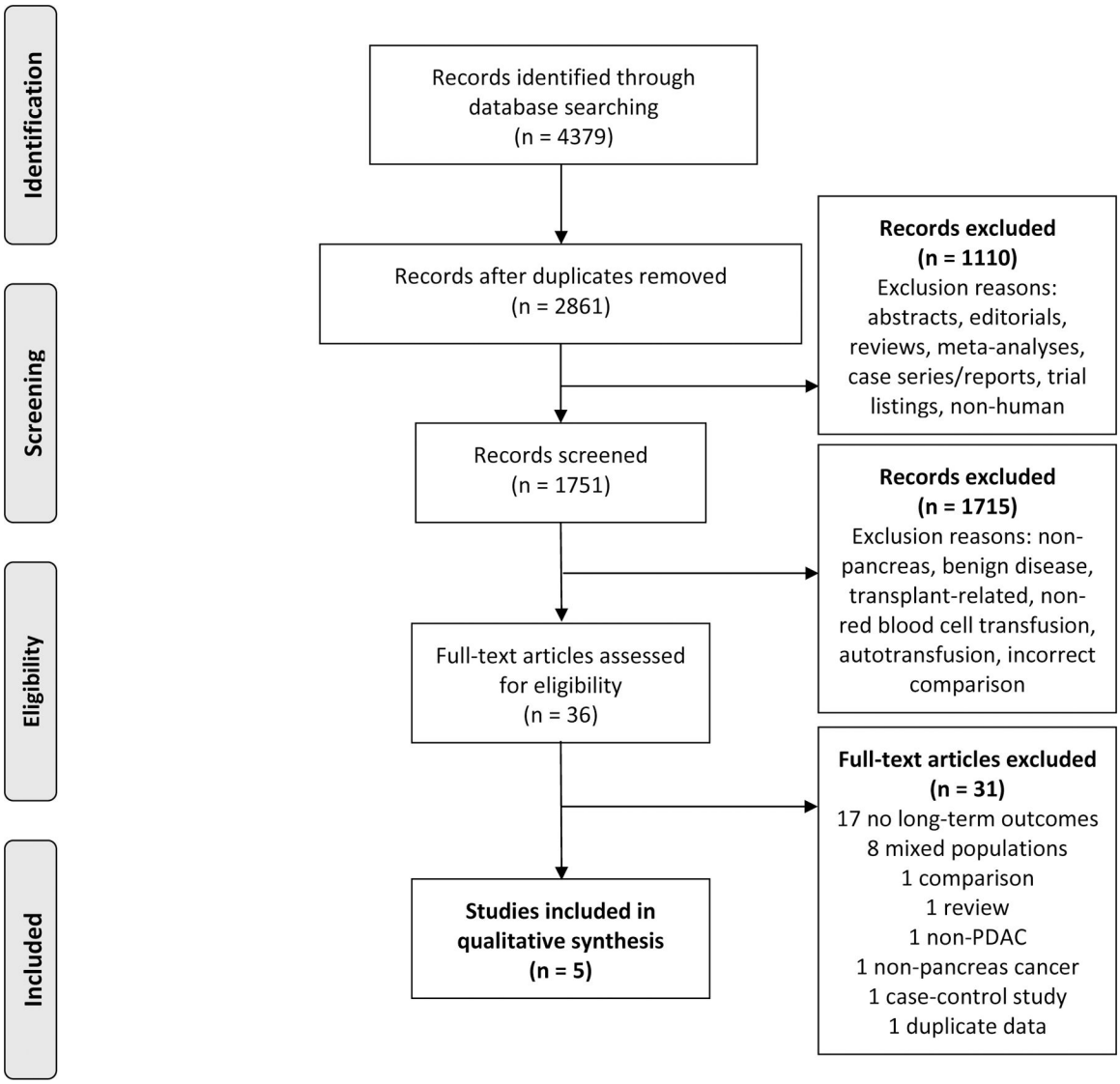

FIGURE 1.

Flow diagram. Flow diagram of study selection process based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards.

TABLE 1.

Study Comparison of Demographic, Tumor, and Surgical Characteristics

Study Characteristics		Patient Demographics											Tumor Characteristics								Surgical Characteristics					
		Sample size		Age, mean (SD) or (IQR), y			Comorbidities, %			Preoperative Labs, mean (SD) or (IQR)				Tumor Size, mean (SD) or (IQR), mm			Stage, %			Operative Time, mean (SD) or [(QR), min			Estimated Blood Loss, mean (SD) or [IQR], mL		
		Transfusion Status		Transfusion Status			Transfusion Status			Transfusion Status				Transfusion Status			Transfusion Status			Transfusion Status			Transfusion Status		
Source (Country)	Study Design (Database, if applicable) Patient selection, population	None	RBCT	None	RBCT	*P*	None	RBCT	*P*	None	RBCT	*P*	Histology	None	RBCT	*P*	None	RBCT	*P*	None	RBCT	*P*	None	RBCT	*P*
Studies that performed matching																										
Abe et al, 2017[16] * (Japan)	Retrospective consecutive patients, single institution	115	33	72 (39–86)	76 (53–85)	0.029	ASA 3–4: 8.7%	ASA 3–4: 17.6%	0.198	Hgb: 22.1 g/dL (16.7–33.5) CA 19–9: 65.4 U/mL (1.0–23848.0)	Hgb: 20.7 g/dL (16.3–32.9) CA 19–9: 372.1 U/mL (16.4–29042.4)	Hgb: <0.001 CA 19–9: <0.001	PDAC	25 (1–75)	35 (15–145)	<0.001	T ≥3: 42.6% N1: 63.5%	T ≥3: 75.8% N1: 72.7%	T: 0.001 N: 0.408	369 (129–727)	546 (195–826)	<0.001	489 (30–1711)	1305 (120–6588)	<0.001
Sutton et al, 2014[19] * (US)	Prospective database (Central Pancreas Consortium) Consecutive patients, 6 institutions	404	Pooled: 293	64.5 (10.7)	Pooled: 67.6	<0.001	CVD: 11.4% Tob: 50.3% DM: 9.8%	Pooled (CVD): 22.9% Pooled (Tob): 52.2% Pooled (DM): 34.1%	CVD: <0.001 † Tob: 0.08 † DM: 0.04 †	–	–	–	PDAC	28 (17)	Pooled: 30	0.028 †	N ≥1: 65.1%	Pooled (N ≥1): 62.8%	0.13 †	318.5 (123.7)	Pooled: 349.5	<0.001 †	468 (17)	Pooled: 955	<0.001 †
			1–2U: 161		1–2U: 67.9 (10.7)			1–2U (CVD): 24.2% 1–2U (Tob): 50.3% 1–2U (DM): 9.8%							1–2U: 29 (17)			1–2U (N ≥1): 67.7%			1–2U: 327.7 (121.5)			1–2U: 679 (43)	
			>2U: 132		>2U: 67.2 (10.3)			>2U (CVD): 21.2% >2U (Tob): 54.6% >2U (DM): 39.4%							>2U: 32 (16)			>2U (N ≥1): 56.8%			>2U: 376.2 (139.7)			>2U: 1291 (121)	
Studies that did not perform matching																										
Kim et al, 2020[17] (South Korea)	Retrospective consecutive patients, single institution	218	69	≥63: 56.0%	≥63: 62.3%	0.356	PMH: 73.4%	PMH: 75.4%	0.751	CA 19–9 ≥750: 18.3%	CA 19–9 ≥750: 29.0%	0.058	PDAC	–	–	–	T ≥3: 8.3% N ≥1: 50.5%	T ≥3: 10.1% N ≥1: 58.0%	T: 0.638 N: 0.285	≥400: 43.6%	≥400: 79.7%	0.064	≥650: 33.5%	≥650: 85.5%	<0.001

Study Characteristics		Patient Demographics											Tumor Characteristics										Surgical Characteristics					
		Sample size		Age, mean (SD) or (IQR), y			Comorbidities, %			Preoperative Labs, mean (SD) or (IQR)				Tumor Size, mean (SD) or (IQR), mm			Stage, %			Operative Time, mean (SD) or [(QR), min			Estimated Blood Loss, mean (SD) or [IQR], mL		
		Transfusion Status		Transfusion Status			Transfusion Status			Transfusion Status				Transfusion Status			Transfusion Status			Transfusion Status			Transfusion Status		
Source (Country)	Study Design (Database, if applicable) Patient selection, population	None	RBCT	None	RBCT	*P*	None	RBCT	*P*	None	RBCT	*P*	Histology	None	RBCT	*P*	None	RBCT	*P*	None	RBCT	*P*	None	RBCT	*P*
Kneuertz et al, 2011[18] (US)	Retrospective – single institution	73	147	62.9	64.9	0.19	CCS ≥1: 28%	CCS ≥1: 49%	0.004	Hgb: 12.8 Alb: 3.2 Tbili: 5.4 INR: 1.03	Hgb: 11.8 Alb: 2.9 Tbili: 8.4 INR: 1.07	Hgb: <0.001 Alb: 0.007 Tbili: 0.003 INR: 0.021	PDAC	31	33	0.23	N ≥1: 66%	N ≥1: 61%	0.56	239	342	<0.001	275	718	<0.001
Yeh et al, 2007[20] (US)	Prospective database consecutive patients, single institution	154	140	≥60: 66.9%	≥60: 87.1%	<0.001	CVD: 9.7%	CVD: 15.7%	0.159	Hgb>12: 63.4% Alb ≥4: 57.8% Tbili >2: 37.0%	Hgb>12: 48.6% Alb≥4: 36.4% Tbili>2: 56.4%	Hgb: <0.001 Alb: <0.001 Tbili: 0.015	Exocrine tumor of pancreas	–	–	–	T3: 89.6% N1: 66.2%	T3: 87.8% N1: 64.3%	T: 0.791 N: 0.456	–	–	–	>700: 32.5%	>700: 68.6%	<0.001

*Only unmatched descriptive data is shown, as matched descriptive data was not reported.

†*P* values for subgroup comparisons only, as pooled values are back-calculated.

Alb, albumin; ASA, American Society of Anesthesiologists; CA 19–9, carbohydrate antigen 19–9; CCS, Charlson comorbidity score; CVD, cardiovascular disease; DM, diabetes mellitus; Hgb, hemoglobin; INR, international normalized ratio; IQR, interquartile range; PDAC, pancreatic ductal adenocarcinoma; PMH, past medical history; RBCT, red blood cell transfusion; SD, standard deviation; Tbili, total bilirubin; Tob, tobacco; U, unit(s).

TABLE 2.

Long-Term Postoperative Survival Outcomes

	RFS, median, mo			DSS, median, mo			OS, median, mo		
	Transfusion Status			Transfusion Status			Transfusion Status		
Source	**None**	**RBCT**	***P***	**None**	**RBCT**	***P***	**None**	**RBCT**	***P***
Studies that performed propensity matching									
Abe et al, 2017[16]	–	–	–	–	–	–	3-yr: 45.7% 5-yr: 28.1%	3-yr: 4.5% 5-yr: 0%	_*
Sutton et al, 2014[19]†	18.3 mo	Pooled†: 13.8 mo	None vs 1–2U: ns	–	–	–	21.0 mo	Pooled‡: 14.0 mo	None vs 1–2U: 0.003
		1–2U: 17.8 mo	1–2U vs >2U: 0.014		–			1–2U: 16.0 mo	1–2U vs >2U: 0.003
		> 2U: 10.2 mo	None vs >2U: <0.001		–			>2U: 11.1 mo	None vs >2U: <0.0001
Studies that did not perform propensity matching									
Kim et al, 2020[17]	12 mo (95% CI, 10–15)	11 mo (95% CI 8–13)	0.031	33 mo (95% CI, 2–38)	20 mo (95% CI, 18–22)	0.01	–	–	–
Kneuertz et al, 2011[18]	15 mo	Pooled: 10 mo 1–2U: 14 mo >2U: 9 mo	0.033	–	–	–	20 mo	Pooled: 15 mo 1–2U: 16 mo >2U: 14 mo	0.003
Yeh et al, 2007[20]	–	–	–	Any: 24 mo Intraop: 24 mo Postop: 26 mo	Any: 19 mo Intraop: 23 mo Postop: 17 mo	Any: 0.036 Intraop: 0.655 Postop: <0.001	–	–	–

*Outcome is significant when risk differences are calculated

†Matched only for the disease–free survival outcome; overall survival outcome is not matched

‡Pooled outcomes back–calculated from data from subgroups

CI indicates confidence internval; Intraop, intraoperative; ns, not significant; Postop, postoperative; RBCT = red blood cell transfusion; U, unit(s).

TABLE 3.

Multivariable Findings and E–Value Sensitivity Analysis

			Multivariable Findings				E–Value Sensitivity Analysis	
Source	**Outcome**	**Study–Specific Cumulative Outcome Incidence***	**Outcome Type**	**Point Estimate**	**95% CI**	***P***	**Point Estimate**	**CI**
Studies that performed matching								
Abe et al, 2017[16]	RFS	>15%	HR	4.31	2.57–7.22	<0.001	4.82	1.59–8.05
	OS	>15%	HR	8.55	4.87–15.02	<0.001	7.69	2.43–12.95
Sutton et al, 2014[19]†	RFS (IOT 1–2U)	<15%	HR	0.7	0.46–1.05	0.081	2.21	1.21–3.21
	RFS (IOT >2U)	<15%	HR	1.92	1.18–3.13	0.009	3.25	1.61–4.89
	RFS (POT 1–2U)	<15%	HR	1.55	1.05–2.28	0.026	2.47	1.19–3.75
	RFS (POT >2U)	<15%	HR	2.06	1.31–3.26	0.002	3.54	1.59–5.49
	OS (POT 1–2U)	<15%	HR	1.35	0.99–1.85	0.056	2.04	1.04–3.04
	OS (POT >2U)	<15%	HR	2.14	1.41–3.23	<0.001	3.7	1.53–5.87
Studies that did not perform matching								
Kim et al, 2020[17]	Recurrence	>15%	HR	1.47	0.99–2.20	0.056	1.94	0.94–2.94
	DSS	>15%	HR	1.94	1.23–3.07	0.004	2.54	0.96–4.12
Kneuertz et al, 2011[18]	RFS	<15%	HR	1.1	1.02–1.18	0.01	1.43	0.27–2.59
	OS	<15%	HR	1.08	1.03–1.12	0.001	1.37	0.16–2.58
Yeh et al, 2007[20]	DSS	>15%	HR	1.7	1.0–2.4	0.051	2.24	1.24–3.24

CI indicates confidence interval; DSS, disease–specific survival; HR, hazard ratio; IOT, intraoperative transfusion; OS, overall survival; POT, postoperative transfusion; RFS, recurrence–free survival; U, unit(s).

*Cumulative outcome incidence extracted from rates reported up to study end–point in each study's population

†Matched only for the disease–free survival outcome, which was analyzed by the log–rank test and not amenable to e–value analysis; outcomes reported in this table are not matched.

TABLE 4.

Summary and Heterogeneity of Studies Reporting Recurrence–Free Survival Outcome

Source	Effect Size (lnHR) (95% CI)	Weight, %	τ^2	I^2, %	H^2
Outcome: Recurrence–free survival			0.2991	91.53	11.81
Abe et al, 2017[16]	1.461 (0.99–1.977)	22.98			
Kim et al, 2020[17]	0.385 (−0.014 to 0.785)	24.86			
Kneuertz et al, 2011[18]	0.095 (0.022–0.168)	28.18			
Sutton et al, 2014 (POT>2U)[19]	0.723 (0.267–1.179)	23.98			
theta	0.632 (0.061–1.202)				

Ln indicates natural log; HR, hazard ratio; CI, confidence interval; POT, post–operative transfusion; U, units.

TABLE 5.

GRADE Summary of Findings and Certainty of Evidence

Outcomes	Study Limitations	Consistency	Directness	Precision	Certainty of Evidence	Comments
Recurrence–free survival RBCT <no transfusion	Observational: serious	Inconsistent	Direct	Imprecise	Very low	All observational studies had serious risk of bias, thus findings were downgraded to very low for study limitations. Findings were rated up for consistency and rated down for imprecision.
Disease–specific survival RBCT <no transfusion	Observational: serious	Inconsistent	Direct	Imprecise	Very low	
Overall survival RBCT <no transfusion	Observational: serious	Consistent	Direct	Imprecise	Very low	

Perioperative packed red blood cell transfusion compared to no transfusion following pancreatic cancer surgery

Population: adults with pancreatic ductal adenocarcinoma who underwent pancreatectomy.

Setting: inpatient

Intervention: red blood cell transfusion

Comparison: no transfusion

RBCT indicates red blood cell transfusion