

The impact of perioperative allogeneic blood transfusion on prognosis of hepatocellular carcinoma after radical hepatectomy

A systematic review and meta-analysis of cohort studies

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Abstract

This meta-analysis aims to clarify the clinical impacts of allogeneic blood transfusion (ABT) on hepatectomy outcome in hepatocellular carcinoma (HCC) patients. A systematic literature search was performed for relevant articles in international and Chinese databases up to May 2018. Random- or fixed-effect meta-analysis was used to pool the effect estimates. Publication bias was assessed by Egger's and Peters's test. Heterogeneity was assessed using the l^2 statistic. The strength of evidence was rated by the Grading of Recommendations Assessment, Development, and Evaluation system. A total of 29 studies met the eligibility criteria. Meta-analysis showed HCC patients in ABT group had lower survival rate at 1, 3, 5, and 10 years after radical hepatectomy than those in no blood transfusion (NBT) group (RR = 0.9, 95%CI: 0.87–0.93, P < .05; RR = 0.83, 95%CI: 0.77–0.89, P < .05; RR = 0.7, 95%CI: 0.65–0.74, P < .05; RR = 0.64, 95%CI: 0.54–0.75, P < .05). Similar results were observed in disease-free survival (DFS) (respectively: RR = 0.86, 95%CI: 0.82–0.91, P < .05; RR = 0.77, 95%CI: 0.67–0.79, P < .05; RR = 0.71, 95%CI: 0.64–0.79, P < .05; RR = 0.72, 95%CI: 1–2.24, P < .05; RR = 1.27, 95%CI: 1.09–1.49, P < .05, respectively), but not statistically significant at 5years (RR = 1.08, 95%CI: 0.98–1.19, P = .512). The HCC patients in ABT group increased postoperative complications occurrence compared with those in NBT group (RR = 1.87, 95%CI: 1.42–2.45, P < .05). This meta-analysis demonstrated that ABT was associated with adverse clinical outcomes for HCC patients undergoing radical hepatectomy, including poor survival, DFS, and complications. Surgeons should reduce blood loss during hepatectomy and avoid perioperative allogenic blood transfusion.

Abbreviations: ABT = allogeneic blood transfusion, DFS = disease-free survival, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, HCC = hepatocellular carcinoma, NBT = no blood transfusion, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis, RR = Relative risk.

Keywords: allogeneic blood transfusion, hepatocellular carcinoma, meta-analysis, prognosis

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the fifth most common cause of cancer-related death worldwide.^[1] Liver transplantation is an alternative treatment for the early stage HCC patients with chronic liver dysfunction, while hepatectomy is still the primary treatment option for HCC patients due to the limited number of available donors.^[2] Improving understanding of the best surgical and perioperative management continues to decrease the perioperative morbidity and mortality of hepatectomy for HCC patients. Especially improved surgical techniques have decreased bleeding during hepatectomy and the transfusion rate has decreased from 62% to 22% over the past 2 decades;^[3,4] Nevertheless, blood transfusion remains necessary when excessive intraoperative bleeding occurs.

Meanwhile, transfusion could cause knownside effects, such as infectious disease, hemolytic transfusion reaction, hepatic ischemia-reperfusion injury, and transfusion-related acute lung injury. Some studies demonstrated that perioperative blood transfusion not only caused such problems, but it could affect long-term survival of HCC patients after radical hepatectomy.^[5] But others reported no significant association between perioperative blood transfusion and prognosis of HCC after radical hepatectomy.^[6] Therefore, the impact of allogeneic blood transfusion (ABT) on postoperative outcomes are still controversial.

In order to clarify the inconsistent issue, a meta-analysis is necessary to be performed. Our study aims to inspect the correlation between ABT and survival rate, disease-free survival (DFS), cancer recurrence, and complications of HCC patients undergoing radical hepatectomy.

2. Material and methods

2.1. Search strategy for eligible studies

We conducted this meta-analysis with adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.^[7] A systematic literature search was conducted in PubMed, Web of Science, Embase, and CBM for relevant articles up to May 2018, using various combinations of the keywords:

hepatocellular carcinoma, HCC, liver cancer, and blood transfusion. References cited in the relevant articles were investigated for any potential and eligible studies.

2.2. Eligibility criteria

Eligibility criteria for all included studies were as follows: evaluation of the correlation between ABT and clinical prognosis (survival rate, DFS, cancer recurrence, and postoperative complications) of HCC patients undergoing radical hepatectomy; it must be clinical studies, and the original data could be obtained; studies focused on autogenic blood transfusion or non-primary HCC were excluded.

2.3. Data extraction and quality assessment

In this meta-analysis, all patients were divided into ABT group and NBT group. ABT was defined as perioperative transfusion of allogeneic blood products, while NBT was defined as patients who did not receive any transfusion. Two authors independently extracted participants' information including first author's name, publication year, patients' age and sex, number of patients included in ABT and NBT group, cancer differentiation, survival rate, DFS, cancer recurrence, and postoperative complications. Discrepancies were resolved through discussion.

The methodological quality of the included studies was assessed independently by 2 authors using the Newcastle–Ottawa scale,^[8] which allocates a maximum of 9 stars each to case selection, comparability of cohorts (ABT and NBT), and outcomes assessment. A study awarded 6 or more stars was considered as a high-quality study. In addition, the strength of evidence was rated by the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE system).^[9]

2.4. Statistical analysis

Statistical analysis was performed using statistical software R (version 3.2.3). For studies that did not show the corresponding

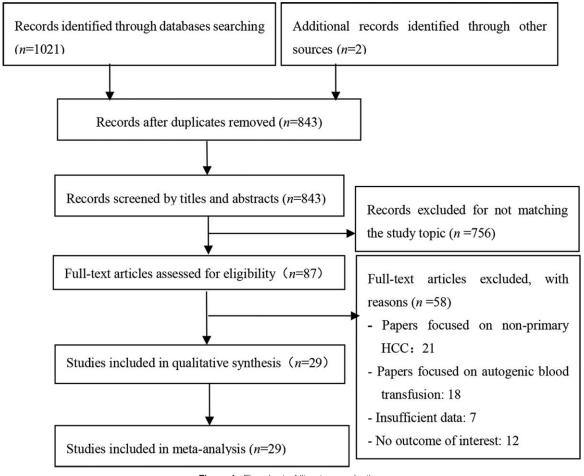


Figure 1. Flowchart of literatures selection.

results, the Engauge Digitizer was applied to extract survival data from the Kaplan-Meier curves (http://sourceforge.net). The relative risk (RR) of survival rate, DFS, cancer recurrence rate, and postoperative complications were considered 4 main outcomes in our study. For each outcome, RR was calculated and reported with 95% confidence interval (CI). In this meta-analysis, χ^2 , and I^2 statistics were used to test possible heterogeneity among studies. If the heterogeneity of any outcome was >50% or P < .05, the random-effect model was used to calculate summary estimate; if not, the fixed-effect model was applied. Meanwhile, the potential impact of transfusion amount and rates, age, cancer size, and participants on the outcomes were assessed by stratified analysis. Besides, sensitivity analysis was conducted to test whether the results of the meta-analysis were sensitive to restrictions on any of the included studies. Egger's and Peters's tests were applied to assess publication bias.

3. Results

3.1. Literature search and study characteristics

The selection of studies for inclusion in the meta-analysis was shown in flow diagram (Fig. 1). Of the initial 1021 citations retrieved, 29 studies met our inclusion criteria and were included in the final meta-analysis.^[5,6,10–36] 5 studies^[12,28–30,35] were prospective cohort studies and 24 studies^[5,6,10,11,13–27,31–34,36] were retrospective cohort studies. Detailed study characteristics were shown in Table 1. Of the 29 studies with a total of 7241

participants, 2908 cases (40.2%) received ABT and 4333 cases (59.8%) were grouped as NBT. Outcomes reported in each study including survival rate (n=19), DFS (n=19), cancer recurrence (n=3), and postoperative complications (n=10). According to the Newcastle–Ottawa scale, all included studies were of high quality. Characteristics of the included studies and quality scores were listed in Table 1.

3.2. Survival rate

In this meta-analysis, there were ten studies providing 1-year survival rate, $^{[5,6,10-13,17,29,33,36]}$ 13 studies providing 3-year survival rate, $^{[5,6,10-13,17,22,24,29,30,33,36]}$ 19 studies providing 5-year survival rate, $^{[5,6,10-15,17-19,22,24,25,29,30,32,33,36]}$ and 6 studies providing 10-year survival rate. $^{[5,6,11,12,15,24]}$ As displayed in (Fig. 2A–D), meta-analyses demonstrated that there was a lower 1-, 3-, 5-, and 10-year survival rate for patients with ABT than those with NBT (respectively: RR=0.9, 95%CI: 0.87–0.93, P < .001; RR=0.83, 95%CI: 0.77–0.89, P < .0001; RR=0.7, 95%CI: 0.65–0.74, P < .001; RR=0.64, 95%CI: 0.54–0.75, P < .001). The heterogeneity of 1-, 5-, and 10-year survival rate was >50%, the random-effect model was used to calculate summary estimate; the heterogeneity of 3-year DFS was < 50%, the fixed-effect model was applied.

Results of the stratified meta-analyses for postoperative 5-year survival rate were shown in Table 2. When stratified by transfusion amount, we found that the impact of transfusion amount on 5-year survival rate was significant (subgroup

Table 1

Characteristics of studies included in the meta-analysis.

			Partic	ipants	Sex	(M/F)	Age (mean)	Liver c	irrhosis	Child	i A/B	Cance	r size, cm	TNM s	tage $+$	Differe	ntiation#	
Author	Country	Design	ABT	NBT	ABT	NBT	ABT	NBT	ABT	NBT	ABT	NBT	ABT	NBT	ABT	NBT	ABT	NBT	Study quality
Wada, 2017 ^[5]	Japan	RCS	198	444	156/42	353/91	66.2	65	49.5%	39.0%	175/23	411/33	5.9	3.6	_	_	143/40	302/111	9
Yang, 2016 ^[10]	China	RCS	234	234	202/32	204/30	49.7	50.1	73.5%	76.5%	200/34	200/34	_	_	_	_	33/201	26/208	7
Xu, 2016 ^[11]	China	RCS	68	154		_	5	1.8		_	21	6/6	_	_	_	_	-		8
Harada, 2015 ^[12]	Japan	PCS	91	388	58/33	261/127	64.4	68	79.1%	55.7%	91/0	388/0	4.1	3	_	_	16/75	51/337	8
Ye, 2013 ^[13]	China	RCS	93	37	69/24	33/4	47.1	50.7	-	_	90/3	36/1	_	_	36/57	18/19	-		6
Kuroda, 2012 ^[6]	Japan	RCS	60	60	50/10	48/12	59.4	60.7	50.0%	58.3%	43/17	46/14	6.2	6.1	_	_	1/59	3/57	9
Okamura, 2011 ^[14]	Japan	RCS	87	289	30	3/73	6	1.4	-	_	354	1/22		3.4	—	—	-		7
Nanashima, 2011 ^[15]	Japan	RCS	100	83	14	8/35	6	65	-	_	-	_	_	_	_	_	-		7
Yang, 2011 ^[16]	China	RCS	164	141	27	9/26	49	49.2	76.7%	76.7%	270)/35		10.3	—	—	-		7
Chen, 2010 ^[17]	China	RCS	87	79	74/13	65/14	47.5	47.4	77.1%	77.1%	-	_	9.6	8.9	59/17	56/17	-		7
Abdel—Wahab, 2010 ^[18]	Egypt	RCS	87	72	11	9/40	5	55	-	_	138	3/21	—	_	—	_	-		7
Choi, 2009 ^[19]	Korea	RCS	94	96	14	3/47	5	51	56.7%	56.7%	-	_	_	_	_	_	-		6
Wang, 2009 ^[20]	China	RCS	62	411	37	9/94	53	3.1	44.4%	44.4%	394	1/79		5.5	_	_	-		8
Sugita, 2008 ^[21]	Japan	RCS	101	123	80/21	92/31	61.7	64.4	62.4%	48.0%	-	_	5.9	4	_	_	13/88*	27/96*	9
Kaibori, 2008 ^[22]	Japan	RCS	269	141	210/59	117/24	64	64.7	41.3%	36.2%	-	_	4.5	2	162/107	102/39	251/18	135/6	9
Sasaki, 2006 ^[23]	Japan	RCS	184	233	309	/108	-	_	67.9%	67.9%	309	/108	_	_	_	_	-		8
Hanazaki, 2005 ^[24]	Japan	RCS	210	158	156/54	122/36	62	63	62.3%	36.1%	146/64	142/16	5.1	3.5	154/56	146/12	-		9
Laurent, 2005 ^[25]	France	RCS	36	72	89	/19	6	64	63.0%	63.0%	-	_		9.3	_	_	-		6
Wei, 2003 ^[26]	China	RCS	45	110	12	2/33	5	52	34.9%	34.9%	-	_		11	_	_	-	_	6
Ercolani, 2003 ^[27]	Italy	RCS	71	153	18	2/42	62	2.5	78.6%	78.6%	185	5/39	_	_	_	_	-	_	6
Sasaki, 2002 ^[28]	Japan	PCS	23	52	59	/16	6	1.7	-	_	46	/29	_	_	_	_	-	_	7
Kwon, 2001 ^[29]	Japan	PCS	53	55	41/12	42/13	62.1	61.6	50.9%	45.5%	40/13	46/9	3.7	3.3	43/10	43/12	51/2	52/3	9
Kitagawa, 2001 ^[30]	Japan	PCS	23	52	-	_	60.2	60.9	55.5%	55.5%	-	_	_	_	_	_	-	_	7
Makino, 2000 ^[31]	Japan	RCS	117	78	85/32	71/7	60.8	60.7	77.8%	61.5%	74/30	58/17	5	3.5	—	—	-		9
Asahara, 1999 ^[32]	Japan	RCS	23	152	19/4	114/38	60	D.1	78.3%	69.1%	-	_	_	—	—	—	2/18*	10/122*	8
Wu, 1999 ^[33]	China	RCS	151	60	131/20	48/12	53	53.5	-	_	-	_	—	—	_	—	-		7
Yamamoto, 1996 ^[34]	Japan	RCS	85	301	31	1/75	59	9.7	59.3%	59.3%	265	/121	—	—	_	—	-		6
ltasaka, 1995 ^[35]	Japan	PCS	38	33	33/5	28/5	58.2	57.9	94.7%	84.8%	34/4	33/0	—	—	_	—	-		9
Matsumata, 1993 ^[36]	Japan	RCS	54	72	43/11	62/10	58.4	57.1	62.3%	52.1%	-	_	4.1	3.4	—	—	-	_	9

ABT = allogeneic blood transfusion, NBT = no blood transfusion, PCS = prospective cohort study, RCS = retrospective cohort study.

⁺ I+II/III+IV.

Cancer differentiation (well + moderate/poor)

* well/moderate + poor.

Study	AB Events Tota	T NBT I Events Total	Risk Ratio	RR	95%-CI	Weight
	150 10					15 101
Wada H 2017	159 19			0.84		15.1%
Yang T 2016	175 23		100		[0.85; 1.04]	11.9%
Xu LN 2016	45 6				[0.68; 0.99]	5.5%
Harada N 2015	83 9 71 9			0.96		15.6%
Ye XR 2013					[0.73; 1.00]	6.9%
Kuroda S 2012	43 6			0.98		4.3%
Chen ZY 2010	62 8 50 5		100		[0.79; 1.15]	5.6%
Kwon AH 2001 Wu Y 1999	106 15				[0.90; 1.06]	13.6% 7.9%
Matsumata T 1993	50 5		100	0.81		
Malsunala 1 1993	50 5	+ 10 12		0.95	[0.87; 1.04]	13.5%
Random effects mode	el 108	9 1583	<u> </u>	0.04	[0.87; 0.96]	100 09/
Heterogeneity: $I^2 = 52\%$,				0.91	[0.87, 0.90]	100.0 %
	$\tau = 0.0031, p =$	0.03	0.8 1 1.25			
A			0.0 1 1.25			
	ABT	NBT				
Study E	vents Total E	vents Total	Risk Ratio	RR	95%-CI	Weight
10000000- - 11						-
Wada H 2017	126 198	369 444		0.77	[0.68; 0.86]	21.1%
Yang T 2016	98 234	111 234			[0.72; 1.08]	10.3%
Xu LN 2016	33 68	93 154			[0.61; 1.06]	5.3%
Harada N 2015	65 91	329 388			[0.73; 0.97]	11.6%
Ye XR 2013	27 93	14 37			[0.46; 1.29]	1.9%
Kuroda S 2012	30 60	28 60			[0.74; 1.55]	2.6%
Chen ZY 2010	18 87	36 79			[0.28; 0.73]	3.5%
Kaibori M 2008	188 269	114 141			[0.77; 0.97]	13.9%
Hanazaki K 2005	124 210	123 158			[0.66; 0.87]	13.0%
Kwon AH 2001	38 53	46 55	<u>_</u>		[0.70; 1.05]	4.2%
Kitagawa K 2001	10 23	41 52			[0.34; 0.90]	2.3%
Wu Y 1999	103 151	42 60			[0.80; 1.19]	5.6%
Matsumata T 1993	40 54	58 72	1-1		[0.76; 1.12]	4.6%
Watsumata 1 1995	40 54	50 12		0.92	[0.70, 1.12]	4.070
Fixed effect model	1591	1934	\$	0.82	[0.77; 0.86]	100 0%
Heterogeneity: $I^2 = 38\%$	$r^{2} = 0.0055$ n	- 0.09		0.02	[0.77, 0.80]	100.078
A STATE OF COMPANY AND A STATE OF COMPANY	, t = 0.0000, p	- 0.08	0.5 1 2			
В			0.0 1 2			
	ΔB					
Study	AB Events Tot		Risk Ratio	RR	95%-CI	Weight
Study		T NBT Il Events Total	Risk Ratio	RR	95%-CI	Weight
	Events Tota	l Events Total	Risk Ratio			000000
Wada H 2017	Events Tota 97 19	B 305 444	Risk Ratio	0.71	[0.61; 0.83]	9.2%
Wada H 2017 Yang T 2016	Events Tota 97 19 55 23	I Events Total 8 305 444 4 67 234	Risk Ratio	0.71 0.82	[0.61; 0.83] [0.60; 1.12]	9.2% 6.1%
Wada H 2017	Events Tota 97 19	I Events Total 8 305 444 4 67 234 8 77 154	Risk Ratio	0.71 0.82	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01]	9.2%
Wada H 2017 Yang T 2016 Xu LN 2016	Events Tota 97 19 55 23 24 6	Events Total 8 305 444 4 67 234 8 77 154 1 287 388	Risk Ratio	0.71 0.82 0.71 0.74	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01]	9.2% 6.1% 5.2%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015	Events Tot 97 19 55 23 24 6 50 9	Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37	Risk Ratio	0.71 0.82 0.71 0.74 0.62	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01] [0.61; 0.90]	9.2% 6.1% 5.2% 8.4%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013	Events Tota 97 19 55 23 24 6 50 9 14 9	Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60	Risk Ratio	0.71 0.82 0.71 0.74 0.62	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01] [0.61; 0.90] [0.29; 1.30] [0.46; 1.49]	9.2% 6.1% 5.2% 8.4% 1.9%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01] [0.61; 0.90] [0.29; 1.30] [0.46; 1.49]	9.2% 6.1% 5.2% 8.4% 1.9% 2.8%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01] [0.61; 0.90] [0.29; 1.30] [0.46; 1.49] [0.55; 0.92] [0.49; 0.85]	9.2% 6.1% 5.2% 8.4% 1.9% 2.8% 6.9%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65	$\begin{array}{l} [0.61;0.83]\\ [0.60;1.12]\\ [0.49;1.01]\\ [0.61;0.90]\\ [0.29;1.30]\\ [0.46;1.49]\\ [0.55;0.92]\\ [0.49;0.85]\\ [0.15;0.51]\\ [0.04;0.29] \end{array}$	9.2% 6.1% 5.2% 8.4% 1.9% 2.8% 6.9% 6.7%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 3 31 72 4 76 96	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.11 0.81	$\begin{array}{l} [0.61; 0.83] \\ [0.60; 1.12] \\ [0.49; 1.01] \\ [0.61; 0.90] \\ [0.29; 1.30] \\ [0.46; 1.49] \\ [0.55; 0.92] \\ [0.46; 0.82] \\ [0.15; 0.51] \\ [0.04; 0.29] \\ [0.67; 0.97] \end{array}$	9.2% 6.1% 5.2% 8.4% 1.9% 2.8% 6.9% 6.7% 2.6% 1.1% 8.6%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9 144 26	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.11 0.81 0.78	$\begin{array}{l} [0.61; 0.83] \\ [0.60; 1.12] \\ [0.49; 1.01] \\ [0.61; 0.90] \\ [0.29; 1.30] \\ [0.46; 1.49] \\ [0.55; 0.92] \\ [0.49; 0.85] \\ [0.15; 0.51] \\ [0.67; 0.97] \\ [0.66; 0.91] \end{array}$	9.2% 6.1% 5.2% 8.4% 1.9% 2.8% 6.9% 6.7% 2.6% 1.1% 8.6% 9.2%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 60 9 144 26 88 21	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158	Risk Ratio	0.71 0.82 0.71 0.62 0.83 0.71 0.65 0.25 0.11 0.81 0.78 0.70	$\begin{matrix} [0.61; 0.83]\\ [0.60; 1.12]\\ [0.49; 1.01]\\ [0.61; 0.90]\\ [0.29; 1.30]\\ [0.55; 0.92]\\ [0.55; 0.92]\\ [0.49; 0.85]\\ [0.15; 0.51]\\ [0.44; 0.29]\\ [0.67; 0.97]\\ [0.66; 0.91]\\ [0.57; 0.85] \end{matrix}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.7% 2.6% 1.1% 8.6% 9.2% 8.2%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 60 9 144 26 88 21 6 3	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 36 79 9 97 31 9 97 141 0 95 158 6 40 72	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.18 0.11 0.81 0.78 0.70 0.30	$\begin{matrix} [0.61; 0.83]\\ [0.60; 1.12]\\ [0.49; 1.01]\\ [0.61; 0.90]\\ [0.29; 1.30]\\ [0.46; 1.49]\\ [0.55; 0.92]\\ [0.49; 0.85]\\ [0.15; 0.51]\\ [0.04; 0.29]\\ [0.67; 0.97]\\ [0.66; 0.91]\\ [0.57; 0.85]\\ [0.14; 0.64] \end{matrix}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.7% 2.6% 1.1% 8.6% 9.2% 8.2% 1.8%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9 144 26 88 21 6 3 28 5	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 9 97 141 0 95 158 6 40 72 3 33 55	Risk Ratio	0.71 0.82 0.71 0.74 0.65 0.83 0.71 0.65 0.28 0.11 0.81 0.70 0.30 0.88	$\begin{matrix} [0.61; 0.83]\\ [0.60; 1.12]\\ [0.49; 1.01]\\ [0.61; 0.90]\\ [0.29; 1.30]\\ [0.46; 1.49]\\ [0.55; 0.92]\\ [0.49; 0.85]\\ [0.15; 0.51]\\ [0.64; 0.29]\\ [0.67; 0.87]\\ [0.66; 0.91]\\ [0.57; 0.85]\\ [0.14; 0.64]\\ [0.63; 1.23] \end{matrix}$	9.2% 6.1% 5.2% 8.4% 1.9% 2.8% 6.9% 6.7% 2.6% 2.6% 1.1% 8.6% 9.2% 8.2% 1.8% 5.6%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9 144 26 88 21 6 3 28 5 6 2	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 6 40 72 3 33 55 3 28 52	Risk Ratio	0.71 0.82 0.71 0.74 0.83 0.71 0.65 0.28 0.11 0.81 0.70 0.30 0.30 0.88 0.48	$\begin{matrix} [0.61; 0.83]\\ [0.60; 1.12]\\ [0.49; 1.01]\\ [0.29; 1.30]\\ [0.29; 1.30]\\ [0.46; 1.49]\\ [0.55; 0.92]\\ [0.47; 0.87]\\ [0.46; 0.51]\\ [0.04; 0.29]\\ [0.67; 0.85]\\ [0.14; 0.64]\\ [0.63; 1.23]\\ [0.23; 1.01] \end{matrix}$	9.2% 6.1% 5.2% 8.4% 1.9% 2.8% 6.9% 6.9% 8.6% 9.2% 8.8% 9.2% 8.2% 1.8% 5.6% 1.9%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 60 9 144 26 88 21 6 3 28 5 26 2	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 6 40 72 3 33 55 3 28 52 3 69 152	Risk Ratio	0.71 0.82 0.71 0.62 0.83 0.71 0.65 0.28 0.11 0.81 0.78 0.30 0.30 0.30 0.48 0.48	$\begin{matrix} [0.61; 0.83]\\ [0.60; 1.12]\\ [0.49; 1.01]\\ [0.61; 0.90]\\ [0.29; 1.30]\\ [0.46; 1.49]\\ [0.55; 0.92]\\ [0.47; 0.55]\\ [0.15; 0.51]\\ [0.47; 0.29]\\ [0.67; 0.97]\\ [0.66; 0.91]\\ [0.57; 0.85]\\ [0.14; 0.64]\\ [0.63; 1.23]\\ [0.23; 1.01]\\ [0.28; 1.17] \end{matrix}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 6.9% 2.6% 1.1% 8.6% 9.2% 1.8% 5.6% 1.9% 2.0%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999	Events Tota 97 19 55 23 24 6 50 9 15 6 37 8 43 10 11 8 4 88 28 55 6 2 6 2 6 2 48 15	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 3 33 55 3 33 55 3 28 52 3 69 152 3 69 152 3 69 152 3 29 60	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.11 0.81 0.70 0.30 0.88 0.48 0.70 0.30	$\begin{matrix} [0.61; 0.83]\\ [0.60; 1.12]\\ [0.49; 1.01]\\ [0.61; 0.90]\\ [0.29; 1.30]\\ [0.46; 1.49]\\ [0.55; 0.92]\\ [0.49; 0.85]\\ [0.15; 0.51]\\ [0.67; 0.97]\\ [0.66; 0.91]\\ [0.57; 0.85]\\ [0.14; 0.64]\\ [0.63; 1.23]\\ [0.23; 1.01]\\ [0.28; 1.17]\\ [0.46; 0.93] \end{matrix}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 6.7% 2.6% 1.1% 8.6% 9.2% 8.2% 8.2% 5.6% 1.9% 5.6% 2.0% 5.3%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 60 9 144 26 88 21 6 3 28 5 26 2	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 3 33 55 3 33 55 3 28 52 3 69 152 3 69 152 3 69 152 3 29 60	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.11 0.81 0.70 0.30 0.88 0.48 0.70 0.30	$\begin{matrix} [0.61; 0.83]\\ [0.60; 1.12]\\ [0.49; 1.01]\\ [0.61; 0.90]\\ [0.29; 1.30]\\ [0.46; 1.49]\\ [0.55; 0.92]\\ [0.47; 0.55]\\ [0.15; 0.51]\\ [0.47; 0.29]\\ [0.67; 0.97]\\ [0.66; 0.91]\\ [0.57; 0.85]\\ [0.14; 0.64]\\ [0.63; 1.23]\\ [0.23; 1.01]\\ [0.28; 1.17] \end{matrix}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 6.9% 2.6% 1.1% 8.6% 9.2% 1.8% 5.6% 1.9% 2.0%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999 Matsumata T 1993	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 60 9 144 26 68 21 6 3 28 5 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 48 15 32 5	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 6 40 72 3 33 55 3 28 52 3 69 152 1 29 60 4 43 72	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.70 0.88 0.70 0.88 0.70 0.88 0.48 0.57 0.66 0.99	$\begin{array}{l} [0.61; 0.83] \\ [0.60; 1.12] \\ [0.49; 1.01] \\ [0.29; 1.30] \\ [0.29; 1.30] \\ [0.29; 1.30] \\ [0.55; 0.92] \\ [0.46; 1.49] \\ [0.55; 0.92] \\ [0.47; 0.97] \\ [0.66; 0.91] \\ [0.66; 0.91] \\ [0.57; 0.85] \\ [0.14; 0.64] \\ [0.63; 1.23] \\ [0.23; 1.01] \\ [0.28; 1.17] \\ [0.46; 0.93] \\ [0.74; 1.33] \end{array}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 2.6% 1.1% 8.6% 9.2% 1.8% 5.6% 9.2% 1.8% 5.2% 1.8% 5.2% 1.9% 5.3% 6.4%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999 Matsumata T 1993 Random effects mode	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9 144 26 88 21 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 32 5 32 5	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 9 97 141 0 95 158 3 33 55 3 33 55 3 28 52 1 29 60 4 43 72 8 2698 2698	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.70 0.88 0.70 0.88 0.70 0.88 0.48 0.57 0.66 0.99	$\begin{matrix} [0.61; 0.83]\\ [0.60; 1.12]\\ [0.49; 1.01]\\ [0.61; 0.90]\\ [0.29; 1.30]\\ [0.46; 1.49]\\ [0.55; 0.92]\\ [0.49; 0.85]\\ [0.15; 0.51]\\ [0.67; 0.97]\\ [0.66; 0.91]\\ [0.57; 0.85]\\ [0.14; 0.64]\\ [0.63; 1.23]\\ [0.23; 1.01]\\ [0.28; 1.17]\\ [0.46; 0.93] \end{matrix}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 2.6% 1.1% 8.6% 9.2% 1.8% 5.6% 9.2% 1.8% 5.2% 1.8% 5.2% 1.9% 5.3% 6.4%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999 Matsumata T 1993 Random effects mode Heterogeneity: I ² = 58%,	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9 144 26 88 21 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 32 5 32 5	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 9 97 141 0 95 158 3 33 55 3 33 55 3 28 52 1 29 60 4 43 72 8 2698 2698		0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.70 0.88 0.70 0.88 0.70 0.88 0.48 0.57 0.66 0.99	$\begin{array}{l} [0.61; 0.83] \\ [0.60; 1.12] \\ [0.49; 1.01] \\ [0.29; 1.30] \\ [0.29; 1.30] \\ [0.29; 1.30] \\ [0.55; 0.92] \\ [0.46; 1.49] \\ [0.55; 0.92] \\ [0.47; 0.97] \\ [0.66; 0.91] \\ [0.66; 0.91] \\ [0.57; 0.85] \\ [0.14; 0.64] \\ [0.63; 1.23] \\ [0.23; 1.01] \\ [0.28; 1.17] \\ [0.46; 0.93] \\ [0.74; 1.33] \end{array}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 2.6% 1.1% 8.6% 9.2% 1.8% 5.6% 9.2% 1.8% 5.2% 1.8% 5.2% 1.9% 5.3% 6.4%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999 Matsumata T 1993 Random effects mode	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9 144 26 88 21 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 6 2 32 5 32 5	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 9 97 141 0 95 158 3 33 55 3 33 55 3 28 52 1 29 60 4 43 72 8 2698 2698	Risk Ratio	0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.70 0.88 0.70 0.88 0.70 0.88 0.48 0.57 0.66 0.99	$\begin{array}{l} [0.61; 0.83] \\ [0.60; 1.12] \\ [0.49; 1.01] \\ [0.29; 1.30] \\ [0.29; 1.30] \\ [0.29; 1.30] \\ [0.55; 0.92] \\ [0.46; 1.49] \\ [0.55; 0.92] \\ [0.47; 0.97] \\ [0.66; 0.91] \\ [0.66; 0.91] \\ [0.57; 0.85] \\ [0.14; 0.64] \\ [0.63; 1.23] \\ [0.23; 1.01] \\ [0.28; 1.17] \\ [0.46; 0.93] \\ [0.74; 1.33] \end{array}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 2.6% 1.1% 8.6% 9.2% 1.8% 5.6% 9.2% 1.8% 5.2% 1.8% 5.2% 1.9% 5.3% 6.4%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999 Matsumata T 1993 Random effects mode Heterogeneity: I ² = 58%,	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 100 11 8 4 8 60 9 144 26 88 21 6 3 28 5 6 2 6 2 48 15 32 5 el 201 $\tau^2 = 0.029, p < 0$	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 6 40 72 3 33 55 3 69 152 3 69 152 3 69 152 3 69 152 3 69 152 3 69 152 4 43 72 8 2698 .01 1		0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.70 0.88 0.70 0.88 0.70 0.88 0.48 0.57 0.66 0.99	$\begin{array}{l} [0.61; 0.83] \\ [0.60; 1.12] \\ [0.49; 1.01] \\ [0.29; 1.30] \\ [0.29; 1.30] \\ [0.29; 1.30] \\ [0.55; 0.92] \\ [0.46; 1.49] \\ [0.55; 0.92] \\ [0.47; 0.97] \\ [0.66; 0.91] \\ [0.66; 0.91] \\ [0.57; 0.85] \\ [0.14; 0.64] \\ [0.63; 1.23] \\ [0.23; 1.01] \\ [0.28; 1.17] \\ [0.46; 0.93] \\ [0.74; 1.33] \end{array}$	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 2.6% 1.1% 8.6% 9.2% 1.8% 5.6% 9.2% 1.8% 5.2% 1.8% 5.2% 1.9% 5.3% 6.4%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999 Matsumata T 1993 Random effects mode Heterogeneity: $J^2 = 58\%$, C	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9 144 26 88 21 6 3 26 2 6 2 48 12 5 32 5 32 5 32 5 32 5 4 7 ² = 0.029, $p < 0$	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 6 40 72 3 33 55 3 69 152 3 69 152 3 69 152 3 69 152 3 69 152 3 69 152 4 43 72 8 2698 .01 1		0.71 0.82 0.71 0.74 0.62 0.83 0.71 0.65 0.28 0.70 0.88 0.70 0.88 0.70 0.88 0.48 0.57 0.66 0.99	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01] [0.49; 1.30] [0.46; 1.49] [0.55; 0.92] [0.49; 0.85] [0.14; 0.29] [0.67; 0.97] [0.66; 0.91] [0.57; 0.85] [0.14; 0.64] [0.53; 1.23] [0.23; 1.01] [0.28; 1.17] [0.46; 0.93] [0.74; 1.33]	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 2.6% 1.1% 8.6% 9.2% 1.8% 5.6% 9.2% 1.8% 5.2% 1.8% 5.2% 1.9% 5.3% 6.4%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999 Matsumata T 1993 Random effects mode Heterogeneity: I ² = 58%,	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9 144 26 88 21 6 3 26 2 6 2 48 12 5 32 5 32 5 32 5 32 5 4 7 ² = 0.029, $p < 0$	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 55 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 3 33 55 3 28 52 3 69 152 1 29 60 4 43 72 8 2698 .01 NBT		0.71 0.82 0.71 0.62 0.83 0.71 0.65 0.28 0.11 0.81 0.78 0.30 0.30 0.30 0.30 0.30 0.48 0.57 0.66 0.99 0.70	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01] [0.49; 1.30] [0.46; 1.49] [0.55; 0.92] [0.49; 0.85] [0.14; 0.29] [0.67; 0.97] [0.66; 0.91] [0.57; 0.85] [0.14; 0.64] [0.53; 1.23] [0.23; 1.01] [0.28; 1.17] [0.46; 0.93] [0.74; 1.33]	9.2% 6.1% 5.2% 8.4% 1.9% 6.7% 2.6% 6.7% 2.6% 8.2% 1.1% 8.6% 9.2% 1.8% 5.6% 1.8% 5.6% 1.9% 5.3% 6.4%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999 Matsumata T 1993 Random effects mode Heterogeneity: $J^2 = 58\%$, C	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 10 11 8 4 8 60 9 144 26 88 21 6 3 26 2 6 2 48 12 5 32 5 32 5 32 5 32 5 4 7 ² = 0.029, $p < 0$	I Events Total 8 305 444 4 67 234 8 77 154 1 287 388 3 9 37 0 18 60 7 173 289 0 15 83 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 6 40 72 3 33 55 3 28 52 3 69 152 1 29 60 4 43 72 8 2698 201 7 1 Events 1 Events Total		0.71 0.82 0.71 0.74 0.63 0.71 0.65 0.28 0.11 0.81 0.70 0.30 0.30 0.30 0.30 0.30 0.48 0.57 0.66 0.99 0.70	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01] [0.49; 1.30] [0.46; 1.49] [0.55; 0.92] [0.49; 0.85] [0.14; 0.29] [0.67; 0.97] [0.66; 0.91] [0.57; 0.85] [0.14; 0.64] [0.53; 1.23] [0.23; 1.01] [0.28; 1.17] [0.46; 0.93] [0.74; 1.33]	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 6.9% 2.6% 1.1% 8.6% 9.2% 1.8% 5.6% 9.2% 1.8% 5.6% 9.2% 1.8% 5.3% 6.4% 100.0%
Wada H 2017 Yang T 2016 Xu LN 2016 Harada N 2015 Ye XR 2013 Kuroda S 2012 Okamura Y 2011 Nanashima A 2011 Chen ZY 2010 Abdel-Wahab M 2010 Choi GH 2009 Kaibori M 2008 Hanazaki K 2005 Laurent C 2005 Kwon AH 2001 Kitagawa K 2001 Asahara T 1999 Wu Y 1999 Matsumata T 1993 Random effects mode Heterogeneity: $I^2 = 58\%$, C	Events Tota 97 19 55 23 24 6 50 9 14 9 15 6 37 8 43 100 11 8 60 9 144 26 88 21 6 3 28 5 6 2 48 15 32 5 6 2 48 15 32 5 61 201 τ^2 = 0.029, $\rho < 0$ AB' Events Tota	I Events Total 8 305 444 4 67 234 8 77 154 8 77 154 1 287 388 3 9 37 0 18 60 7 36 79 7 36 79 7 31 72 4 76 96 9 97 141 0 95 158 3 33 55 3 28 52 3 69 152 2 9 60 4 43 72 8 2698 01 7 NBT NBT 1 Events Total 3 211 444		0.71 0.74 0.74 0.62 0.83 0.71 0.65 0.28 0.11 0.81 0.78 0.70 0.30 0.30 0.30 0.30 0.30 0.57 0.66 0.99 0.70 RR	[0.61; 0.83] [0.60; 1.12] [0.49; 1.01] [0.29; 1.30] [0.29; 1.30] [0.46; 1.49] [0.55; 0.92] [0.47; 0.97] [0.66; 0.91] [0.67; 0.97] [0.66; 0.91] [0.63; 1.23] [0.23; 1.01] [0.28; 1.17] [0.28; 1.17] [0.46; 0.93] [0.74; 1.33] [0.62; 0.78]	9.2% 6.1% 5.2% 8.4% 1.9% 6.9% 6.7% 2.6% 1.1% 8.6% 9.2% 1.1% 8.6% 9.2% 1.8% 5.6% 1.9% 2.0% 5.3% 6.4% 100.0%
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Figure 2. Forest plot of postoperative survival rate associated with ABT for HCC. (A) for 1-year survival rate, (B) for 3-year survival rate, (C) for 5-year survival rate, and (D) for 10-year survival rate. ABT = allogeneic blood transfusion, HCC = hepatocellular carcinoma.

differences P < .05), even low transfusion amount might decrease the 5-year survival rate (compared to high transfusion amount group, 5-year survival rate of low transfusion amount group decreased by about 55%). When examining differences over cancer size, we also found that cancer size had a significant impact on 5-year survival rate (subgroup differences P < .05). Compared to studies with small cancer size, 5-year survival rate of studies with large cancer size decreased by about 45%. In the stratified analysis, we did not find that there was the association between transfusion rate and 5-year survival rate.

 Table 2

 Stratified analysis for 5-year survival rate, 5-year DFS and complication.

		5-year OS						
Subgroup	No. of studies	RR (95%CI)	ŕ	P [*]				
Transfusion amoun	t							
>788 ml	4	0.78 (0.70, 0.87)	0.0%	<.0001				
≼788 ml	4	0.30 (0.14, 0.65)	84.0%					
NA	11	0.73 (0.67, 0.79)	0.0%					
Transfusion rate								
>42.8%	12	0.70 (0.65, 0.77)	69.1%	.6495				
≪42.8%	7	0.68 (0.62, 0.76)	10.7%					
Age								
>60.96 year	8	0.70 (0.66, 0.77)	16.5%	.3064				
<60.96 year	11	0.66 (0.59, 0.75)	72.4%					
Cancer size								
>4.42 cm	3	0.42 (0.20, 0.88)	74.9%	.0010				
≼4.42 cm	7	0.75 (0.69, 0.81)	0.0%					
NA	9	0.64 (0.57, 0.72)	75.0%					
Participants								
>248	6	0.74 (0.68, 0.80)	0.0%	.0259				
≪248	13	0.63 (0.57, 0.70)	73.3%					
Study design								
PCS	3	0.74 (0.63, 0.88)	13%	.3776				
RCS	16	0.68 (0.60, 0.78)	63%					

		5-year DFS						
Subgroup	No. of studies	RR (95%CI)	ŕ	P				
Transfusion amount								
>876 mL	3	0.69 (0.52, 0.92)	0.0%	.8305				
≼876 mL	4	0.62 (0.32, 1.20)	69.7%					
NA	12	0.73 (0.65, 0.82)	34.0%					
Transfusion rate								
>37.8%	11	0.75 (0.65, 0.86)	40.7%	.2782				
≼37.8%	8	0.66 (0.56, 0.79)	30.3%					
Age								
>61.62 years	9	0.74 (0.57, 0.96)	57.0%	.9279				
<61.62 years	9	0.70 (0.59, 0.83)	0.0%					
NA	1	0.69 (0.50, 0.95)	0.0%					
Cancer size								
>4.87 cm	4	0.59 (0.32, 1.09)	67.0%	.7808				
≼4.87 cm	7	0.72 (0.62, 0.85)	0.0%					
NA	8	0.75 (0.57, 0.98)	51.0%					
Participants								
>252	6	0.70 (0.61, 0.81)	0.0%	.7345				
≼252	13	0.73 (0.62, 0.86)	51.1%					
Study design								
PCS	4	0.59 (0.43, 0.80)	0.0%	.2980				
RCS	15	0.73 (0.65, 0.82)	39%					
		Comp	lications					
Subgroup	No. studies	RR (95%CI)	ŕ	P [*]				
Transfusion amount								
>788 mL	3	1.23 (0.98, 1.55)	0.0%	.0039				
≼788 mL	5	2.15 (1.69, 2.74)	17.0%					

≪788 mL	5	2.15 (1.69, 2.74)	17.0%	
NA	2	2.66 (1.18, 6.00)	64.0%	
Transfusion rate				
>38.56%	6	1.61 (1.32, 1.98)	68.1%	.0089
≼38.56%	4	2.26 (1.94, 2.62)	83.1%	
Age				
>63.47 year	3	1.93 (1.71, 2.19)	39.3%	<.0001
<63.47 year	7	1.58 (1.39, 1.8)	55.7%	
Cancer size				
>5.28 cm	4	1.59 (1.31, 1.94)	34.0%	.0086
≼5.28 cm	5	2.31 (1.50, 3.54)	78.0%	

(continued)

Table 2	l
(continued).

		Complications							
Subgroup	No. studies	RR (95%CI)	ŕ	P [*]					
NA	1	0.99 (0.70, 1.41)	0.0&						
Participants									
>283	5	2.12 (1.82, 2.46)	84.0%	.0259					
≤283	5	1.58 (1.29, 1.94)	58.4%						
Study design									
PCS	3	1.24 (0.90, 1.70)	14.0%	.0812					
RCS	7	2.12 (1.57, 2.86)	78.0%						

 $\mathsf{DFS}\!=\!\mathsf{disease}\text{-free survival}, \ \mathsf{NA}\!=\!\mathsf{not} \ \mathsf{available}, \ \mathsf{NO}.\!=\!\mathsf{number}, \ \mathsf{OS}\!=\!\mathsf{overall} \ \mathsf{survival}, \ \mathsf{RR}\!=\!\mathsf{relative} \ \mathsf{risk}.$

Test for subgroup differences (fixed-effect model), between subgroups P value.

3.3. Disease-free survival

In this meta-analysis, there were 13 studies providing 1-year DFS, ^[5,6,10,12,17,20,21,24,25,29–31,36] 16 studies providing 3-year DFS, ^[5,6,10,12,15,17,20,21,24,25,27–31,36] 19 studies providing 5-year DFS, ^[5,6,10,12,15,17,19–21,23–25,27–32,36] and 4 studies providing 10-year DFS. ^[5,12,23,24] As displayed in (Fig. 3A–D), perioperative ABT was associated with a significant increased risk in reducing 1-, 3-, 5-, and 10-year DFS (respectively: RR=0.86, 95%CI: 0.82–0.91, P < .05; RR=0.77, 95%CI: 0.67–0.79, P < .05; RR= 0.71, 95%CI: 0.64–0.79, P < .05; RR=0.62, 95%CI: 0.48–0.8, P < .05). The heterogeneity of 3-year DFS was >50%, the random-effect model was applied to calculate summary estimate; the heterogeneity of 1-, 5-, and 10-year DFS was <50%, the fixed-effect model was used.

Results of the stratified meta-analyses for postoperative 5-year DFS were shown in Table 2. When stratified by transfusion amount, transfusion rate, age, cancer size, and sample size, we did not find that they had a significant impact on 5-year DFS (subgroup differences P>.05).

3.4. Cancer recurrence rate

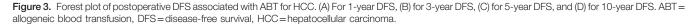
The cancer recurrence data were available in 3 studies.^[15,27,34] As shown in Figure 4A–C, meta-analysis demonstrated cancer recurrence rates at 1 and 3 years after radical hepatectomy for HCC patients were higher in the ABT group than in NBT group (respectively: RR=1.5, 95% CI: 1–2.24, P < .05; RR=1.27, 95% CI: 1.09–1.49, P < .05), but not statistically significant at 5years (RR=1.08, 95% CI: 0.98–1.19, P = .512).

3.5. Postoperative complication rate

Ten studies reported the relationship between ABT and postoperative complication rate.^[5,6,12,14,16,17,22,26,29,35] Metaanalysis demonstrated that postoperative complication rate was higher in ABT group than in NBT group (RR=1.87, 95%CI: 1.42–2.45, P < .05) (Fig. 5). Significant heterogeneity among studies was present ($I^2 = 78\%$), and the random-effect model was applied.

Results of the stratified meta-analyses for postoperative complication rate were shown in Table 2. When stratified by transfusion amount, we found that the impact of transfusion amount on postoperative complication rate was significant (subgroup differences P < .05), even low transfusion amount might increase postoperative complication rate (compared to

	ABT	NBT		
Study	Events Total Ev		Risk Ratio	RR 95%-Cl Weight
Wada H 2017	125 198	311 444		0.90 [0.80; 1.02] 18.4%
Yang T 2016	122 234	132 234	- <u>ja</u> -	0.92 [0.78; 1.09] 12.7%
Harada N 2015	61 91	312 388		0.83 [0.72; 0.97] 11.4%
Kuroda S 2012	38 60	37 60		1.03 [0.78; 1.36] 3.6%
Chen ZY 2010	20 87	25 79		0.73 [0.44; 1.20] 2.5%
Wang CC 2009	32 62	323 411		0.66 [0.51; 0.84] 8.1%
Sugita S 2008 Hanazaki K 2005	60 101 154 210	77 120 134 158		0.93 [0.75; 1.14] 6.8% 0.86 [0.78; 0.96] 14.7%
Laurent C 2005	10 30	48 68 -		0.86 [0.78; 0.96] 14.7% 0.47 [0.28; 0.80] 2.8%
Kitagawa K 2001	19 23	49 52		0.88 [0.72; 1.07] 2.9%
Kwon AH 2001	41 53	42 55	<u></u>	1.01 [0.82; 1.25] 4.0%
Makino Y 2000	81 117	65 78		0.83 [0.71; 0.97] 7.5%
Matsumata T 1993	40 54	58 72		0.92 [0.76; 1.12] 4.8%
Fixed effect mode Heterogeneity: $I^2 = 2$		2219 0.17		0.86 [0.82; 0.91] 100.0%
А			0.5 1 2	
Study	ABT Events Total	NBT Events Total	Risk Ratio	RR 95%-Cl Weight
Wada H 2017	74 198	185 444	-	0.90 [0.73; 1.11] 9.6%
Yang T 2016	66 234	77 234		0.86 [0.65; 1.13] 8.5%
Harada N 2015	31 91	190 388		0.70 [0.51; 0.94] 8.0%
Kuroda S 2012	20 60	16 60	100	1.25 [0.72; 2.17] 4.6%
Nanashima A 2011	48 100	27 83		1.48 [1.02; 2.14] 6.9%
Chen ZY 2010 Wang CC 2009	12 87 24 62	22 79 238 411		0.50 [0.26; 0.93] 3.8% 0.67 [0.48; 0.92] 7.6%
Sugita S 2008	30 101	40 120		0.89 [0.60; 1.32] 6.6%
Hanazaki K 2005	69 210	85 158		0.61 [0.48; 0.78] 9.1%
Laurent C 2005	4 30	34 68 -		0.27 [0.10; 0.68] 2.1%
Ercolani G 2003	28 71	90 153		0.67 [0.49; 0.92] 7.8%
Sasaki Y 2002	6 23	27 52		0.50 [0.24; 1.05] 3.1%
Kitagawa K 2001	5 23	26 52		0.43 [0.19; 0.99] 2.6%
Kwon AH 2001	27 53	26 55	<u>- 10 -</u>	1.08 [0.73; 1.58] 6.7%
Makino Y 2000	43 117	32 78		0.90 [0.63; 1.28] 7.1%
Matsumata T 1993	18 54	37 72		0.65 [0.42; 1.01] 5.9%
Random effects me Heterogeneity: $I^2 = 60$			· · · · · · · · · · · · · · · · · · ·	0.77 [0.67; 0.90] 100.0%
B			0.2 0.5 1 2 5	
Study	ABT Events Total E	NBT vents Total	Risk Ratio	RR 95%-CI Weight
Wada H 2017	49 198	137 444	素	0.80 [0.61; 1.06] 13.4%
Yang T 2016	34 234	46 234		0.74 [0.49; 1.11] 7.3%
Harada N 2015	22 91	146 388	-	0.64 [0.44; 0.94] 8.8%
Kuroda S 2012	13 60	10 60		1.30 [0.62; 2.73] 1.6%
Nanashima A 2011		20 83	-	1.49 [0.94; 2.37] 3.5%
Chen ZY 2010	10 87	22 79		0.41 [0.21; 0.82] 3.7%
Wang CC 2009	19 62 32 91	180 411 51 96	and a	0.70 [0.47; 1.03] 7.5% 0.66 [0.47; 0.93] 7.9%
Choi GH 2009 Sugita S 2008	17 101	26 120		0.78 [0.45; 1.35] 3.8%
Sasaki Y 2006	42 184	77 233	and the second s	0.69 [0.50; 0.95] 10.8%
Hanazaki K 2005	44 210	55 158	-	0.60 [0.43; 0.84] 10.0%
Laurent C 2005	2 30	26 68		0.17 [0.04; 0.69] 2.5%
Ercolani G 2003	18 71	46 153		0.84 [0.53; 1.34] 4.6%
Sasaki Y 2002	1 23	16 52 -		0.14 [0.02; 1.00] 1.6%
Kitagawa K 2001	5 23	21 52		0.54 [0.23; 1.25] 2.0%
Kwon AH 2001	10 53	14 55		0.74 [0.36; 1.52] 2.2%
Makino Y 2000	27 117	19 78	-14	0.95 [0.57; 1.58] 3.6%
Asahara T 1999	2 23	38 152		0.35 [0.09; 1.35] 1.6%
Matsumata T 1993	14 54	27 72		0.69 [0.40; 1.19] 3.7%
Fixed effect mode		2988		0.71 [0.64; 0.79] 100.0%
Heterogeneity: $I^2 = 3$	$3\%, \tau^2 = 0.0289, p =$	0.08	0.1 0.5 1 2 10	
C	ABT	NBT	0.1 0.01 2 10	
	Events Total E		Risk Ratio	RR 95%-CI Weight
Study				
Wada H 2017	26 198	77 444		0.76 [0.50; 1.14] 33.0%
Wada H 2017 Harada N 2015	26 198 10 91	78 388 —		0.55 [0.29; 1.01] 20.6%
Wada H 2017 Harada N 2015 Sasaki Y 2006	26 198 10 91 20 184	78 388 — 47 233 -		0.55 [0.29; 1.01] 20.6% 0.54 [0.33; 0.88] 28.9%
Wada H 2017 Harada N 2015 Sasaki Y 2006 Hanazaki K 2005	26 198 10 91 20 184 17 210	78 388 — 47 233 - 22 158 —		0.55 [0.29; 1.01] 20.6% 0.54 [0.33; 0.88] 28.9% 0.58 [0.32; 1.06] 17.5%
Wada H 2017 Harada N 2015 Sasaki Y 2006	26 198 10 91 20 184 17 210	78 388 — 47 233 -	0.5 1 2	0.55 [0.29; 1.01] 20.6% 0.54 [0.33; 0.88] 28.9%



high transfusion amount group, postoperative complication rate of low transfusion amount group increased by about 75%). Meanwhile, we also found that postoperative complication rate was associated with the transfusion rate (subgroup differences P < .05). Compared to studies with high-transfusion rate, postoperative complication rate of studies with low transfusion rate increased by about 40%. When examining differences over age, cancer size, and sample size, we also found that they had a significant impact on postoperative complication rate (subgroup differences P < .05).

Study	Events	ABT Total	Events	NBT Total		Ratio	RR	95%-CI	Weight
1-year REC Yamamoto J 1996 Fixed effect model Heterogeneity: not app		85 85	59	301 301				[1.00; 2.24] [1.00; 2.24]	7.5% 7.5%
3-year REC Ercolani G 2003 Yamamoto J 1996 Fixed effect model Heterogeneity: $l^2 = 09$		71 85 156 p = 0.58	47 175 8	153 301 454	-	***	1.23	[0.96; 1.97] [1.05; 1.45] [1.09; 1.49]	8.6% 22.3% 31.0%
5-year REC Ercolani G 2003 Yamamoto J 1996 Nanashima A 2011 Random effects mo		71 85 100 256	80 213 62	153 301 83 537		↓ ↓ ↓	1.23 0.86	[0.86; 1.42] [1.10; 1.37] [0.71; 1.04] [0.98; 1.19]	14.7% 27.2% 19.6% 61.5%
Heterogeneity: $I^2 = 82$.%, τ ⁻ = 0	.0368, p	o < 0.01		0.5 1	2			

Figure 4. Forest plot of postoperative recurrence associated with ABT for HCC. (A) For 1-year recurrence, (B) for 3-year recurrence, and (C) for 5-year recurrence. ABT=allogeneic blood transfusion, HCC=hepatocellular carcinoma.

Study	Events	ABT Total	Events	NBT Total		Risk Ratio	RR	95%-CI	Weight
Wada H 2017	67	198	38	444			- 395	[2.76; 5.67]	12.0%
Harada N 2015	7	91	17	388				[0.75; 4.11]	6.2%
Kuroda S 2012	16	60	5	60				[1.25; 8.18]	5.5%
Okamura Y 2011	63	87	114	289				[1.51; 2.23]	14.1%
Yang T 2011	68	164	45	141			1.30	[0.96; 1.76]	12.8%
Chen ZY 2010	17	87	9	79			- 1.72	[0.81; 3.63]	7.1%
Kaibori M 2008	72	269	13	141				[1.67; 5.05]	9.4%
Wei AC 2003	36	45	50	110		-		[1.37; 2.26]	13.5%
Kwon AH 2001	14	53	10	55			1.45	[0.71; 2.98]	7.4%
Itasaka H 1995	24	38	21	33		- -	0.99	[0.70; 1.41]	12.1%
Random effects model		1092		1740		-	1.87	[1.42; 2.45]	100.0%
Heterogeneity: $I^2 = 78\%$, τ	² = 0.1284	l, p < 0	.01		0.2 ().5 1 2	5		

Figure 5. Forest plot of postoperative complications rate associated with ABT for HCC. ABT=allogeneic blood transfusion, HCC=hepatocellular carcinoma.

3.6. Quality of evidence of the primary outcomes

The GRADE system was applied to assess the evidence for the outcomes, and the quality of evidence was summarized in Table 3. As a result, the overall quality of evidence for the outcomes was low. Thus, further prospective studies are likely to have an important impact on the confidence in the effect estimate and may change the current estimate.

3.7. Sensitivity analysis

Sensitivity analysis was performed for 5-year survival rate and postoperative complication rate by excluding one study at a time and calculating the pooled RRs for the remaining studies (Supplementary Information, http://links.lww.com/MD/C569). The results demonstrated that no individual study had excessive impact on the stability of the pooled effect and that the result of this analysis was robust.

3.8. Publication bias

Publication bias was measured by the Egger's and Peters's test. Egger's test for 5-year survival rate, 5-year DFS, and postoperative complication rate did not show the asymmetry typically associated with publication bias (P value: .0937, .1629, and .6988, respectively). Evidence of publication bias was also not seen with the Peters's test of 5-year survival rate (P=.1527),

Table 3

Strength of evidence for outcomes of HCC patients with ABT compared with NBT.

	Illustrative comp	arative risk [*] (95%CI)			
Outcomes	Assumed risk NBT (per 1000)	Corresponding risk ABT (per 1000)	Relative effect RR (95%CI)	No. of participants (studies)	Quality of evidence (GRADE)
Survival rate					
1-year survival rate	895	805 (778 to 832)	0.9 (0.87 to 0.93)	2672 (10 studies)	$\oplus \oplus \bigcirc \bigcirc^{\dagger,\ddagger}$ low
3-year survival rate	726	603 (559 to 646)	0.83 (0.77 to 0.89)	3525 (13 studies)	$\oplus \oplus \oplus \bigcirc^{\dagger}$ moderate
5-year survival rate	581	407 (378 to 430)	0.7 (0.65 to 0.74)	4716 (19 studies)	$\oplus \oplus \bigcirc \bigcirc^{\dagger,\ddagger}$ low
10-year survival rate	393	252 (212 to 295)	0.64 (0.54 to 0.75)	2014 (6 studies)	$\oplus \bigcirc \bigcirc^{\dagger,\ddagger,\$}$ very low
Disease-free survival					
1-year DFS	727	661 (632 to 698)	0.91 (0.87 to 0.96)	3539 (13 studies)	$\oplus \oplus \bigcirc \bigcirc^{\dagger,\$}$ low
3-year DFS	460	354 (308 to 414)	0.77 (0.67 to 0.9)	4021 (16 studies)	$\oplus \oplus \bigcirc \bigcirc^{\dagger,\ddagger}$ low
5-year DFS	327	232 (209 to 258)	0.71 (0.64 to 0.79)	4800 (19 studies)	$\oplus \oplus \oplus \bigcirc^{\dagger}$ moderate
10-year DFS	183	114 (88 to 147)	0.62 (0.48 to 0.8)	1906 (4 studies)	$\oplus \oplus \bigcirc \bigcirc^{\dagger, \S}$ low
Cancer recurrence	661	714 (648 to 787)	1.08 (0.98 to 1.19)	793 (3 studies)	$\oplus \bigcirc \bigcirc^{\dagger,\ddagger,\$}$ very low
Complication	185	346 (263 to 453)	1.87 (1.42 to 2.45)	2832 (10 studies)	$\oplus \bigcirc \bigcirc \bigcirc^{\dagger,\ddagger,\$}$ very low

GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

* The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%Cl).

[†]Risk of bias was unclear or high in the study/studies.

* Serious unexplained inconsistency (large heterogeneity, P<.05, point estimates, and confidence intervals vary considerably).

[§] Imprecision due to few events and confidence intervals include appreciable benefit or harm.

[¶] Definition of postoperative complication varied or was unclear.

ABT=allogeneic blood transfusion, GRADE=Grading of Recommendations Assessment, Development, and Evaluation, HCC=hepatocellular carcinoma, NBT=no blood transfusion, RR=relative risk.

5-year DFS (P=.1019), and postoperative complication rate (P=.1373).

4. Discussion

Although perioperative ABT is very common in hepatectomy, the clinical impact of ABT on HCC patients undergoing radical hepatectomy remains controversial, especially in connection to recurrence. In this meta-analysis, perioperative blood transfusion adversely affected long-term prognosis of HCC patients undergoing radical hepatectomy. Our study showed that perioperative blood transfusion of any amount correlates with poorer survival rate and disease-free survival, but not with recurrence. The pooled RR values for 5-year survival rate and 5year DFS after radical hepatectomy all were 0.7 in this metaanalysis, which meant that 5- survival rate and 5-DFS of ABT group were reduced by about 30% compared to NBT group. In stratified analyses, we found that the impact of transfusion amount on 5-year survival rate was significant (subgroup differences P < .05), even low transfusion amount might decrease the 5-year survival rate of HCC patients. However, we did not find that there was the association between transfusion amount and 5-year DFS (subgroup differences P > .05). In our analysis, there was no statistical significance between high and low transfusion rate for the survival rate and disease-free survival (subgroup differences P > .05); therefore, it was believed that transfusion itself mediated its effects on the survival rate and disease-free survival rather than the transfusion rate, which was consistent with Wada et al.^[5] Similar adverse effect of ABT on clinical prognosis was also observed in other malignancies. For example, a recent meta-analysis performed by Cata and his team on bladder cancer demonstrated that ABT was significantly associated with poor survival rate (HR = 1.27).^[37]

Regarding cancer recurrence, Wada et al^[5] and Nanashima et al^[15] reported that ABT did not promote recurrence; however, Ercolani et al,^[27] Asahara et al,^[32] and Yamamoto et al^[34]

reported ABT could increase the recurrence rate of HCC after radical hepatectomy. Meanwhile, the meta-RR for 5 years was 1.08 in this meta-analysis (P=.512). That is to say, patients in ABT and NBT group had a similar chance of cancer recurrence. In our analysis, postoperative complication rate was significantly higher in ABT group than in NBT group, which was speculated that immunosuppression modulated by blood transfusion induced postoperative complication rate.^[38] The absolute peripheral blood lymphocyte count is significantly reduced in patients who receive ABT ^[21] and one study reported that the natural killer cell activity of transfused patients was reduced on postoperative day 7.^[29] Our results supported the consensus that ABT induced postoperative complication rate and adversely affected the survival of HCC after radical hepatectomy.

Further, we reviewed clinical practice guidelines for liver cancer from China,^[39] the United States,^[40] Europe,^[41] Singapore,^[42] and South Korea,^[43] and found that only Korea's guideline referred to intraoperative transfusion, and stated one reason why hepatic resection had recently become safer was the reduction in the case of intraoperative hemorrhage and transfusion. Korea's guideline stated blood transfusion compromised anticancer immunologic mechanisms and increased postoperative recurrence.^[43] The most commonly reported mechanisms of transfusion-related immunomodulation included decreased function of killer cells, decreased ratio of helper-tosuppressor T lymphocytes, decreased efficacy of antigen presentation, induced tolerance for specific antigens, and suppression of hematopoiesis.^[44] Different from others, Procter and colleagues^[45] reported that depletion of extracellular arginine in serum, an amino acid essential for normal immunity, might be the mechanism of the immunosuppressive effect of packed red blood cells. However, it also had been speculated that the infusion of growth factors (vascular endothelial growth factor and transforming growth factor-b) and an enhanced inflammatory response as a result of the exposure of the recipient immune system to donor microparticles could also stimulate spread and

proliferation of cancer cells.^[46] Our meta-analysis was not designed to investigate these possibilities; however, our results supported the hypothesis that the perioperative administration of ABT was an independent risk factor for reduced survival rate and DFS after radical hepatectomy for HCC similar to what has been reported for other cancers such as bladder and colon.^[37,47]

The quality of the evidence varied for different outcomes (Table 3). The quality of the evidence of most outcomes was low and very low. The chief reason was that most of the included studies were retrospective cohort studies, although all studies were of high quality evaluated by the Ottawa-Newcastle score to grade; consequently, the risk of confounding factors was not clear. The included studies collected patients with widely varied stages of disease, including TNM I, II, III, and IV. Stage of the disease was the most important prognostic factor of recurrence and survival in HCC patients. Besides, the disease stage was a significant confounder that was hard to control in retrospective cohort studies. Moreover, the patients with advanced disease were more likely to receive adjuvant therapy, which might be another confounder. Small sample sizes resulted in wide confidence intervals for 10-year survival rate, 10-year DFS, and cancer recurrence, while other factors decreased the quality of the evidence. Future studies should measure differences in clinically important outcomes.

There were several limitations that must be taken into account in this meta-analysis. Most included studies were retrospective cohort studies, and many confounding factors cannot be eliminated, which may contribute significantly to the heterogeneity, such as staging systems, surgical techniques, surgical approach, adjuvant therapies, transfusion criteria, and supportive care, etc. Thus, the results should be explained with caution. Theoretically, a large-scale randomized clinical trial could avoid many of these limitations but would be very difficult to implement. In this situation, a randomized clinical trial would be unethical because it would be unacceptable to administer a transfusion without a clinical indication or to withhold transfusion from a patient who needed blood.

5. Conclusion

In conclusion, despite the quality of the evidence varied for different outcomes, our findings suggested that perioperative blood transfusion had an adverse effect on prognosis of HCC patients after radical hepatectomy, which might reduce the survival rate and disease-free survival, and increase postoperative complication rate. To promote long-term outcomes, surgeons should reduce bleeding during liver resection and avoid perioperative allogenic blood transfusion. Besides, the overall quality of the evidences was poor due to imprecision and risk of bias, which might weaken our confidence in these results. A prospective large-scale study, in which the confounding factors were strictly balanced, was needed.

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