ORIGINAL ARTICLE

Systematic review and meta-analysis of surgery for hilar cholangiocarcinoma with arterial resection

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Abstract

Background: With the advances in multimodality treatment, an analysis of the outcome of arterial resections (AR) in surgery of cholangiocarcinoma is lacking. The aim of this meta-analysis was to summarize the currently available evidence onof AR for the treatment of cholangiocarcinoma.

Methods: A systematic literature search was carried out according to PRISMA guidelines.

Results: 10 retrospective cohort studies published from 2007 to 2020 with 2530 patients (408 AR group and 2122 control group) were identified. Higher in-hospital mortality rates (6.8% vs 3.3%, OR 2.65, 95% CI [1.27; 5.32], p = 0.009), higher morbidity rates (Clavien-Dindo classification $\geq$3) (52% vs 47%, OR 1.44, 95% CI [1.02; 1.75], p = 0.04) and lower 1-year, 3-year and 5-year survival rates (54% vs 69%, OR 0.55, 95% CI [0.34; 0.91 p = 0.02), (34% vs 38%, OR 0.74, 95% CI [0.55; 0.98, p = 0.03), (18% vs 29%, OR 0.54, 95% CI [0.39; 0.75, p = 0.0002) were observed in the AR group when compared to the control group.

Conclusion: Evidence from non-randomized studies shows a higher morbidity and mortality and shorter long-term survival in patients undergoing AR. However, the results are prone to selection bias, and only randomized trials comparing AR and palliative treatments AR might reveal a possible benefit of AR.

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Background

Cholangiocarcinoma has an estimated incidence of 1–2 per 100,000 persons per year[1] and constitutes the second most common primary hepatic malignancy.[2] The effect of systemic treatment is limited in most patients and surgery with complete removal of the tumor is the only option offering a chance of cure or at least of long-term freedom from tumor with 20–30% 5-year overall survival.[3,4] Most cholangiocarcinomas arise in the bile duct bifurcation. They are commonly referred to as hilar cholangiocarcinomas or Klatskin tumors.[5] Due to the proximity of vascular structures to the bile duct bifurcation, tumor invasion of the portal vein, the proper hepatic artery or the contralateral hepatic artery (i.e. a tumor arising from the left bile duct invading the right hepatic artery) occur in a relevant proportion of cases.

Vascular and especially arterial resection (AR) and reconstruction during surgical removal of hilar cholangiocarcinoma is a debated issue.[6] Although it is the only way of facilitating complete resection if the vessels are invaded, there are concerns of high postoperative morbidity and mortality rates following vascular reconstruction, including hemorrhage and liver failure, which might offset the potential survival advantage gained from complete removal of the tumor. However, thanks to technical improvements in microvascular anastomoses and to a growing experience with liver transplants in many centers, the surgical approaches for hilar cholangiocarcinoma have generally become more aggressive in recent years and concurrently the number of studies assessing feasibility, safety and oncological effectiveness of AR and arterial reconstruction has been growing.[7–11]

To summarize the currently available evidence on the topic, we conducted a systematic review with meta-analysis.

Methods

The literature search and data analysis were conducted in accordance with the PRISMA Guidelines (support material 1).[12] The study has been prospectively registered in the PROSPERO database.[13] The study protocol was also published a priori.[14]

Search strategy

The PubMed/Medline, Cochrane Library, Cinahl, ClinicalTrials.gov (clinical trials registry) and Web of Science Core Collection databases were searched through their respective online search engines. The search was performed on studies published between database inception and the defined search date December 9, 2020. The search strategies used in the single databases are displayed in the support material 2. Furthermore, the reference lists of the included studies were manually searched to find relevant articles. Abstracts and full-text reviews were evaluated independently in an unblinded standardized manner by two authors (AR and NW) to assess eligibility for inclusion. Disagreements between reviewers was resolved by consensus; if no agreement could be reached, a third author (JU) decided if the respective study was included.

Inclusion and exclusion criteria

Articles in English, German, Spanish, Portuguese, and Italian language were considered. Studies reporting resection of cholangiocarcinoma, both primary and secondary, in curative intent including resection of a segment of the hepatic artery with a control group of patients undergoing resection without arterial resection were included. Studies with an irrelevant abstract or title or with less than five patients were excluded, as were reviews, case reports, comments, and letters. Details of the study selection process are summarized in a PRISMA flowchart (Fig. 1).

Data collection

Data were extracted separately by two authors (AR and UR) and presented in a tabular fashion. The following descriptive data were documented for each selected study: first author, year of publication, inclusion period, country where the study was conducted, sample size and median follow up time (Table 1). Patient and operation characteristics were documented: age, gender, ASA classification, ECOG performance status, preoperative chemotherapy, type of operation, type of vessel resection and reconstruction, duration of surgery and blood loss. The following predefined outcomes were also extracted (Table 2):

- Mortality (30-day, In-Hospital, 90-day, and 100-day).
- Morbidity (any type of complication, surgical and medical, as defined in the single studies, Clavien-Dindo classification ≥ 3 [15]).
- Vessel complications (thrombosis of the portal vein or hepatic artery, stenosis of these vessels, and formation of pseudoaneurysms).
- Liver failure (as defined in the single studies).
- Postoperative bleeding (within 48 h or as defined in the single studies), survival time, actuarial survival (2-, 3- and 5-year survival), complete resection rate, proportion of patients with no resection during surgery, rate of histologically confirmed arterial invasion and lymph node positivity (number of positive lymph nodes and lymph node ratio).
- Overall reoperation rate.
- Length of hospital stay.
- Survival time.
- Proportion of patients with no resection during surgery.
- Rate of histologic arterial invasion.
- Lymph node positivity (number of positive lymph nodes and lymph node ratio).

In addition, subgroup analysis for patients with concomitant portal vein resection and patients who had undergone neoadjuvant chemotherapy prior to resection was carried out. Risk of bias was assessed using the ROBINS-I tool (risk of bias in non-randomized studies of interventions).[16]

Statistical analysis

The Review Manager (RevMan) software, version 5.3 (Cochrane Collaboration, Oxford, UK) was used. If a given outcome was reported in two or more studies, meta-analysis was performed. The magnitude of the effect estimate was visualized by forest plots. Odds Ratios (OR) were calculated for binary data and weighted mean differences for continuous data. The 95% confidence interval (CI), heterogeneity and statistical significance are reported for each outcome. The X^2 and the Kruskal–Wallis tests were used for evaluation of statistical significance. $P < 0.05$ was considered statistically significant. When the studies did not report mean and standard deviation, these were calculated using the methods described by the guidelines of the Cochrane Collaboration[17] and Hozo *et al.*[18] As not all studies reported time-to-event data and hazard ratios, the survival analysis was performed with weighted rates.

Results

From the 7628 articles, 10 cohort studies[19–28] from three countries (Japan, China, USA) published between 2007 and 2020 were included in the meta-analysis. The enrolment period of these studies ranged from 1981 to 2018. In these studies, a total of 2530 patients (408 patients in the AR group and 2122 in the control group) were included. The study features, patient and operation characteristics are presented in Table 1 the risk of bias assessment is presented in Table 3. No meta-analysis of duration of surgery could be performed as only one study

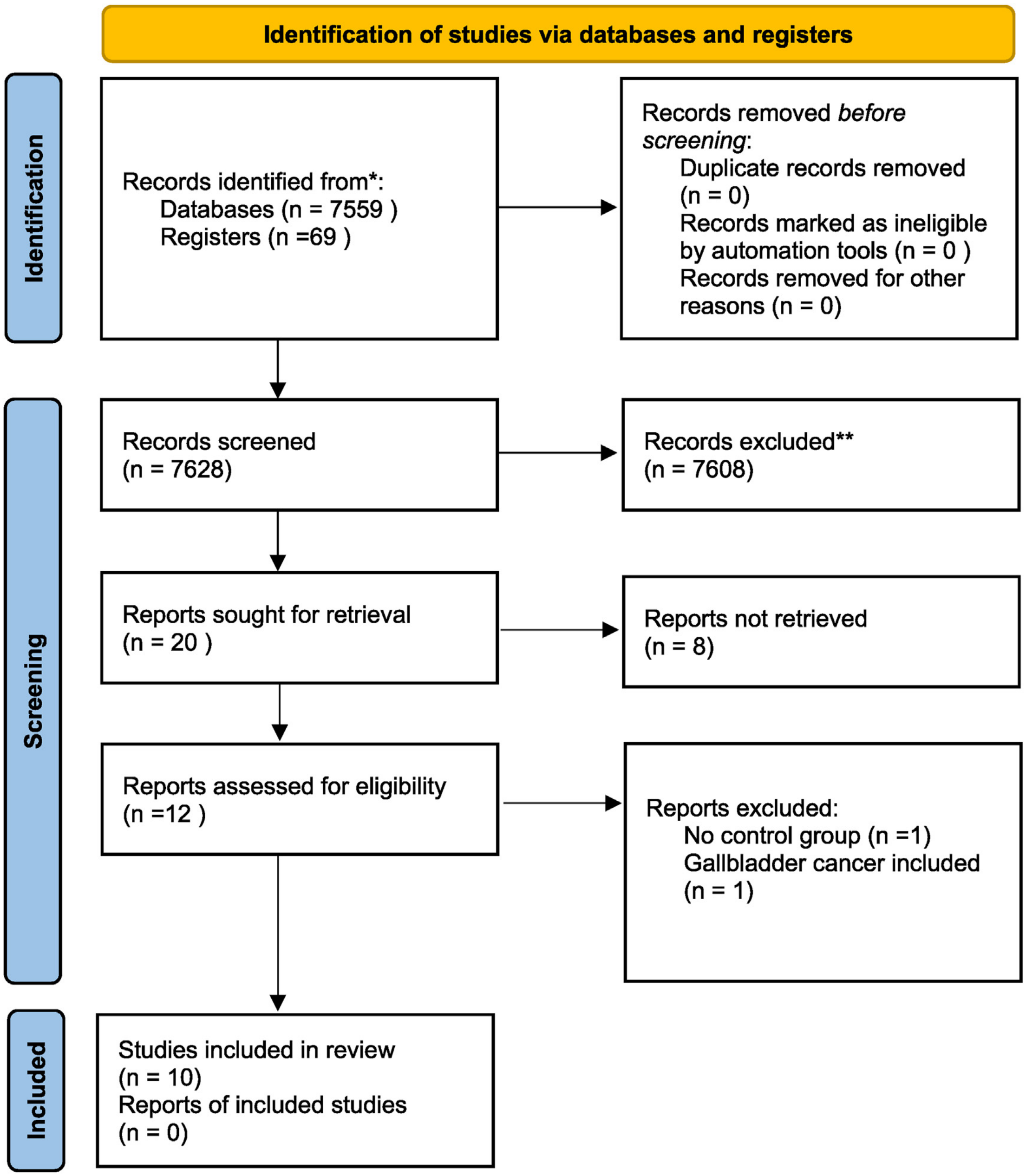


Figure 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

reported standard deviation of the mean. No meta-analysis was performed on 30-day mortality as only the study from Schimizzi *et al.*[27] reported on this outcome. Also, only the study Matsuyama *et al.*[24] reported on 90-day mortality, not allowing a meta-analysis on this outcome. No study reported on 100-day mortality. No subgroup analysis for patients with portal vein resection was performed as no data differentiating which patients in the AR group had a vein resection were provided. In addition, no subgroup analysis on patients who had undergone neoadjuvant chemotherapy prior to resection was performed, as only one study reported on this subject. Regarding adjuvant chemotherapy three studies did not report on this outcome.[20,21,23] Three studies reported that patients did not receive adjuvant chemotherapy.[19,22,25] From four studies that included patients undergoing adjuvant chemotherapy, only three reported on rates.[24,26–28] In these three studies, patients undergoing arterial resection received more frequently adjuvant treatment as compared to patients in the No AR group (AR: 98/202 patients, 49%, No AR: 242/981 patients, 25%, $p < 0.05$).

Weighted median survival was 30.4 months in the AR group and 42 months in the control group (data from five studies). Regarding blood loss, a favorable mean difference for the

Table 1 Descriptive data from the included studies

Study	Group/Sample Size	Inclusion Period	Country	Median follow up (months)
Miyazaki *et al*., 2007	AR n = 9	1981–2004	Japan	–
	No AVR n = 118			
	VR n = 34			
Igami *et al*., 2009	AR n = 53	2001–2008	Japan	–
	No AVR n = 176			
	VR n = 69			
Yu *et al*., 2014	AR n = 47	1998–2010	China	–
	No AVR n = 166			
	VR = 25			
Wang *et al*., 2015	AR = 24	2005–2012	China	–
	No AVR = 114			
	VR = 16			
Matsuyama *et al*., 2016	AR n = 44	1992–2014	Japan	38.2
	No AVR n = 74			
	VR n = 54			
Noji *et al*., 2016	AR n = 28	2000–2015	Japan	–
	No AR n = 181			
Peng *et al*., 2016	AR n = 26	2005–2012	China	18
	No AR n = 35			
Schimizzi *et al*., 2017	AR n = 12	1998–2015	USA	22
	No AVR = 170			
	VR n = 19			
Higuchi *et al*., 2018	AR n = 19	2000–2016	Japan	–
	No AVR n = 174			
	VR n = 56			
Mizuno *et al*., 2020	AR n = 146	2001–2018	Japan	59
	No AVR n = 484			
	VR n = 157			

AR: arterial resection; AVR: arterial and venous resection; VR: venous resection

control group could be verified, but the result was not statically significant (221.95, 95% CI [−229.77, 673.68], p = 0.34) (Fig. 2).

Concerning in-hospital mortality, this meta-analysis showed higher mortality rates in the AR group compared to the control group (6.8% vs 3.3%, OR 2.65, 95% CI [1.27; 5.32], p = 0.009) (Fig. 3). In this meta-analysis regarding morbidity, higher rates were observed in the AR group (55% vs 46%, OR 1.44, 95% CI [0.67; 3.09], p = 0.003) (Fig. 4a). In this meta-analysis regarding morbidity defined as Clavien-Dindo classification ≥ 3, statically significant higher rates could be verified in the AR group (52% vs 47%, OR 1.44, 95% CI [1.02; 1.75], p = 0.04) (Fig. 4b). Six studies reported on vascular complications, with lower rates in the control group (13% vs 5%, OR 3.53, 95% CI [2.26; 5.53, $p < 0.00001$) (Fig. 5). Liver failure rates were higher in the AR group, but the difference was not statically significant (26% vs 16%, OR 2.50, 95% CI [0.95; 6.54, p = 0.06) (Fig. 6). Postoperative bleeding was more frequent in the AR group (4% vs 2%, OR 2.19, 95% CI [1.06; 4.52, p = 0.03) (Fig. 7).

Concerning actuarial survival, 1-year, 3-year and 5-year survival rates were lower in the AR group compared to the control group, respectively (54% vs 69%, OR 0.55, 95% CI [0.34; 0.91 p = 0.02) (Fig. 8), (34% vs 38%, OR 0.74, 95% CI [0.55; 0.98, p = 0.03) (Fig. 9), (18% vs 29%, OR 0.54, 95% CI [0.39; 0.75, p = 0.0002) (Fig. 10).

R0 resection rates were slightly higher in the control group, but the difference was not statistically significant (68% vs 75%, OR 0.70, 95% CI [0.46; 1.07, p = 0.10) (Fig. 11).

Table 2 Patient and operation characteristics from the include studies

Study	Group	Age (Mean ± SD)	Gender (Male) (%)	ASA (3 and 4) %	ECOGPS	Preoperative chemotherapy (%)	Type of operation	Type of vessel resection and reconstruction	Duration of surgery (min)	Blood loss (mL)
Miyazaki et al., 2007	AR n = 9	59 ± 9	78	–	–	–	Hepatectomy	HA	–	1726 ± 1253
	No AVR n = 118	65 ± 11	63	–	–	–	Hepatectomy	–	–	1523 ± 1147
	VR n = 34	64 ± 9	53	–	–	–	Hepatectomy	PV, HV and IVC	–	1975 ± 1474
Igami et al., 2009	AR n = 53	–	–	–	–	–	Hepatectomy	HA	–	–
	No AVR n = 176	–	–	–	–	–	Hepatectomy	–	–	–
	VR n = 69	–	–	–	–	–	Hepatectomy	PV	–	–
Yu et al., 2014	AR n = 47	–	–	–	–	–	Hepatectomy	HA	–	–
	No AVR n = 166	–	–	–	–	–	Hepatectomy	–	–	–
	VR = 25	–	–	–	–	–	Hepatectomy	PV	–	–
Wang et al., 2015	AR = 24	60 ± 9	75	–	–	–	Hepatectomy	HA, Vein graft, E–E Anastomosis	–	1175 ± 713
	No AVR = 114	57 ± 12	61	–	–	–	Hepatectomy	–	–	527 ± 596
	VR = 16	53 ± 7	25	–	–	–	Hepatectomy	PV E–E Anastomosis	–	980 ± 511
Matsuyama et al., 2016	AR n = 44	69	61	–	–	–	Trisectionectomy, Hemihepatectomy, Caudate lobectomy, bile duct resection, Pancreatoduodenectomy	HA E–E Anastomosis	914 ± 148	2212 ± 2192
	No AVR n = 74	69	74	–	–	–	Trisectionectomy, Hemihepatectomy, Caudate lobectomy, bile duct resection, Pancreatoduodenectomy	–	703 ± 134	1929 ± 1387
	VR n = 54	70	72	–	–	–	Trisectionectomy, Hemihepatectomy, Caudate lobectomy, bile duct resection, Pancreatoduodenectomy	PV E–E Anastomosis, Interposition	773 ± 128	1981 ± 1926
Noji et al., 2016	AR n = 28	67	71	–	–	–	Hepatectomy	HA	771	1930
	No AR n = 181	69	71	–	–	–	Hepatectomy	–	638	1750
Peng et al., 2016	AR n = 26	59 ± 7	69	–	–	–	Left Hepatectomy	HA	–	327 ± 146
	No AR n = 35	63 ± 7	57	–	–	–	Left Hepatectomy	–	–	400 ± 209
Schimizzi et al., 2017	AR n = 12	52	50	67	–	25	Right and Left hepatectomy, Caudate resection	RHA, LHA, Vein Graft	–	2100
	No AVR n = 170	66	40	71	–	4	Radical Cholecystectomy, Right and Left hepatectomy, Pancreaticoduodenectomy, Caudate resection	–	–	1011
	VR n = 19	62	53	89	–	5	Right and Left hepatectomy, Caudate resection	PV, Venous/ Prosthetic Patch/Conduit	–	1020
Higuchi et al., 2018	AR n = 19	67	63	–	–	–	Hepatectomy	HA	520	1580
	No AVR n = 174	70	72	–	–	–	Hepatectomy	–	389	1234
	VR n = 56	69.5	68	–	–	–	Hepatectomy	PV	415	1364

Table 2 (*continued*)

Study	Group	Age (Mean ± SD)	Gender (Male) (%)	ASA (3 and 4) %	ECOGPS	Preoperative chemotherapy (%)	Type of operation	Type of vessel resection and reconstruction	Duration of surgery (min)	Blood loss (mL)
Mizuno et al., 2020	AR n = 146	67	49	–	–	–	Hepatectomy, combined pancreatoduodenectomy	HA, E–E Anastomosis, Graft, rotating artery	685	1491
	No AVR n = 484	69	67	–	–	–	Hepatectomy, combined pancreatoduodenectomy	–	550	1078
	VR n = 157	67	68	–	–	–	Hepatectomy, combined pancreatoduodenectomy	PV,E–E Anastomosis, Graft, direct suture	610	1498

AR: arterial resection; No AVR: no arterial and venous resection; VR: venous resection; ASA: American Society of Anesthesiologists classification; ECOGPS: Eastern Cooperative Oncology Group performance status

Study	Group	Mortality in-hospital (%)	Mortality 30-day (%)	Mortality 90-day (%)	Mortality 100-day (%)	Morbidity (%)	Morbidity – Clavien Dindo III-V (%)	Vascular complications (%)	Liver failure (%)	Postoperative bleeding (%)	Reoperation rate (%)	Mean survival (Months)	Median survival (Months)
Miyazaki et al., 2007	AR = 9	33	–	–	–	78	–	11	–	11	–	–	7
	No AVR = 118	4	–	–	–	36	–	4	–	4	–	–	–
	VR = 34	9	–	–	–	38	–	3	–	3	–	–	11
Igami et al., 2009	AR n = 53	–	–	–	–	–	–	–	–	–	–	–	–
	No AVR n = 176	–	–	–	–	–	–	–	–	–	–	–	–
	VR n = 69	–	–	–	–	–	–	–	–	–	–	–	–
Yu et al., 2014	AR n = 47	–	–	–	–	40.4	–	–	–	–	–	–	–
	No AVR n = 166	–	–	–	–	12.1	–	–	–	–	–	–	–
	VR = 25	–				32	–	–	–	–	–	–	–
Wang et al., 2015	AR = 24	4	–	–	–	41.7	–	4	–	4	–	–	26
	No AVR = 114	4	–	–	–	35.1	–	2	–	2	–	–	32
	VR = 16	0	–	–	–	37.5	–	0	–	0	–	–	20
Matsuyama et al., 2016	AR n = 44	9	–	9	–	81.8	66	14	11	7	–	–	–
	No AVR n = 74	4	–	4	–	82.4	49	8	8	3	–	–	–
	VR n = 54	3.7	–	3.7	–	70.3	43	6	7	4	–	–	–
Noji et al., 2016	AR n = 28	3.6	–	–	–	–	57.1	–	31	9	–	–	–
	No AR n = 181	6.6	–	–	–	–	51.3	–	32	7	–	–	–
Peng et al., 2016	AR n = 26	7.7	–	–	–	42.9	19	0	12	0	–	–	49
	No AR n = 35	8.6	–	–	–	57.7	14	0	6	0	–	–	24
Schimizzi et al., 2017	AR n = 12	–	0	–	–	50	67	–	0	–	–	–	33
	No AVR = 170	–	7	–	–	69	61	–	4	–	–	–	21
	VR n = 19	–	16	–	–	68	47	–	16	–	–	–	24
Higuchi et al., 2018	AR n = 19	16	–	–	–	–	47	26	–	5.3	–	–	–
	No AVR n = 174	1.7	–	–	–	–	33	3	–	1.7	–	–	–
	VR n = 56	5.4	–	–	–	–	45	13	–	1.8	–	–	–
Mizuno et al., 2020	AR n = 146	4	–	–	–	–	51	16	34	1.4	–	–	29
	No AVR n = 484	1	–	–	–	–	48	3	22	0.4	–	–	61
	VR n = 157	3	–	–	–	–	48	10	34	1.3	–	–	34

AR: arterial resection; No AVR: no arterial and venous resection; VR: venous resection;

Study	Group	1-year survival (%)	2-year survival (%)	3-year survival (%)	5-year survival (%)	Adjuvant chemotherapy (Yes/No//%)	R0 (%)	R1 (%)	R2 (%)	No resection (%)	pTNM
Miyazaki et al., 2007	AR = 9	11	–	11	0	No	67	–	–	–	–
	No AVR = 118	–	–	–	–	No	65	–	–	–	–
	VR = 34	42	0	16	13	No	56	–	–	–	–
Igami et al., 2009	AR n = 53	66	–	15	4	No	–	–	–	–	–
	No AVR n = 176	74	–	34	14	No	–	–	–	–	–
	VR n = 69	62	–	17	7	No	–	–	–	–	–
Yu et al., 2014	AR n = 47	40	–	19.1	6.4	–	–	–	–	–	–
	No AVR n = 174	62.6	–	27.6	21.8	–	–	–	–	–	–
	VR = 25	48	–	20	0	–	–	–	–	–	–
Wang et al., 2015	AR = 24	–	–	–	25	–	–	–	–	–	–
	No AVR = 114	–	–	–	35.7	–	–	–	–	–	–
	VR = 16	–	–	–	25	–	–	–	–	–	–
Matsuyama et al., 2016	AR n = 44	–	–	–	22	45.4	80	20	0	–	–
	No AVR n = 74	–	–	–	46	12.1	74	26	0	–	–
	VR n = 54	–	–	–	51	51.8	80	20	0	–	–
Noji et al., 2016	AR n = 28	61	–	36	18	–	71	–	–	–	–
	No AR n = 181	80	–	54	27	–	81	–	–	–	–
Peng et al., 2016	AR n = 26	61.9	41.6	29.7	14.8	No	72.3	–	–	–	–
	No AR n = 35	58.2	50.7	44.3	23.6	No	80	–	–	–	–
Schimizzi et al., 2017	AR n = 12	–	–	–	–	53	67	33	0	–	–
	No AVR = 170	–	–	–	–	53	70	30	0	–	–
	VR n = 19	–	–	–	–	42	74	26	0	–	–
Higuchi et al., 2018	AR n = 19	–	–	–	14.5	Yes	63	37	0	0	–
	No AVR n = 174	–	–	–	45.8	Yes	66	34	0	0	–
	VR n = 56	–	–	–	21	Yes	63	37	0	0	–
Mizuno et al., 2020	AR n = 146	–	–	45	27	49	64	36	1	–	–
	No AVR n = 484	–	–	53	35	9	85	14	1	–	–
	VR n = 157	–	–	32	18	40	69	27	4	–	–

AR: arterial resection; No AVR: no arterial and venous resection; VR: venous resection; Proportion of macroscopically complete (R0), microscopically incomplete (R1), and macroscopically incomplete (R2) resection; histopathological tumor stage (pTNM)

Regarding adjuvant chemotherapy

Study	Group	Proportion of patients with histologically confirmed arterial tumor invasion (%)	Mean of tumor-positive lymph nodes and of retrieved lymph nodes	Median of tumor-positive lymph nodes and of retrieved lymph nodes
Miyazaki et al., 2007	AR = 9	–	–	–
	No AVR = 118	–	–	–
	VR = 34	–	–	–
Igami et al., 2009	AR n = 53	–	–	–
	No AVR n = 176	–	–	–
	VR n = 69	–	–	–
Yu et al., 2014	AR n = 47	–	–	–
	No AVR n = 174	–	–	–
	VR = n = 25	–	–	–
Wang et al., 2015	AR = 24	–	–	–
	No AVR = 114	–	–	–
	VR = 16	–	–	–

Table 2 (*continued*)

Study	Group	Proportion of patients with histologically confirmed arterial tumor invasion (%)	Mean of tumor-positive lymph nodes and of retrieved lymph nodes	Median of tumor-positive lymph nodes and of retrieved lymph nodes
Matsuyama et al., 2016	AR n = 44	32	–	–
	No AVR n = 74	7	–	–
	VR n = 54	9	–	–
Noji et al., 2016	AR n = 28	22	–	–
	No AR n = 181	12	–	–
Peng et al., 2016	AR n = 26	–	–	–
	No AVR n = 35	–	–	–
Schimizzi et al., 2017	AR n = 12	–	–	–
	No AVR = 170	–	–	–
	VR n = 19	–	–	–
Higuchi et al., 2018	AR n = 19	–	–	–
	No AVR n = 174	–	–	–
	VR n = 56	–	–	–
Mizuno et al., 2020	AR n = 146	–	–	–
	No AVR n = 484	–	–	–
	VR n = 157	–	–	–

AR: arterial resection; No AVR: no arterial and venous resection; VR: venous resection.

Table 3 Risk of bias assessed using the ROBINS-I tool (risk of bias in non-randomized studies of interventions)[8]

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Miyazaki et al. 2007	Moderate: Difference between three resection groups analysed and reported	Low: Included eligible patients defined, baseline characteristics, intervention and follow up same	Low: Intervention (vascular resection) defined for all patient/ groups	Low: Single intervention of interest (vascular resection)	Low: Reasons for missing (not included) reported	Serious: Operative morbidity not defined, Survival stated and reported	Serious: Operative morbidity and mortality stated in analysis and reported, operative morbidity not defined before analysis (classification or something)- > several postop complications reported
Igami et al. 2009	Moderate: Patients have been divided into three groups (retrospective) and no differences between groups have been reported	Low: Included eligible patients defined, baseline characteristics, intervention and follow up same	Low: All surgery approaches for different groups stated and performed in the same hospital (assuming the same team/ surgeon)	Low: Intervention stated as surgical resection with curative intent - > single intervention	Low: Missings (death) stated and regression analysis accordingly	Serious: Morbidity and mortality reported (absolute and %), survival reported Both outcomes not defined beforehand Morbidity not defined beforehand	Moderate
Yu et al. 2014	Moderate: Difference among predefined groups analysed and stated (p511)	Moderate: in and exclusion criteria stated, predefined groups observed according to differences	Low: Intervention stated as vascular resection in surgical	Low: Single intervention of interest (vascular resection)	Low: missings stated (death during surgery) IPD and aggregated data pooled for	serious: Complications stated and reported as outcome but not defined	Moderate

(*continued on next page*)

Table 3 (*continued*)

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
			management of HCCA for all participants		outcomes (complications and long-term survival)		
Wang et al. 2015	Moderate: Difference between three resection groups analysed and reported	Low: All patients with resectable hilar cholangiocarcinoma have been included	Low: Surgical intervention for all patients, stated and reported	Low: Resection and reconstruction approaches reported (Table 1)	Low: Missings/death reported and analysed via Kaplan-Maier	Low: Outcome measures defined and reported accordingly	Low: Outcomes predefined and reported
Matsuyama et al. 2016	Low: Patients divided into three groups - > characteristics compared (including p-Values) - > no differences between groups	Low: All eligible patients included	Low: Surgery with curative intent, procedures reported	Low: Intervention stated as surgical resection with curative intent - > single intervention	Low: Missings/death reported and analysed	Low: Outcome measurements defined and reported accordingly	Low: outcomes which have been reported have been beforehand
Noji et al. 2016	Low: Analysis for potential cofounders stated defined before analysis	Low: Eligible patient included, exclusion reported	Low: Surgical approach reported and the same with all patients	Low: Intervention stated as surgical resection with curative intent - > single intervention	Low: Missing reported, Potentially confounding analysed via binary logistic regression	Low: Survival, morbidity and mortality according to Calvien-Dindo pre-defined outcomes have been reported based on definition	Low: Survival, morbidity and mortality according to Calvien-Dindo pre-defined outcomes have been reported
Peng et al. 2016	Low: Patients divided into two groups - > characteristics compared (including p-Values) - > no differences between groups	Low: All patients undergoing radical left hepatectomy for hilar cholangiocarcinoma have been included in the study	Low: Intervtion the same for all patients	Low: Single intervention for all patients, surgical procedure reported, differences and reasons why are stated	Low: Missings/deaths reported and reported (Kapla-Maier)	Low: Outcome measurements defined and reported accordingly	Low: outcomes which have been reported have been beforehand
Schimizzi et al. 2018	Low: potential confounder stated and collected (age, race comorbidities); statistical analysis described but not specifically focused on confounding	Low: Included eligible patients defined, baseline characteristics, intervention and follow up same	Low: Intervention status stated (Table 2A)	Low: Single intervention of interest (Vascular resection)	Low: OS and RFS stated as outcome and reported	Moderate: OS defined and RFS defined	Low
Higuchi et al. 2018	Moderate: Patient groups have been analysed regarding differences before intervention (surgery), p-value have been reported too	Low: Included eligible patients defined, baseline characteristics, intervention and follow up same	Low: Surgical approach reported and all included patients	Low: Intervention same for all patients, HARs performed by general surgeon and changed to plastic surgeons due to more experience in microscopic surgery (calculations done and stated with and without patients undergoing intervention by general surgeon)	Low: uni and multivariate analysis of outcomes, all analysis reported	Moderate: Outcome measurement appropriate and could not be influenced by knowledge of intervention received	Moderate

Table 3 (*continued*)

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Mizuno et al. 2020	Low: Patients divided into two groups and two subgroups (for patients with VR) - > characteristics compared (including p-Values) - > no differences between groups	Low: Eligible patient included, exclusion reported	Low: Surgical procedure stated and the same except intervention of VR	Low: intervention VR can be deviated ("control": no VR)	Low: Missings/deaths reported and reported (Kapla-Maier)	Moderate: OS defined beforehand and reported accordingly, all other outcomes stated (no definition e.g. TNM etc)	Moderate

Discussion

In this systematic review and meta-analysis, we have assessed the impact of arterial resection in surgery for cholangiocarcinoma. Most patients with perihilar cholangiocarcinoma present with unresectable disease and have a poor survival. Adjuvant chemotherapy provides significant improvement in overall survival with any adjuvant therapy after surgery compared with surgery only (HR 0.74; 95% CI, 0.67 to 0.83; P < 0.001).[29] Nevertheless, sensitivity and response to chemotherapy is generally rather poor. In most patients, liver transplantation is not a viable option due to the highly selective criteria. Therefore, complete surgical resection offers the only chance of cure or at least longer-term survival. In a previous meta-analysis on the topic published in 2013, resection of the hepatic artery in surgery for cholangiocarcinoma was shown to have higher morbidity and mortality rates.[30] The authors concluded that arterial resection has no proven benefit. Since the publication of the mentioned meta-analysis, several larger studies on the topic have been published, which was the motivation for us to conduct the present systematic review with meta-analysis. In contrast to the previous study, we only performed an analysis on arterial resections and only included studies reporting exclusively on cholangiocarcinoma. We also provide an extended analysis on multiple outcomes specifically regarding arterial resection. Furthermore, only studies with a control group were included.

Our results mostly corroborate those of the previous meta-analysis. Morbidity and mortality rates, although deemed acceptable in absolute terms, were shown to be substantially higher for AR while AR did not result in a higher probability of microscopically complete resection and long-term survival was shorter. Given the non-randomized design of all included studies, which implies a considerable selection bias, these findings do not necessarily mean that AR is detrimental to long-term survival in patients which would otherwise not be resected at all but only receive palliative treatment. To provide a valid information on the value of AR in such patients, a randomized controlled trial would be necessary. It needs to be noted that in the included studies, there was no clear differentiation if AR was planned a priori or performed due to intraoperative injury of the hepatic artery. An indication for the latter could be that histological arterial invasion was shown in only 28% of patients in the AR group in the studies where it was reported.[23,24]

Neoadjuvant chemotherapy might improve resectability and outcomes for patients with locally advanced cholangiocarcinoma and several clinical trials are currently evaluating its role for the treatment of cholangiocarcinoma However, results will be available only in several years from now. In our analysis, only the study by Schimizzi et al.[27] reported on neoadjuvant chemotherapy with a higher proportion of patients who underwent neoadjuvant chemotherapy in the AR group. Interestingly, a higher median survival was observed in the AR group when compared to patients who underwent combined arterial and venous resection or venous resection alone (33, 21 and 24 months, respectably).

In addition to neoadjuvant or perioperative chemotherapy alone, chemotherapy combined with transplantation may be an alternative for patients with arterial invasion. According to the guidelines of the British Society of Gastroenterology, a liver transplantation may be considered in highly selected patients in specialized centers after neoadjuvant chemotherapy.[31] Similarly, the guidelines of the European Association for the Study of the Liver (EASL) state that in patients with neoadjuvant therapy concepts, liver transplantation may be considered.[32] In a study involving patients from 10 US hospitals that compared transplantation with resection for hilar cholangiocarcinoma, among all patients who underwent curative-intent surgery, transplantation was associated with improved 5-year survival (64% vs 18%). Of note, many of the transplant cases in the aforementioned study were relatively early stage cholangiocarcinomas, and many of them were cases of sclerosing cholangitis, making a direct comparison to our patient collective not possible.[33] A meta-analysis from 2012, which included 14 studies, addressed the efficacy and safety of liver transplantation in patients with cholangiocarcinoma. Neoadjuvant therapies provided better outcomes with OR for 1-, 3- and 5-year pooled survival of OR 0.83 (95% CI = 0.57–0.98), OR 0.57 (95% CI = 0.18–0.92) and OR 0.65 (95% CI = 0.40–0.87).[34] In a prospective study involving 21 patients who underwent liver transplantation after

Study or Subgroup	AR Mean	AR SD	AR Total	No AR Mean	No AR SD	No AR Total	Weight	Mean Difference IV, Random, 95% CI
Matsuyama 2016	2,212	2,192	44	1,951	1,629	128	19.1%	261.00 [−445.49, 967.49]
Miyazaki 2007	1,726	1,253	9	1,624	1,237	34	14.5%	102.00 [−816.16, 1020.16]
Peng 2016	327	146	26	400	209	35	35.5%	−73.00 [−162.13, 16.13]
Wang 2015	1,175	713	24	583	603	130	30.9%	592.00 [288.50, 895.50]
Total (95% CI)			**103**			**327**	**100.0%**	**221.95 [−229.77, 673.68]**

Heterogeneity: $Tau^2 = 147720.16$; $Chi^2 = 17.64$, df = 3 (P = 0.0005); $I^2 = 83\%$
Test for overall effect: Z = 0.96 (P = 0.34)

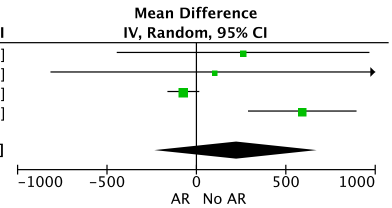


Figure 2 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding blood loss. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

Study or Subgroup	AR Events	AR Total	No AR Events	No AR Total	Weight	Odds Ratio M-H, Random, 95% CI
Higuchi 2018	3	19	6	230	15.5%	7.00 [1.60, 30.62]
Matsuyama 2016	4	44	5	138	17.3%	2.66 [0.68, 10.38]
Miyazaki 2007	3	9	8	152	14.4%	9.00 [1.89, 42.75]
Mizuno 2020	6	146	10	641	23.6%	2.70 [0.97, 7.56]
Noji 2016	1	28	12	181	9.4%	0.52 [0.07, 4.18]
Peng 2016	2	26	3	35	11.1%	0.89 [0.14, 5.74]
Wang 2015	1	24	5	130	8.6%	1.09 [0.12, 9.74]
Total (95% CI)		**296**		**1507**	**100.0%**	**2.60 [1.27, 5.32]**
Total events	20		49			

Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 8.78$, df = 6 (P = 0.19); $I^2 = 32\%$
Test for overall effect: Z = 2.62 (P = 0.009)

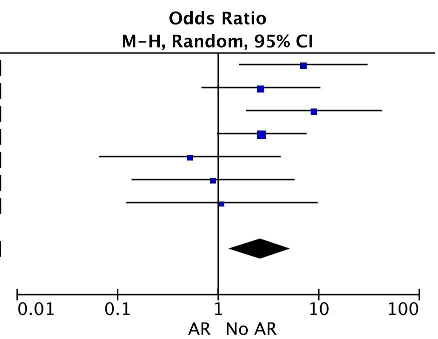
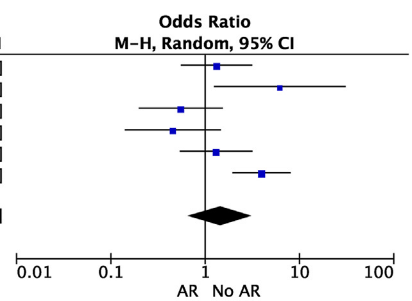


Figure 3 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding mortality. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

a

Study or Subgroup	AR Events	AR Total	No AR Events	No AR Total	Weight	Odds Ratio M-H, Random, 95% CI
Matsuyama 2016	36	44	99	128	18.3%	1.32 [0.55, 3.15]
Miyazaki 2007	7	9	55	152	11.7%	6.17 [1.24, 30.76]
Peng 2016	11	26	20	35	16.7%	0.55 [0.20, 1.54]
Schimizzi 2017	6	12	130	189	15.3%	0.45 [0.14, 1.47]
Wang 2015	10	24	46	130	18.1%	1.30 [0.54, 3.17]
Yu 2014	19	47	28	191	19.9%	3.95 [1.95, 8.01]
Total (95% CI)		**162**		**825**	**100.0%**	**1.44 [0.67, 3.09]**
Total events	89		378			

Heterogeneity: $Tau^2 = 0.64$; $Chi^2 = 17.98$, df = 5 (P = 0.003); $I^2 = 72\%$
Test for overall effect: Z = 0.93 (P = 0.35)



b

Study or Subgroup	AR Events	AR Total	No AR Events	No AR Total	Weight	Odds Ratio M-H, Random, 95% CI
Higuchi 2018	9	19	82	230	8.3%	1.62 [0.63, 4.16]
Matsuyama 2016	29	44	59	128	14.5%	2.26 [1.11, 4.62]
Mizuno 2020	75	146	307	641	57.0%	1.15 [0.80, 1.65]
Noji 2016	16	28	94	181	11.4%	1.23 [0.55, 2.76]
Peng 2016	5	26	5	35	4.0%	1.43 [0.37, 5.56]
Schimizzi 2017	8	12	113	189	4.8%	1.35 [0.39, 4.62]
Total (95% CI)		**275**		**1404**	**100.0%**	**1.34 [1.02, 1.75]**
Total events	142		660			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.97$, df = 5 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 2.10 (P = 0.04)

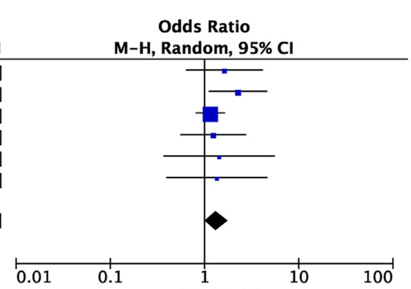


Figure 4 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding morbidity. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

Study or Subgroup	AR Events	AR Total	No AR Events	No AR Total	Weight	Odds Ratio M-H, Random, 95% CI
Higuchi 2018	5	19	13	230	14.8%	5.96 [1.86, 19.10]
Matsuyama 2016	6	44	9	128	16.7%	2.09 [0.70, 6.24]
Miyazaki 2007	1	9	6	152	4.0%	3.04 [0.33, 28.38]
Mizuno 2020	23	146	31	641	61.1%	3.68 [2.07, 6.53]
Peng 2016	0	26	0	36		Not estimable
Wang 2015	1	24	2	130	3.4%	2.78 [0.24, 31.96]
Total (95% CI)		**268**		**1317**	**100.0%**	**3.53 [2.26, 5.53]**
Total events	36		61			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.75$, df = 4 (P = 0.78); $I^2 = 0\%$
Test for overall effect: Z = 5.52 (P < 0.00001)

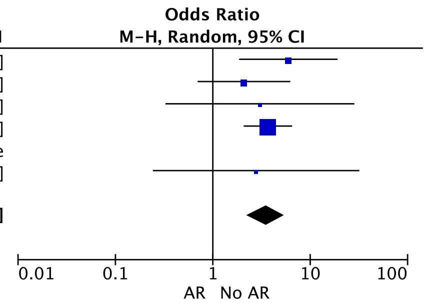


Figure 5 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding vascular complications. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

Study or Subgroup	AR Events	AR Total	No AR Events	No AR Total	Weight	Odds Ratio M-H, Random, 95% CI
Matsuyama 2016	5	44	10	128	22.7%	1.51 [0.49, 4.70]
Mizuno 2020	50	146	159	641	31.5%	1.58 [1.07, 2.32]
Noji 2016	9	28	6	181	22.7%	13.82 [4.43, 43.04]
Peng 2016	3	26	2	35	14.8%	2.15 [0.33, 13.92]
Schimizzi 2017	0	12	10	189	8.3%	0.68 [0.04, 12.36]
Total (95% CI)		**256**		**1174**	**100.0%**	**2.50 [0.95, 6.54]**
Total events	67		187			

Heterogeneity: $Tau^2 = 0.73$; $Chi^2 = 13.28$, df = 4 (P = 0.01); $I^2 = 70\%$
Test for overall effect: Z = 1.86 (P = 0.06)

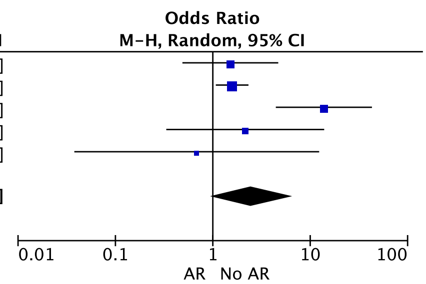


Figure 6 Forest plot of pooled odds ratio with 95% CI for AR vs no AR liver failure. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

neoadjuvant chemotherapy, overall survival was 100% (95% CI 100-100) at 1 year, 83.3% (27.3–97.5) at 3 years, and 83.3% (27.3–97.5) at 5 years.[35] None of the studies included in our meta-analysis reported on a liver transplantation group. A probable limitation of studies addressing this question is that only few patients qualify for liver transplantation due to the very strict indication criteria.[36]

This meta-analysis has some limitations. The main drawback is that it is exclusively based on retrospective studies with heterogeneous outcome definitions and study-arms. The retrospective study design could also represent a problem in terms of selection bias. The long inclusion period does not necessary reflect contemporary surgical techniques. The results are based on a non-randomized, uncontrolled comparison of patients with

Study or Subgroup	AR Events	AR Total	No AR Events	No AR Total	Weight	Odds Ratio M-H, Random, 95% CI
Higuchi 2018	1	19	4	230	10.4%	3.14 [0.33, 29.58]
Matsuyama 2016	3	44	4	128	22.2%	2.27 [0.49, 10.56]
Miyazaki 2007	1	9	6	152	10.5%	3.04 [0.33, 28.38]
Mizuno 2020	2	146	4	641	18.0%	2.21 [0.40, 12.19]
Noji 2016	3	28	13	181	30.0%	1.55 [0.41, 5.83]
Peng 2016	0	26	0	35		Not estimable
Wang 2015	1	24	2	130	8.8%	2.78 [0.24, 31.96]
Total (95% CI)		**296**		**1497**	**100.0%**	**2.19 [1.06, 4.52]**
Total events	11		33			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.49$, df = 5 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 2.12 (P = 0.03)

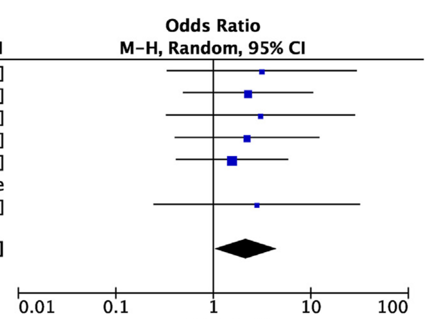


Figure 7 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding postoperative bleeding. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

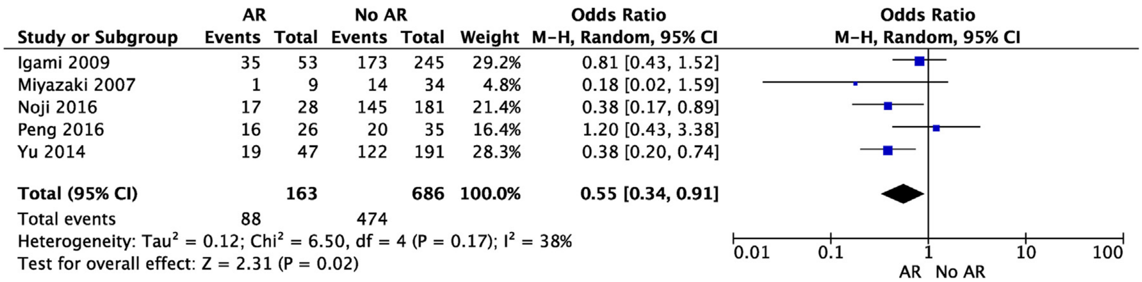


Figure 8 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding 1-year survival. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

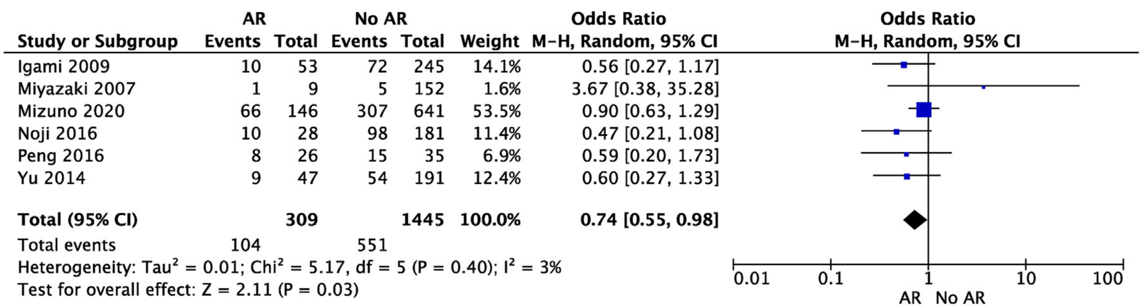


Figure 9 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding 3-year survival. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

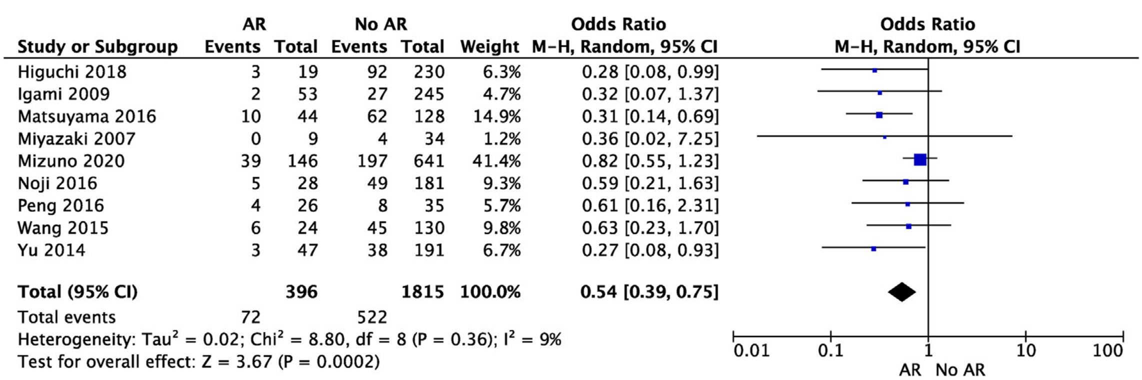


Figure 10 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding 5-year survival. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

different backgrounds. There was no clear distinction across all the studies concerning potential differences between groups receiving adjuvant therapy. Since individual patient data were not available, it is not possible to estimate the effects of adjuvant chemotherapy on outcome in this group of patients. When reported, more patients in the AR group received adjuvant chemotherapy so that this confounder should be taken in account when interpreting the results. Furthermore, a few of the studies reported on liver resection combined with pancreatic resection.[24,27,28] In these patients, pancreatic resection was performed if the tumor extended distally to the intrapancreatic bile duct or pancreatic head. This heterogeneity is another limitation of the study. The PRISMA guidelines were followed to ensure transparency and standardized reporting, but the risk of

	AR		No AR			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Higuchi 2018	12	19	150	230	13.2%	0.91 [0.35, 2.41]
Matsuyama 2016	35	44	98	128	16.0%	1.19 [0.51, 2.75]
Miyazaki 2007	7	9	97	152	6.0%	1.98 [0.40, 9.89]
Noji 2016	20	28	147	181	14.6%	0.58 [0.23, 1.42]
Peng 2016	19	26	28	35	9.7%	0.68 [0.20, 2.25]
Schimizzi 2017	8	12	133	189	9.2%	0.84 [0.24, 2.91]
Total (95% CI)		**284**		**1556**	**100.0%**	**0.70 [0.46, 1.07]**
Total events	194		1172			

Heterogeneity: Tau² = 0.11; Chi² = 9.30, df = 6 (P = 0.16); I² = 36%
Test for overall effect: Z = 1.64 (P = 0.10)

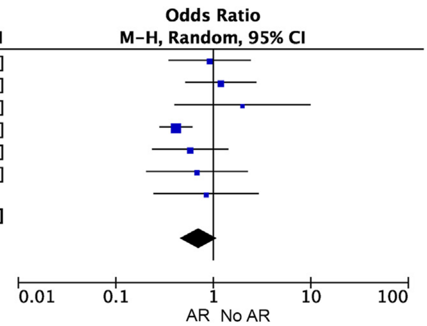


Figure 11 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding R0. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

bias is still considerable. Moreover, the number of studies and patients were relatively small. Therefore, the data should be carefully interpreted, and applied. Further, analysis, e.g. a network-meta-analysis on comparing arterial resections with non-surgical therapies are necessary in the future. The strength of this meta-analysis is that all available studies providing comparative information on the outcome of patients undergoing surgery for cholangiocarcinoma with arterial resection with a control group were included.

Conclusion

Evidence from non-randomized studies shows higher morbidity and mortality rates and shorter long-term survival in patients with cholangiocarcinoma undergoing AR. However, the results are prone to selection bias, and only randomized trials comparing AR with and without neoadjuvant therapy and palliative treatment in patients with cholangiocarcinoma and arterial invasion might reveal a possible benefit of arterial resection.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

AR and MG conducted the literature search. AR conducted the statistical analysis. AR outlined, wrote, and drafted the manuscript. All authors critically revised the manuscript and read and approved the final version of the manuscript.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.04.002.