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Short-term and long-term clinical outcomes of combined major vessel resection for hilar cholangiocarcinoma: a propensity score analysis

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Purpose: In the treatment of hilar cholangiocarcinoma (HCCA), combined resection of important hepatic vessels remains controversial. The purpose of this study was to compare the postoperative complications and prognosis of combined and non-combined major vessel resections in patients undergoing radical resection for HCCA.
Methods: In this study, patients with HCCA who underwent curative resection between January 2007 and December 2018 were retrospectively enrolled. Postoperative complications and prognosis between the groups were compared using propensity score-matching (PSM) analysis.
Results: There were 310 patients included in this study. The portal vein resection (PVR) and hepatic artery resection (HAR) groups had a higher incidence of postoperative complications than the control group. Patients in the HAR group had an increased risk of abdominal and pleural effusion after surgery. Patients who underwent combined PVR had better overall survival (OS; P = 0.020) and disease-free survival (DFS; P = 0.020). After curative-intent resection, patients in the HAR group had improved OS (P = 0.027) and DFS (P = 0.023). The postoperative complications of combined vascular resection (VR) did not worsen long-term survival for patients.
Conclusion: In patients with HCCA, combined VR improved prognosis. The postoperative complications of combined VR do not worsen patient survival. Therefore, radical surgical resection is recommended.
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Key Words: Klatskin tumor, Vessel resection, Postoperative complications, Propensity score, Cohort studies

INTRODUCTION

In spite of its high prevalence, hilar cholangiocarcinoma (HCCA) accounts for more than half of all intrahepatic and extrahepatic cholangiocarcinomas [1]. Surgical resection is the only effective way for patients with HCCA to achieve a better prognosis [2]. Although HCCA grows slowly, its invasive growth around the hepatic hilum leads to vascular involvement at an early stage, making surgical resecti on difficult and increasing the non-R0 resection rate [3]. Currently, patients undergoing R0 resection have a 5-year survival rate of 25%–45%, but if it is not performed, patients have a 5-year survival rate of only 0%–23% [4].

With the advancement of surgical techniques, a growing number of studies have demonstrated that vascular invasion, while unfavorable for prognosis, is not an absolute contraindication for surgical resection. An effective therapeutic outcome can be achieved by resecting and reconstructing the

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portal vein (PV) or hepatic artery (HA) that may be invaded by the tumor [5,6]. Aggressive resection has resulted in a higher R0 resection rate, but combined major vessel resection has also increased the incidence of perioperative complications and mortality [7]. Therefore, the clinical value of combined resection of important hepatic vessels in HCCA remains controversial.

A series of clinical studies on this topic has been published by surgical experts worldwide. However, owing to the specificity of the disease and ethical constraints, the vast majority of studies are still retrospective, and their findings are inevitably subject to various biases. Propensity score-matching (PSM) analysis can reduce bias due to lack of randomization [8]; thus, no study has conducted PSM analysis on this topic. Combined with the conclusions of previous studies, the present study hypothesized that combined vascular resection (VR) would improve the prognosis for patients. At the same time, the cumulative postoperative complications of VR would only modestly worsen long-term survival compared to the benefit from prognosis and should not be an argument to deny combined VR. This single-center retrospective cohort study was conducted to test these hypotheses.

METHODS

Setting

Retrospective data were collected on patients with HCCA who underwent radical resection at West China Hospital, Sichuan University between January 2007 and December 2018. The West China Hospital Ethics Committee approved this study (No. 2022-1774). The preoperative diagnosis of HCCA was based on the biliary tract cancer guidelines by European Society for Medical Oncology in 2023 [9]. All patients signed an informed consent form for surgery before surgery.

Criteria for inclusion and exclusion

This study had the following inclusion criteria: (1) age of >18 years; (2) no contraindication for hepatectomy; (3) radical resection of HCCA at our hospital; and (4) HCCA confirmed by pathology.

As for the exclusion criteria, they were as follows: (1) other primary malignancies besides HCCA; (2) severe dysfunction of vital organs (e.g., heart, kidney, and liver); and (3) patients with palliative surgical resections.

Owing to extensive lymph nodes (LNs) metastasis or 4 or more LNs metastasis in patients with stage IVA, we did not perform extended radical resection for this category of patients. These patients underwent R1 resection in combination with postoperative adjuvant therapy. To more fully summarize the overall situation of the patients, we also included patients with stage IVA who underwent surgery.

Basic characteristics assessment of patients

The preoperative assessment includes basic patient information, clinical laboratory indicators, medical imaging indicators, and data related to postoperative adjuvant chemotherapy. The basic information of the patients mainly included: sex, age, and any other comorbidities (e.g., cardiovascular or respiratory diseases). Preoperative clinical laboratory indicators included serum CA 19-9 (IU/mL), total bilirubin (TB; μmol/L), direct bilirubin (DB; μmol/L), serum albumin (g/L), AST (IU/L), ALT (IU/L), PT (sec), etc. The indicators of medical imaging examination (contrast-enhanced ultrasound, CT, MRI, etc.) include the size, number, location of the malignancy, and the Bismuth type of HCCA [10]. The data related to postoperative adjuvant chemotherapy include adjuvant chemotherapy regimen, number of chemotherapy cycles, and severe toxicity during chemotherapy. When the imaging examination is inconsistent with the pathological examination, the pathological examination shall prevail.

Surgical technique

The scope of radical resection should include the hilar and extrahepatic bile ducts above the pancreas, regional LNs, and the entire block of the partial liver (the caudate lobe was also included). As a general rule, liver resections are classified according to Bismuth type. R0 resection should be accompanied by standardized regional LN dissection [11], including the N1 and N2 stations.

When performing VR, the following criteria are usually taken into account: difficulty separating the vasculature from the tumor, suspicion of blood vessel invasion (malignancies in close proximity to the vasculature on preoperative CT/MRI), and the presence of intraoperative vascular invasion. Conditions without VR include the following: without blood vessel invasion; distant metastasis of malignancies; extensive invasion of vascular contralateral to the tumor; 2 PV branches invaded by the tumor; the tumor extension beyond the second branch of the blood vessel; the longitudinal axis of main PV encircled by extensive tumors with obstruction [3,12].

For instances in which preoperative evaluations did not indicate any encroachment upon the PV, yet intraoperatively revealed mild tumor infiltration within the PV, the surgical intervention encompassed resection of both the PV bifurcations and the left/right branch of the PV [13]. The compromised segment was meticulously subjected to a continuous transverse suturing process to achieve closure. In scenarios wherein the invasion of the PV assumes a more extensive scope [13,14], particularly during hemihepatectomies or extended hemihepatectomies, a circular resection of a segment within the left or right branch of PV is executed, followed by a direct end-to-end anastomosis. When the length of PV resection is >3 cm, artificial vascular reconstruction is employed to reinstate

the physiologic PV blood flow.

For the HA and proper HA invasion, the methods of HA resection (HAR) and HA reconstruction include end-to-end anastomosis of arterial resection performed directly for arterial resection length of <3 cm, arterial resection length of >3 cm, and end-to-end anastomosis of the left gastric artery to the HA. There has been a relatively low incidence of invasions of the left HA because of the spatial separation between it and the confluence of the bile ducts. Therefore, the indications for HAR involved in this study are mainly combined with resection and reconstruction of the proper HA or the right HA [15,16].

Postoperative pathological examination

Microscopic examination of paraffin sections from postoperative specimens is the gold standard for pathological diagnosis. All the specimens from the included patients were histopathologically confirmed by experienced pathologists. TNM stage, differentiation, tumor diameter, full-thickness bile duct wall invasion, LN metastasis, vascular tumor thrombus, liver parenchymal invasion, liver capsule invasion, and nerve invasion were examined pathologically. The R0 resection margins must be tumor-free on both macroscopic and microscopic inspection. The HCCA is staged using the 8th edition of the American Joint Committee on Cancer classification [17].

Postoperative complications and short-term outcomes

Surgery-related short-term clinical outcomes included total blood loss recorded in the surgical records, blood transfusion, and duration of surgery. An examination of liver function and routine blood tests were done on day 1, day 3, day 5, and day 7 after surgery to detect postoperative liver failure, jaundice, postoperative hemorrhage or infection. For patients with infection symptoms, ultrasonography or chest and abdomen CT were used to further check the cause of infection (pulmonary infection, abdominal infection, or biliary-enteric anastomotic fistula, etc.). A daily physical examination was performed to check for biliary leakage, ascites, gastrointestinal obstruction, pleural effusion, and incision infection. In addition, we also recorded the occurrence of some rare complications in patients (e.g., thoracic chylous effusion, acute renal insufficiency, acute left heart failure, etc.), the incidence of secondary procedures during hospitalization, and information related to the length of stay.

In this study, our definition of postoperative liver failure follows "50-50 criteria" [18]. The occurrence of postoperative ascites was defined according to the daily abdominal drainage volume (>500 mL per day over a period of 3 days) after operation [19]. A progressive drop in hemoglobin levels over 30 g/L was defined as postoperative hemorrhage following hepatectomy [20]. For 3 days or more after an operation, bile leakage is considered if the bilirubin level in the peritoneal drainage fluid is greater than 3 times the serum level [21].

Follow-up program and long-term outcomes

Patients are followed up within 1 year of discharge every 3 months for the first year after surgery and then every 6 months after that. A routine blood test, liver and kidney function tests, serum tumor markers, and whole abdominal enhanced CT/MRI were part of the follow-up. There were 2 key clinical outcomes: overall survival (OS) and disease-free survival (DFS). OS refers to the time from the end of radical resection to the death of the malignancy. DFS refers to the time from the end of radical resection to tumor recurrence.

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Corp.) and R software ver 4.1.1 (The R Foundation). To minimize bias caused by non-randomized grouping, we applied PSM analysis after identifying baseline characteristic mismatches between the 2 groups. A list of the variables selected for the propensity score model appears in Table 1. When data are normally distributed, they are presented as means (standard deviations), but if not, they are presented as medians (range). Categorical variable data are presented as quantities and corresponding percentages. The Student t-test was used to compare normally distributed continuous data and the Mann-Whitney U-test was used for comparing skewed-distributed data, and the Fisher exact test was used to compare ordinal data. The Kaplan-Meier method was used to describe survival data, and the log-rank test was used to compare differences among subgroups of patients. To identify prognostic factors, univariate and multivariate analyses were performed. Variables with a P-value of <0.1 in univariate analysis were included in multivariate analysis. A P-value of <0.05 (2-sided) was considered to be statistically significant.

RESULTS

Baseline characteristics

A total of 310 patients diagnosed with HCCA in our hospital from January 2007 to December 2018 were evaluated retrospectively. We divided these patients into 3 subgroups (205 in the non-VR subgroup, 68 in the PV resection [PVR] subgroup, and 37 in the HAR subgroup) according to the surgical technique. Before PSM, the following characteristics were not significantly different between the 2 groups: sex, age, hypertension, history of cardiovascular accident, diabetes, chronic obstructive pulmonary disease, serum CA 19-9, TB, DB, albumin, ALT, AST, PT, preoperative biliary drainage, preoperative PV embolization, differentiation, invasion of the

Table 1. Baseline characteristics of patients in the PVR group and non-PVR group before and after PSM matching

Characteristic	Before matching (n = 273)		P-value	After 1:2 matching (n = 170)		P-value
	PVR group	Non-PVR group		PVR group	Non-PVR group	
No. of patients	68	205		62	108	
Sex, female:male	29:39	95:110	0.596	26:36	50:58	0.582
Age (yr)	59 (34–76)	59 (20–78)	0.463	59 (35–76)	59 (20–78)	0.992
Hypertension	8 (11.76)	39 (19.02)	0.169	8 (12.90)	18 (16.67)	0.512
History of cardiovascular accident	1 (1.47)	2 (0.97)	0.734	1 (1.61)	2 (1.85)	>0.999
Diabetes	3 (4.41)	10 (4.88)	0.876	2 (3.22)	5 (4.63)	0.966
COPD	1 (1.47)	7 (3.41)	0.410	1 (1.61)	2 (1.85)	>0.999
Serum CA 19-9 (IU/L)	193.4 (0.6–1,000.0)	263.7 (0.6–1,000.0)	0.904	193.4 (0.6–1,000.0)	337.8 (0.6–1,000.0)	0.381
Total bilirubin (μmol/L)	113.2 (7.1–437.5)	174.1 (7.8–543.4)	0.099	111.8 (7.1–437.5)	162.2 (7.8–543.4)	0.619
Direct bilirubin (μmol/L)	99.8 (2.0–348.9)	150.6 (2.1–410.9)	0.109	99.8 (2.0–348.9)	138.0 (2.1–410.9)	0.543
Albumin (g/L)	38.2 (23.0–47.2)	37.9 (13.8–50.2)	0.344	38.0 (23.0–47.2)	37.9 (13.8–50.1)	0.972
ALT (IU/L)	93.0 (14.0–967.0)	114.0 (13.0–720.0)	0.143	95.5 (14.0–967.0)	114.0 (14.0–686.0)	0.350
AST (IU/L)	72.0 (19.0–530.0)	91.0 (14.0–533.0)	0.095	72.0 (19.0–530.0)	91.0 (17.0–513.0)	0.288
PT (sec)	11.3 (8.5–14.2)	11.1 (8.6–20.3)	0.465	11.2 (8.5–14.2)	11.1 (8.6–15.5)	0.605
Preoperative biliary drainage	14 (20.59)	31 (15.12)	0.292	13 (20.97)	21 (19.44)	0.811
Preoperative portal vein embolization	1 (1.47)	2 (0.97)	0.734	1 (1.61)	1 (0.93)	>0.999
Bismuth staging			0.005*			0.417
I	0 (0)	0 (0)		0 (0)	0 (0)	
II	1 (1.47)	36 (17.56)		1 (1.61)	4 (3.70)	
IIIa	11 (12.79)	28 (13.66)		11 (17.74)	17 (15.74)	
IIIb	30 (34.88)	63 (30.73)		27 (43.55)	37 (34.26)	
IV	26 (30.23)	78 (38.05)		23 (37.10)	50 (46.30)	
TNM staging			<0.001*			0.264
I	3 (4.41)	43 (20.98)		3 (4.84)	18 (16.67)	
II	17 (25.00)	90 (43.90)		16 (25.81)	35 (32.41)	
IIIA	17 (25.00)	16 (7.80)		17 (27.42)	12 (11.11)	
IIIB	22 (32.35)	20 (9.76)		19 (30.65)	20 (18.52)	
IIIC	9 (13.24)	30 (14.63)		7 (11.29)	19 (17.59)	
IVA	0 (0)	6 (2.93)		0 (0)	4 (3.70)	
Differentiation			0.079			0.886
High	21 (30.88)	88 (42.93)		20 (32.25)	36 (33.33)	
Medium or low	47 (69.12)	117 (57.07)		42 (67.74)	72 (66.67)	
Tumor diameter (cm)	4.0 (1.1–9.5)	2.7 (0.9–10.1)	<0.001*	3.6 (1.1–9.5)	3.1 (0.9–10.1)	0.075
Invasion of the whole bile duct	48 (70.59)	139 (67.80)	0.669	43 (69.35)	74 (68.52)	0.910
Bile duct cancerous embolus	8 (11.76)	19 (9.27)	0.550	7 (11.29)	13 (12.04)	0.884
Liver parenchymal invasion	49 (72.06)	84 (40.98)	<0.001*	44 (70.97)	67 (62.04)	0.239
Liver capsule invasion	18 (26.47)	27 (13.17)	0.010*	16 (25.81)	22 (20.37)	0.413
Nerve invasion	34 (50.00)	90 (43.90)	0.382	31 (50.00)	46 (42.59)	0.350

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Table 1. Continued

Characteristic	Before matching (n = 273)		P-value	After 1:2 matching (n = 170)		P-value
	PVR group	Non-PVR group		PVR group	Non-PVR group	
ASA PS classification			0.880			0.607
I	0 (0)	3 (1.46)		0 (0)	3 (2.78)	
II	42 (61.76)	120 (58.54)		39 (62.90)	59 (54.63)	
III	26 (38.24)	81 (39.51)		23 (37.10)	45 (41.67)	
IV	0 (0)	1 (0.49)		0 (0)	1 (0.93)	
R0 resection	49 (72.06)	170 (82.97)	0.051	45 (72.58)	86 (79.63)	0.293
Type of hepatectomy			<0.001*			0.433
Parenchyma-preserving hepatectomy	1 (1.47)	50 (24.39)		1 (1.61)	3 (2.78)	
Mesohepatectomy	8 (11.76)	24 (11.71)		6 (9.68)	10 (9.26)	
Hemihepatectomy	50 (73.53)	124 (60.49)		48 (77.42)	88 (81.48)	
Trisectionectomy	9 (13.24)	7 (3.41)		7 (11.29)	7 (6.48)	
Postoperative adjuvant chemotherapy	65 (95.58)	194 (94.46)	>0.999	59 (95.16)	102 (94.44)	>0.999
Capecitabine monotherapy	26 (40.00)	81 (41.75)	0.970	23 (38.98)	43 (42.16)	0.949
Gemcitabine + cisplatin	18 (27.69)	46 (23.71)		16 (27.12)	28 (27.45)	
Capecitabine + oxaliplatin	10 (15.38)	31 (15.98)		10 (16.95)	14 (13.73)	
5-Fluorouracil + oxaliplatin	11 (16.92)	36 (18.56)		10 (16.95)	17 (16.67)	
CTCAE grade III, IV toxicity	3 (4.41)	14 (7.22)	0.657	3 (5.08)	11 (10.78)	0.216

Values are presented as median (range) or number (%).
PVR, portal vein resection; PSM, propensity score-matching; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; PS, physical status; CTCAE, common terminology criteria for adverse events.
*$P < 0.05$.

Table 2. Baseline characteristics of patients in HAR group and non-HAR group before and after PSM matching

Characteristic	Before matching (n = 242)		P-value	After 1:2 matching (n = 96)		P-value
	HAR group	Non-HAR group		HAR group	Non-HAR group	
No. of patients	37	205		33	63	
Sex, female:male	18:19	95:110	0.796	15:18	34:29	0.428
Age (yr)	62 (38–78)	59 (20–78)	0.032*	61.2 (38–73)	60.5 (31–76)	0.752
Hypertension	7 (18.92)	39 (19.02)	0.988	6 (18.18)	10 (15.87)	0.773
History of cardiovascular accident	2 (5.41)	2 (0.97)	0.052	1 (3.03)	2 (3.17)	>0.999
Diabetes	2 (5.41)	10 (4.88)	0.892	1 (3.03)	1 (1.59)	>0.999
COPD	1 (2.70)	7 (3.41)	0.824	1 (3.03)	3 (4.76)	>0.999
Serum CA 19-9 (IU/L)	334.2 (0.6–1,000.0)	263.7 (0.6–1,000.0)	0.368	506.2 (0.6–1,000.0)	414.6 (0.6–1,000.0)	0.489
Total bilirubin (μmol/L)	174.8 (14.8–413.3)	174.1 (7.8–543.4)	0.677	182.6 (14.8–413.3)	185.3 (10.3–458.4)	0.972
Direct bilirubin (μmol/L)	148.4 (5.8–340.4)	150.6 (2.1–410.9)	0.734	151.7 (5.8–340.4)	152.5 (3.8–368.8)	0.963
Albumin (g/L)	38.3 (28.0–44.4)	37.9 (13.8–50.2)	0.843	37.1 (28.5–44.4)	37.5 (26.5–50.1)	0.994
ALT (IU/L)	88.0 (16.0–598.0)	114.0 (13.0–720.0)	0.234	129.9 (16.0–598.0)	122.3 (15.0–720.0)	0.963
AST (IU/L)	72.0 (32.0–432.0)	91.0 (14.0–533.0)	0.320	113.9 (32.0–432.0)	103.0 (19.0–387.0)	0.890
PT (sec)	11.0 (9.3–18.3)	11.1 (8.6–20.3)	0.271	11.4 (9.3–18.3)	11.4 (8.6–15.2)	0.844
Preoperative biliary drainage	8 (21.62)	31 (15.12)	0.322	6 (18.18)	9 (14.29)	0.618
Preoperative portal vein embolization	0 (0)	2 (0.97)	0.546	0 (0)	0 (0)	-
Bismuth staging			0.331			0.433
I	0 (0)	0 (0)		0 (0)	0 (0)	
II	5 (13.51)	36 (17.56)		5 (15.15)	13 (20.63)	
IIIa	2 (5.41)	28 (13.66)		2 (6.06)	8 (12.70)	
IIIb	11 (29.73)	63 (30.73)		11 (33.33)	16 (25.40)	
IV	19 (51.35)	78 (38.05)		15 (45.45)	26 (41.27)	
TNM staging			<0.001*			0.925
I	0 (0)	43 (20.98)		0 (0)	6 (9.52)	
II	5 (13.51)	90 (43.90)		5 (15.15)	21 (33.33)	
IIIA	13 (35.14)	16 (7.80)		13 (37.50)	4 (6.35)	
IIIB	13 (35.14)	20 (9.76)		11 (33.33)	10 (15.87)	
IIIC	6 (16.22)	30 (14.63)		4 (12.12)	16 (25.40)	
IVA	0 (0)	6 (2.93)		0 (0)	6 (9.52)	
Differentiation			0.133			0.885
High	11 (29.73)	88 (42.93)		10 (30.30)	20 (31.75)	
Medium or low	26 (70.27)	117 (57.07)		23 (69.70)	43 (68.25)	
Tumor diameter (cm)	2.7 (1.5–8.1)	2.7 (0.9–10.1)	0.808	2.9 (1.5–8.1)	2.8 (0.9–6.1)	0.763
Invasion of the whole bile duct	29 (78.38)	139 (67.80)	0.199	27 (81.81)	53 (84.13)	0.773
Bile duct cancerous embolus	3 (8.11)	19 (9.27)	0.821	3 (9.09)	4 (6.35)	0.938
Liver parenchymal invasion	13 (35.14)	84 (40.98)	0.505	13 (37.50)	27 (42.86)	0.744
Liver capsule invasion	7 (18.92)	27 (13.17)	0.354	6 (18.18)	11 (17.46)	0.930
Nerve invasion	21 (56.76)	90 (43.90)	0.149	17 (51.52)	35 (55.56)	0.706

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Table 2. Continued

Characteristic	Before matching (n = 242)		P-value	After 1:2 matching (n = 96)		P-value
	HAR group	Non-HAR group		HAR group	Non-HAR group	
ASA PS classification			0.519			0.987
I	1 (2.70)	3 (1.46)		1 (3.03)	2 (3.17)	
II	23 (62.16)	120 (58.54)		21 (63.64)	41 (65.08)	
III	13 (35.14)	81 (39.51)		11 (33.33)	20 (31.75)	
IV	0 (0.00)	1 (0.49)		0 (0.00)	0 (0.00)	
R0 resection	32 (86.49)	170 (82.97)	0.592	28 (84.85)	57 (90.48)	0.628
Type of hepatectomy			0.684			0.115
Parenchyma-preserving hepatectomy	8 (21.62)	50 (24.39)		6 (18.18)	21 (33.33)	
Mesohepatectomy	7 (18.92)	24 (11.71)		7 (21.21)	5 (7.94)	
Hemihepatectomy	21 (56.76)	124 (60.49)		20 (60.61)	35 (55.56)	
Trisectionectomy	1 (2.70)	7 (3.41)		0 (0.00)	2 (3.17)	
Postoperative adjuvant chemotherapy	33 (89.19)	194 (94.46)	0.206	31 (93.94)	59 (93.65)	>0.999
Capecitabine monotherapy	12 (36.36)	81 (41.75)	0.681	11 (35.48)	22 (37.29)	0.951
Gemcitabine + cisplatin	9 (27.27)	46 (23.71)		8 (25.81)	14 (23.73)	
Capecitabine + oxaliplatin	5 (15.15)	31 (15.98)		5 (16.13)	7 (11.86)	
5-Fluorouracil + oxaliplatin	7 (21.21)	36 (18.56)		7 (22.58)	16 (27.12)	
CTCAE grade III, IV toxicity	4 (12.12)	14 (7.22)	0.538	4 (12.90)	2 (3.39)	0.202

Values are presented as median (range) or number (%).
PVR, portal vein resection; PSM, propensity score-matching; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; PS, physical status; CTCAE, common terminology criteria for adverse events.
*$P < 0.05$.

whole bile duct, bile duct cancerous embolus, nerve invasion, American Society of Anesthesiologists (ASA) physical status (PS) classification, R0 resection, and postoperative adjuvant chemotherapy. Baseline characteristics in terms of age, Bismuth staging, TNM staging, tumor diameter, liver parenchymal invasion, liver capsule invasion, and type of hepatectomy showed significant differences before matching (Tables 1, 2). According to 1:2 matching, there were 62 PVR patients and 108 non-VR patients in the PVR subgroup, and 33 HAR patients and 63 non-VR patients in the HAR subgroup. All baseline characteristics were balanced between patient groups after matching. A comparison of pre- and post-PSM group baseline characteristics is shown in Tables 1 and 2. Supplementary Table 1 shows the surgical resection and pathological basic information of patients undergoing combined VR.

Short-term clinical outcomes in the portal vein resection group

Table 3 shows the short-term clinical outcomes (surgery-related outcomes and postoperative complications) of the patients in the PVR and non-VR groups. Except for the Clavien-Dindo (CD) grade [22], perioperative clinical outcomes were not statistically significantly different between the 2 groups. There was a higher frequency of postoperative complications in the PVR group compared to the control group (after PSM, P = 0.019).

Short-term clinical outcomes in the hepatic artery resection group

Table 4 shows the surgery-related outcomes and postoperative complications of the patients in the HAR and non-VR groups before and after PSM matching. Patients in the HAR group

Table 3. Short-term clinical outcomes of patients in PVR group and non-PVR group before and after PSM matching.

Variable	Before matching (n = 273)		P-value	After matching (n = 170)		P-value
	PVR group (n = 68)	Non-PVR group (n = 205)		PVR group (n = 62)	Non-PVR group (n = 108)	
Intraoperative hemorrhage (mL)	600 (100–3,000)	600 (50–3,100)	0.760	765.3 (100–3,000)	889.6 (100–3,100)	0.173
Intraoperative transfusion	37 (54.41)	88 (42.93)	0.100	35 (56.45)	59 (54.63)	0.818
Operation time (min)	420 (225–965)	385 (105–680)	0.025*	429.8 (225–965)	408.2 (105–680)	0.499
Second surgery during hospitalization	3 (4.41)	19 (9.27)	0.202	3 (4.84)	10 (9.26)	0.457
Total postoperative infection	13 (19.12)	50 (24.39)	0.371	13 (20.97)	33 (30.56)	0.176
Pulmonary infection	6 (8.82)	19 (9.27)	0.912	6 (9.68)	10 (9.26)	0.928
Abdominal infection	8 (11.76)	28 (13.66)	0.689	8 (12.90)	18 (16.67)	0.512
Incisional infection	3 (4.41)	7 (3.41)	0.995	2 (3.23)	7 (6.48)	0.578
Sepsis	0 (0)	1 (0.49)	>0.999	0 (0)	0 (0)	-
Liver abscess	0 (0)	1 (0.49)	>0.999	0 (0)	0 (0)	-
Abdominal effusion	6 (8.82)	16 (7.80)	0.789	6 (9.68)	10 (9.26)	0.928
Pleural effusion	6 (8.82)	13 (6.34)	0.673	6 (9.68)	7 (6.48)	0.649
Bile leakage	11 (16.18)	32 (15.61)	0.911	11 (17.74)	18 (16.67)	0.858
Postoperative hemorrhage	5 (7.35)	10 (4.88)	0.639	4 (6.45)	7 (6.48)	>0.999
Biliary-enteric anastomotic fistula	1 (1.47)	1 (0.49)	0.437	1 (1.62)	1 (0.93)	>0.999
Thoracic chylous effusion	1 (1.47)	0 (0)	0.249	1 (1.62)	0 (0)	0.365
Gastrointestinal obstruction	2 (2.94)	2 (0.98)	0.557	2 (3.23)	1 (0.93)	0.623
Postoperative hepatic insufficiency	4 (5.88)	10 (4.88)	0.994	4 (6.45)	6 (5.56)	>0.999
Postoperative pulmonary insufficiency	0 (0)	2 (0.98)	>0.999	0 (0)	1 (0.93)	>0.999
Postoperative renal insufficiency	1 (1.47)	3 (1.46)	>0.999	1 (1.62)	1 (0.93)	>0.999
Postoperative cardiac insufficiency	1 (1.47)	0 (0)	0.249	1 (1.62)	0 (0)	0.365
Clavien-Dindo grade						
I	6 (8.82)	13 (6.34)	0.001*	6 (9.68)	7 (6.48)	0.019*
II	13 (19.12)	45 (21.95)		13 (20.97)	27 (25.00)	
IIIa	7 (10.29)	2 (0.98)		6 (9.68)	1 (0.93)	
IIIb	1 (1.47)	17 (8.29)		1 (1.61)	8 (7.41)	
IV	8 (11.76)	12 (5.85)		8 (12.90)	8 (7.41)	
Length of hospital stay (day)	19 (10–79)	17 (5–115)	0.252	22.5 (10–79)	22.6 (5–92)	0.966
Postoperative hospital stay (day)	13 (7–71)	11 (5–103)	0.144	16.3 (7–71)	16.1 (5–86)	0.759
ICU treatment time (day)	1 (0–12)	1 (0–21)	0.231	1.4 (0–12)	1.6 (0–20)	0.590

Values are presented as median (range) or number (%).
PVR, portal vein resection; PSM, propensity score-matching; ICU, intensive care unit.
*P < 0.05.

Table 4. Short-term clinical outcomes of patients in HAR group and non-HAR group before and after PSM matching

Variable	Before matching (n = 242)		P-value	After matching (n = 96)		P-value
	HAR group (n = 37)	Non-HAR group (n = 205)		HAR group (n = 33)	Non-HAR group (n = 63)	
Intraoperative hemorrhage (mL)	600 (100–2,000)	600 (50–3,100)	0.402	500 (100–2,000)	600 (50–3,000)	0.556
Intraoperative transfusion	17 (45.95)	88 (42.93)	0.733	17 (51.52)	28 (44.44)	0.510
Operation time (min)	405 (245–720)	385 (105–680)	0.187	405 (245–720)	400 (185–680)	0.443
Second surgery during hospitalization	3 (8.11)	19 (9.27)	>0.999	2 (6.06)	2 (3.17)	0.893
Total postoperative infection	8 (21.62)	50 (24.39)	0.717	6 (18.18)	10 (15.87)	0.773
Pulmonary infection	1 (2.70)	19 (9.27)	0.312	1 (3.03)	3 (4.76)	>0.999
Abdominal infection	5 (13.51)	28 (13.66)	0.981	4 (12.12)	6 (9.52)	0.965
Incisional infection	2 (5.40)	7 (3.41)	0.907	1 (3.03)	1 (1.59)	>0.999
Sepsis	0 (0)	1 (0.49)	>0.999	0 (0)	0 (0)	-
Liver abscess	0 (0)	1 (0.49)	>0.999	0 (0)	0 (0)	-
Abdominal effusion	8 (21.62)	16 (7.80)	0.022*	8 (24.24)	4 (6.35)	0.028*
Pleural effusion	5 (13.51)	13 (6.34)	0.234	4 (12.12)	0 (0)	0.022*
Bile leakage	11 (29.73)	32 (15.61)	0.039*	10 (30.30)	9 (14.29)	0.061
Postoperative hemorrhage	5 (13.51)	10 (4.88)	0.045*	5 (15.15)	2 (3.17)	0.084
Biliary-enteric anastomotic fistula	0 (0)	1 (0.49)	>0.999	0 (0)	0 (0)	-
Gastrointestinal obstruction	2 (5.40)	2 (0.98)	0.112	1 (3.03)	0 (0)	0.344
Postoperative hepatic insufficiency	2 (5.40)	10 (4.88)	0.893	1 (3.03)	3 (4.76)	>0.999
Postoperative pulmonary insufficiency	0 (0)	2 (0.98)	>0.999	0 (0)	1 (1.59)	>0.999
Postoperative renal insufficiency	0 (0)	3 (1.46)	>0.999	0 (0)	1 (1.59)	>0.999
Postoperative cardiac insufficiency	1 (2.70)	0 (0)	0.153	1 (3.03)	0 (0)	0.344
Clavien-Dindo grade						
I	5 (13.51)	13 (6.34)	0.407	2 (16.06)	4 (6.35)	<0.001*
II	14 (37.84)	45 (21.95)		13 (39.39)	14 (22.22)	
IIIa	2 (5.41)	2 (0.98)		0 (0)	2 (3.17)	
IIIb	2 (5.41)	17 (8.29)		2 (6.06)	1 (1.59)	
IV	4 (10.81)	12 (5.85)		3 (9.09)	3 (4.76)	
Length of hospital stay (day)	19 (10–50)	17 (5–115)	0.478	19 (10–50)	17 (9–38)	0.216
Postoperative hospital stay (day)	13 (7–31)	11 (5–103)	0.313	13 (7–31)	11 (5–28)	0.132
ICU treatment time (day)	1 (0–7)	1 (0–21)	0.349	1 (0–7)	1 (0–5)	0.114

Values are presented as median (range) or number (%).
PVR, portal vein resection; PSM, propensity score-matching; ICU, intensive care unit.
*P < 0.05.

had an increased risk of abdominal effusion (after PSM, 24.24% *vs.* 6.35%; P = 0.028) and pleural effusion (after PSM, 12.12% *vs.* 0.00%; P = 0.022) after surgery. A higher incidence of postoperative complications was also observed in the HAR group (after PSM, P < 0.001).

Long-term survival in the portal vein resection group after propensity score-matching

The median follow-up time was 39.6 months. During follow-up, 135 patients (79.41%) experienced postoperative tumor recurrence, 124 patients (72.94%) died, and only 20 patients (11.76%) survived over 5 years. OS and DFS were significantly better among patients who underwent combined PVR. The median OS and DFS for patients receiving PVR were 31.4 months and 19.4 months, respectively, while these 2 metrics were only 18.4 months and 13.0 months, respectively, in patients who did not receive PVR (OS, P = 0.020; DFS, P = 0.020) (Fig. 1).

Long-term survival in the hepatic artery resection group after propensity score-matching

In this cohort of 96 individuals after PSM, 76 patients (79.17%) experienced tumor recurrence, 73 (76.04%) died during follow-up, and only 5 (5.21%) survived for >5 years. HAR was associated with longer OS and DFS after curative-intent resection than non-HAR. In the HAR group, the median OS was 9.0 months longer than in the non-HAR group (27.4 months *vs.* 18.4 months, P = 0.027), and the median DFS was also 8.8 months longer (23.5 months *vs.* 14.7 months, P = 0.023) (Fig. 2).

Effect of postoperative complications on prognosis

Ninety-six patients underwent combined resection of the

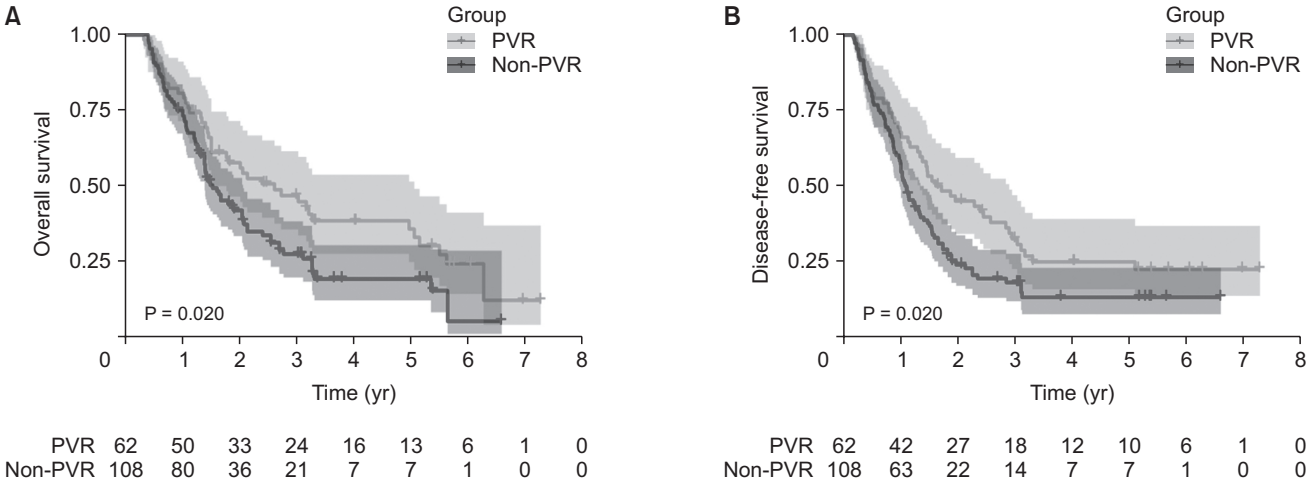

Fig. 1. After propensity score-matching matching. Overall survival (A) and disease-free survival (B) for patients in the portal vein resection (PVR) group and non-PVR group (n = 170).

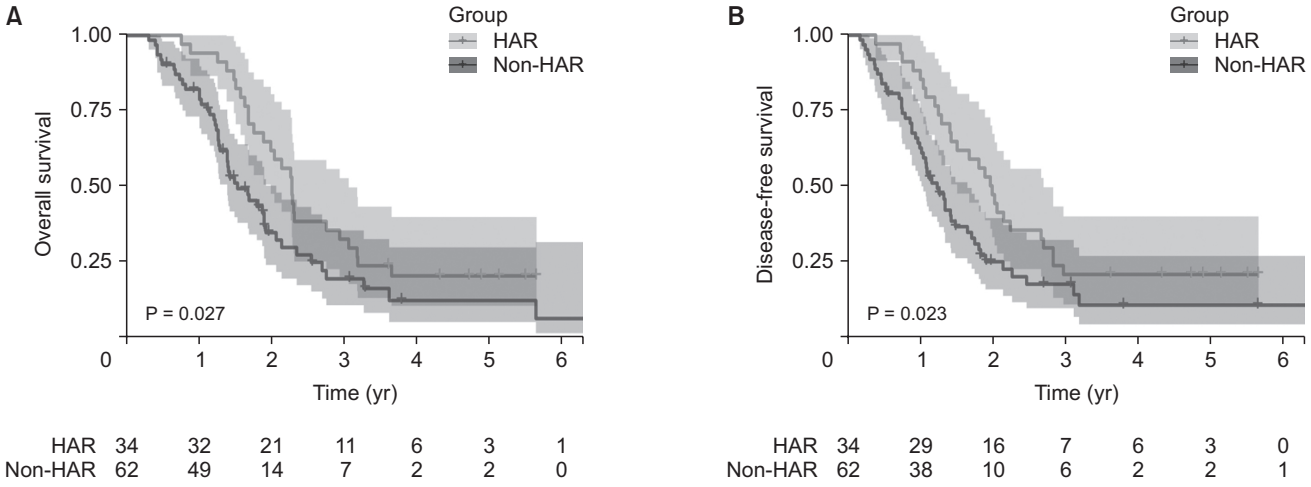

Fig. 2. After propensity score-matching matching. Overall survival (A) and disease-free survival (B) for patients in the hepatic artery resection (HAR) group and non-HAR group (n = 94).

major vessels (PVR and HAR) after PSM were included in this study. Patient groups were divided according to postoperative complications (with or without). Neither OS (P = 0.618) nor DFS (P = 0.589) differed statistically significantly between groups (Fig. 3A, B). Subgroup analysis showed that neither CD grade I/II complications (OS, P = 0.394; DFS, P = 0.518) nor CD grade III/IV complications (OS, P = 0.864; DFS, P = 0.887) significantly affected patient prognosis (Fig. 3C–F).

Prognostic factors for patients in the portal vein resection group after propensity score-matching

Supplementary Table 2 and Table 5 present univariate and multivariate Cox regression analyses of OS and DFS for patients in the PVR group.

The results showed that PVR (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.46–0.98; P = 0.041) was associated with better OS on post-PSM multivariable analysis. Increased TB (HR, 1.02; 95% CI, 1.00–1.03; P = 0.029) and postoperative pleural effusion (HR, 2.13; 95% CI, 1.07–4.24; P = 0.032) were associated with poor prognosis.

As for the prognostic factors related to DFS, PVR (HR, 0.64; 95% CI, 0.45–0.92; P = 0.017) was associated with better DFS. Liver capsule invasion (HR, 1.70; 95% CI, 1.14–2.54; P = 0.010) and higher ASA PS classification (HR, 1.38; 95% CI, 1.01–1.89; P = 0.042) were associated with worse DFS.

Prognostic factors for patients in hepatic artery resection group after propensity score-matching

Supplementary Table 2 shows the results of univariate analysis. Multivariable Cox regression analysis showed that

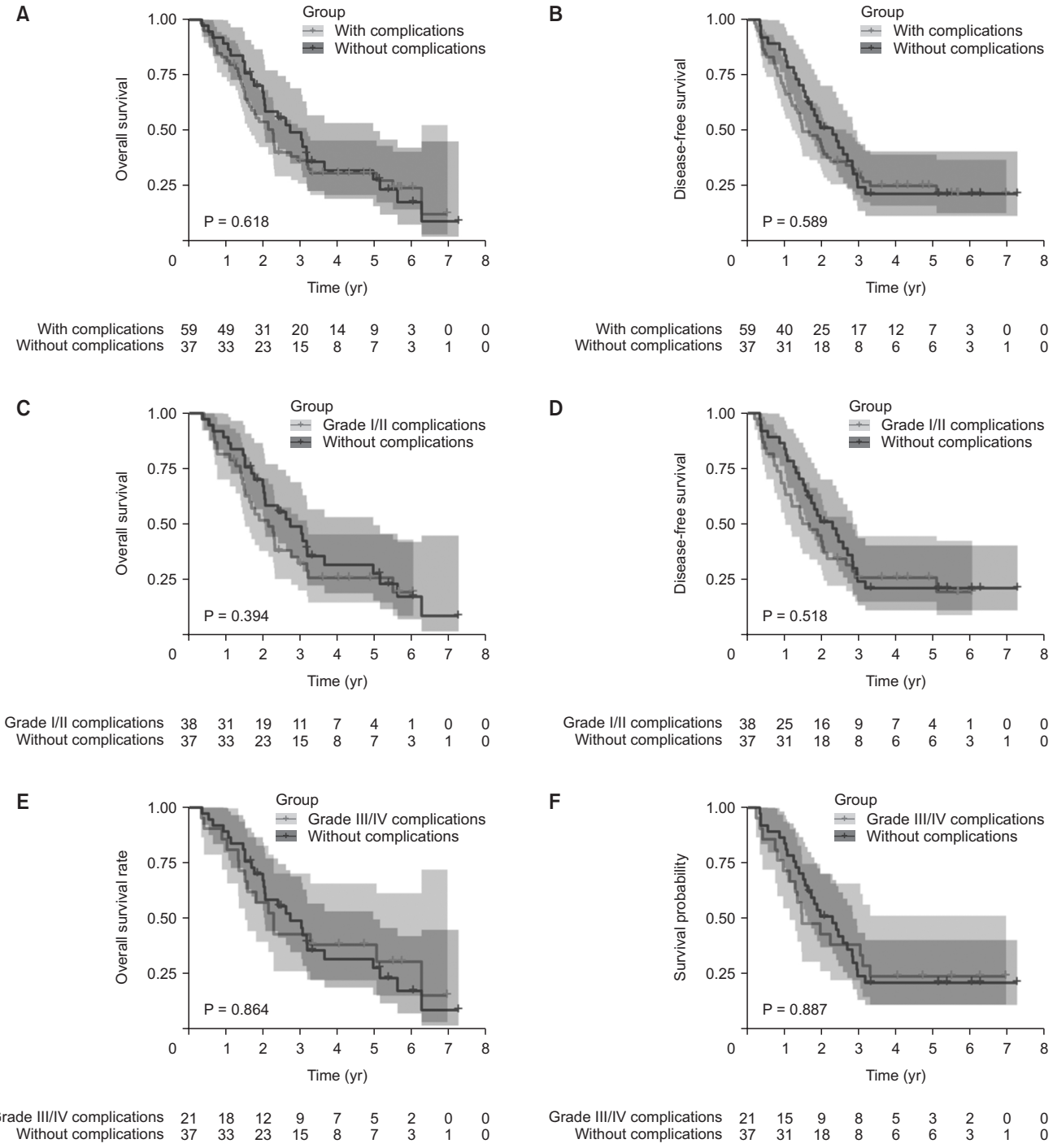

Fig. 3. After propensity score-matching matching. (A, B) Impact of overall postoperative complications on the prognosis of patients who underwent major vessel resection. (C, D) Impact of Clavien-Dindo grade I/II postoperative complications on the prognosis of patients who underwent major vessel resection. (E, F) Impact of Clavien-Dindo grade III/IV postoperative complications on the prognosis of patients who underwent major vessel resection. (A, C, E) Overall survival; (B, E, F)

HAR (HR, 0.59; 95% CI, 0.36–0.97; P = 0.038) and without liver parenchymal invasion (HR, 0.49; 95% CI, 0.29–0.81; P = 0.005) contributed to longer OS for patients. Postoperative gastrointestinal obstruction (HR, 18.48; 95% CI, 2.22–154.10; P = 0.007) and postoperative incisional infection (HR, 6.85; 95% CI, 1.52–30.93; P = 0.012) were identified as independent predictors of poor OS (Table 5).

For DFS, without liver parenchymal invasion (HR, 0.58; 95% CI, 0.36–0.94; P = 0.025) and HAR (HR, 0.60; 95% CI, 0.37–0.97; P = 0.037) were contributed to better DFS, while postoperative

Table 5. Multivariable Cox regression analysis for OS and DFS after PSM matching

Variable	HR (95% CI)	P-value
OS		
PVR *vs.* non-PVR		
Direct.bilirubin	1.02 (1.00–1.03)	0.029*
Pleural effusion	2.13 (1.07–4.24)	0.032*
PVR	0.67 (0.46–0.98)	0.041*
HAR vs. non-HAR		
Liver parenchymal invasion	0.49 (0.29–0.81)	0.005*
Gastrointestinal obstruction	18.48 (2.22–154.10)	0.007*
Incisional infection	6.85 (1.52–30.93)	0.012*
HAR	0.59 (0.36–0.97)	0.038*
DFS		
PVR vs. non-PVR		
PVR	0.64 (0.45–0.92)	0.017*
Liver capsule invasion	1.70 (1.14–2.54)	0.010*
ASA PS classification	1.38 (1.01–1.89)	0.042*
HAR vs. non-HAR		
Incisional infection	9.01 (1.99–40.69)	0.004*
Liver parenchymal invasion	0.58 (0.36–0.94)	0.025*
HAR	0.60 (0.37–0.97)	0.037*

OS, overall survival; DFS, disease-free survival; PSM, propensity score-matching; HR, hazard ratio; CI, confidence interval; PVR, portal vein resection; HAR, hepatic artery resection; ASA, American Society of Anesthesiologists; PS, physical status.
*P < 0.05.

incisional infection (HR, 9.01; 95% CI, 1.99–40.69; P = 0.004) was associated with shorter DFS (Table 5).

DISCUSSION

The bifurcation of the bile duct was close to that of the PV. Adhesion or invasion of tumors to the bifurcation of the PV remains a technical challenge during hepatectomy for HCCA. Additionally, because most patients remain asymptomatic at presentation and are usually diagnosed at a late stage, most patients have involvement of vital tissue structures at the time of diagnosis, further increasing the difficulty of surgical resection. Even in cases where the tumor does not actually invade the PV or HA, the fibrotic reaction induced by a tumor can still cause fibrous tissue-containing tumor cells to extend into the blood vessels. This inevitably increases the risk of residual tumor cells adhering to the outer wall of the blood vessels while peeling off the vessels, thereby reducing the R0 resection rate.

To further improve the R0 resection rate, malignancy combined with vital VR offers the opportunity to obtain a radical cure in patients with HCCA. Owing to the involvement of important blood vessels (HA or PV) in surgery, some studies suggest that this increases the risk of postoperative complications and mortality [3]. However, other studies hold the view that combined VR is one of the most effective measures for improving the OS of patients with HCCA [7]. In addition, more than 1 study has also shown that different types of combined VR (PVR or HAR) may also lead to differences in the risk of postoperative complications and prognosis of patients [3,12,14-16,18-21,23-25]. To further investigate the impact of combined PVR or HAR on postoperative complications and prognosis, we performed a PSM analysis.

Our study found that the patients in the VR group (PVR or HAR) had a better prognosis (OS and DFS) than those in the non-VR group after PSM (Fig. 1, 2). Compared to the control group, the PVR group and the HAR group had more postoperative complications. Patients in the HAR group had an increased risk of abdominal and pleural effusion after surgery. Even if postoperative complications occur in patients with combined VR, they do not worsen their long-term survival (Fig. 3).

Currently, postoperative complications are an important factor in surgical decision-making. It is known that postoperative complications can adversely affect cancer patients' long-term outcomes in different ways. For example, immunosuppression, malnutrition, muscle depletion, and delayed adjuvant therapy all contribute to poor long-term outcomes [26]. Serious postoperative complications can worsen long-term survival in patients with malignancies undergoing surgical treatment, as has been demonstrated in tumors of many sites (e.g., gastric, esophageal, and pancreatic cancers) [27-30]. Therefore, the impact of complications after combined VR on the prognosis of patients with HCCA is crucial in deciding the surgical approach. In this study, we found that overall postoperative complications after combined VR did not affect patient prognosis. Similar outcomes have been reported in esophageal and pancreatic cancer. For patients with advanced esophageal cancer [27], postoperative complications were not predictive of patient prognosis. Similarly, in pancreatic cancer [30], while severe complications were found to have a negative impact on patient prognosis, this effect became insignificant when the study variables were expanded to include overall complications. These results indicate that the primary determinant of prognosis in patients with HCCA is the tumor itself, rather than postoperative complications. Given that curative R0 resection is the only means by which patients can achieve a clinical cure, aggressive curative surgery including resection of major blood vessels is necessary.

Our study is the only study that used PSM analysis to assess the prognostic significance of combined VR on patients with HCCA. In addition to focusing on patient survival rates, we also focused on the impact of postoperative complications on patient prognosis. In this study, PSM was used to match the 2 groups of patients, minimizing retrospective study bias.

Despite the fact that these findings provide new evidence for clinical diagnosis and treatment, it is important to consider some limitations of the study when interpreting them. First, as this was a retrospective study, this inevitably introduces bias. In addition, this study's sample size was quite small because of the relatively special population it included. This also led to the fact that we only subgrouped patients based on the combined resection of the different entering hepatic vessels. We were unable to further subgroup the resection of different branches of the PV and HA. Third, this was a single-center study, which may have led to universal conclusions of the study subject to certain restrictions. For further verification, randomized controlled studies and large-scale multicenter prospective cohort studies are needed.

In conclusion, this is the only study to use PSM analysis to evaluate the prognostic impact of combined VR on the prognosis of patients with HCCA. Combined VR (PVR or HAR) improves OS and DFS in patients with HCCA. Postoperative complications of combined VR do not worsen long-term survival. Radical surgical resection may be the better choice for patients with HCCA.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1 and 2 can be found via https://doi.org/10.4174/astr.2023.105.5.319.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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