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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Postoperative Infectious Complications Worsen Long-Term Survival After Curative-Intent Resection for Hepatocellular Carcinoma

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ABSTRACT

Background. Postoperative infectious complications may be associated with a worse long-term prognosis for patients undergoing surgery for a malignant indication. The current study aimed to characterize the impact of postoperative infectious complications on long-term oncologic outcomes among patients undergoing resection for hepatocellular carcinoma (HCC).

Methods. Patients who underwent curative-intent resection for HCC between 2000 and 2017 were identified from an international multi-institutional database. The relationship between postoperative infectious complications, overall survival (OS), and recurrence-free survival (RFS) was analyzed.

Results. Among 734 patients who underwent HCC resection, 269 (36.6%) experienced a postoperative complication (Clavien–Dindo grade 1 or 2 [$n = 197$, 73.2%] vs grade 3 and 4 [$n = 69$, 25.7%]). An infectious complication was noted in 81 patients (11.0%) and 188 patients (25.6%) had non-infectious complications. The patients with infectious complications had worse OS (median: infectious complications [46.5 months] vs no complications [106.4 months] [$p < 0.001$] and non-infectious complications [85.7 months] [$p < 0.05$]) and RFS (median: infectious complications [22.1 months] vs no complications [45.5 months] [$p < 0.05$] and non-infectious complications [38.3 months] [$p = 0.139$]) than the patients who had no complication or non-infectious complications. In the multivariable analysis, infectious complications remained an independent risk factor for OS (hazard ratio [HR], 1.7; $p = 0.016$) and RFS (HR, 1.6; $p = 0.013$). Among the patients with infectious complications, patients with non-surgical-site infection (SSI) had even worse OS and RFS than patients with SSI (median OS: 19.5 vs 70.9 months [$p = 0.010$]; median RFS: 12.8 vs 33.9 months [$p = 0.033$]).

Conclusion. Infectious complications were independently associated with an increased long-term risk of tumor

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recurrence and death. Patients with non-SSI versus SSI had a particularly worse oncologic outcome.

Keywords Hepatocellular · Resection · Infection · Complications · Outcomes

Hepatocellular carcinoma (HCC), the most common primary liver malignancy, has a high case-fatality rate with a poor survival.[1] Although resection is the main curative-intent treatment option,[2] it is associated with a high incidence of postoperative recurrence and a 5-year survival of only 40% to 60%.[3] In turn, considerable efforts have been made to stratify patients relative to prognosis. Risk stratification has the potential to guide disease surveillance strategies, as well as to inform consideration of adjuvant therapy.

To date, most prognostic factors have been related to tumor-specific characteristics such as tumor size, tumor number, and the presence of vascular invasion.[4,5] Other factors related to surgical technique and perioperative care also may have an impact on long-term survival. In turn, identification of modifiable perioperative factors may facilitate targeting of these areas for quality improvement and potentially improved oncologic outcomes.

Postoperative complications can occur with some degree of frequency after major surgery, and infection represents one of the most common types of complications. Infectious complications have been associated with the need for invasive procedures, prolonged hospital stay, and increased costs of care.[6–8] In addition, some data suggest that perioperative infectious complications may have an impact on long-term oncologic outcomes for patients undergoing surgery for a malignant indication. To this point, perioperative infectious complications have been correlated with a worse prognosis after liver resection for colorectal liver metastasis.[9–11] However, data concerning the impact of perioperative complications on long-term outcomes after hepatectomy for HCC have not been well-defined. In fact, the few studies examining long-term survival after resection of HCC have had single-center cohorts with a limited sample size.[12–15] Although one larger case series has been reported, this cohort of patients largely consisted of Eastern patients with hepatitis B virus (HBV)-related HCC.[16] As such, the current study aimed to characterize the impact of postoperative infectious complications on long-term oncologic outcomes for patients undergoing curative-intent resection for HCC using an East-West international multi-institutional database.

METHODS

Study Population and Data Collection

Patients who underwent curative-intent resection for HCC between January 2000 and January 2017 were included in the analytic cohort. Data were retrieved from a multi-institutional database with information from nine major international hepatobiliary centers: The Ohio State University Wexner Medical Center, Columbus, OH, USA (n = 100), University of Verona, Verona, Italy (n = 56), Ospedale San Raffaele, Milano, Italy (n = 48), Curry Cabral Hospital, Lisbon, Portugal (n = 167), APHP, Beaujon Hospital, Clichy, France (n = 83), Westmead Hospital, Sydney, Australia (n = 88), Stanford University, Stanford, CA, USA (n = 80), Fundeni Clinical Institute, Bucharest, Romania (n = 77), and University of Ottawa, Ottawa, Canada (n = 44).

Patients who died within 30 days (n = 9, 1.2%) were excluded. The Institutional Review Board of each participating institution approved the study protocol.

Data on patient demographic and tumor characteristics were collected from medical records. The variables analyzed were age, sex, American Society of Anesthesiologists (ASA) physical status classification, preoperative cirrhosis, infection with HBV or hepatitis C virus (HCV), serum α-fetoprotein levels (AFP), type of surgery (i.e., minimally invasive surgery [MIS] vs open surgery), extent of resection (i.e., major vs minor), largest tumor size, number of lesions, Barcelona Clinic Liver Cancer (BCLC) stage, pathologic tumor grade, microvascular invasion, liver capsule involvement, and resection margin status on final pathology (i.e., R0, R1).

Data on postoperative complications within 30 days after hepatic resection were recorded and graded according to the Clavien–Dindo classification.[17] The infectious complications included surgical-site infection (SSI; wound or intraabdominal), pneumonia, urinary tract infection, and systemic sepsis. Non-infectious complications included bile leak, ascites, pleural effusion, abdominal hemorrhage, wound dehiscence, acute liver dysfunction, respiratory problems, cardiovascular problems, ileus, acute renal dysfunction, deep venous thrombosis, and other complications.[18]

The patients were regularly followed after surgery with ultrasound, abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) scanning. Overall survival (OS) was calculated from the date of surgery and censored at the date of death or last follow-up visit. Recurrence-free survival (RFS) was defined as the time from the date of surgery to tumor recurrence. The study was approved by the institutional review boards of each participating institutions.

Statistical Analysis

Clinicopathologic variables were summarized using frequencies and percentages for categorical variables and medians and interquartile ranges (IQR) for continuous covariates. Categorical covariates were compared using the chi-square test or Fisher's exact test, and continuous variables were compared with the Mann–Whitney *U* test. Both OS and RFS were calculated by the Kaplan–Meier method, and differences were compared using the log-rank test. Univariate analysis was performed to screen potential risk factors of OS. Factors with p values lower than 0.05 were included to identify independent risk factors using the multivariate Cox regression model.

All statistical analyses were performed using SPSS version 23.0 (IBM SPSS, Chicago, IL, USA). A two-tailed p value lower than 0.05 was considered to indicate statistical significance.

RESULTS

Baseline Characteristics

The 734 patients who met the inclusion criteria and underwent curative-intent resection for HCC had a median patient age of 66 years (IQR, 57–73 years). The majority of the patients were male (n = 554, 75.5%). Most of the patients had a solitary tumor (n = 645, 87.9%) with a median tumor size of 5.2 cm (IQR, 3.2–9.0 cm). Most tumors were categorized as BCLC stage 0 or A (n = 570, 77.7%). Major liver resections (≥4 segments) were performed for 269 patients (36.6%). The median preoperative AFP level was 13.0 ng/ml (IQR, 3.1–140.0), and the majority of the patients presented with well-compensated Child-Pugh class A liver function (n = 456, 62.1%). At histopathologic examination, most patients (n = 536, 73%) had well-differentiated to moderately differentiated tumors, whereas a subset had microvascular invasion (n = 221, 30.1%) (Table 1).

Among the 269 (36.6%) patients who experienced postoperative complications, 213 (29%) had only one complication, whereas 56 (7.6%) had two or more complications (Table 2). The severity of the complications varied. Whereas 197 (73.2%) of 269 patients had minor complications (Clavien–Dindo grade 1 or 2), 69 (25.7%) had a major complication (Clavien–Dindo grade 3 or 4). Of the 269 patients who had some type of complication, an infectious complication was noted in 81 (11%) patients, with 188 (25.6%) patients having only non-infectious complications. Among patients with infectious complications, 51 (6.9%) patients experienced an SSI, while the infectious complication was non-SSI in 31 (4.2%) patients (Table 2). Patients with infectious complications were older, more likely to have a larger tumor, and were more likely to have undergone a major hepatectomy than patients without infectious complications (all $p < 0.05$; Table 1).

Impact of Postoperative Complications on OS and Recurrence

The median follow-up period for the entire cohort was 27.2 months (IQR, 14.4–49.7 months). Median 1-, 3- and 5-year OS among the entire cohort was 90.1 months, 92.6%, 75.7%, and 63.5%, respectively. Median, 1-, 3-, and 5-year RFS was 40.6 months, 75.3%, 51.9%, and 41.0%, respectively. Patients with postoperative complications had worse OS (median OS: with complications, 74.3 months vs without complications, 103.4 months [p = 0.005]; Fig. 1a) and RFS (median: with complications, 29.4 months vs without complications, 47.5 months [p = 0.010]; Fig. 1b).

On multivariable analysis, overall complications were independently associated with worse RFS (referent, without complications: hazard ratio [HR], 1.4; 95% confidence interval [CI], 1.1–1.8; p = 0.009), but not worse OS (referent, without complications: HR, 1.2; 95% CI, 0.8–1.7; p = 0.430). Notably, long-term survival did not differ between patients with multiple complications versus individuals with a single complication (median OS: multiple complications, 54.3 months vs a single complication, 74.3 months [p=0.464]; median RFS: multiple complications, 18.7 vs single complication, 35.9 months [p = 0.104]; Fig. S1) or between the patients with major complications versus patients with minor complications (median OS: major complications, 74.3 vs minor complications, 70.9 months [p = 0.183]; median RFS: major complications, 25.6 vs minor complications, 33.9 months [p = 0.995]; Fig. S2).

The prognostic impact of postoperative complications was further analyzed according to complication type. Patients with infectious complications had reduced OS (median: with infectious complications, 46.5 vs with non-infectious complications, 85.7 months [p = 0.013] vs with no complications, 106.4 months [$p < 0.001$]; Fig. 2a) and decreased RFS (median: with infectious complications, 22.1 vs non-infectious complications, 38.3 months [p = 0.139] vs with no complications, 45.5 months [p = 0.022; Fig. 2b). Compared with the patients who had non-infectious complications or no complications. In contrast, prognosis did not differ between patients with no complications and those with non-infectious complications (OS, p = 0.218; RFS, p = 0.464; Fig. 2).

Further analyses were performed on only patients who experienced a complication categorized according to non-infectious versus infectious complications. Of note, patients with infectious complications had worse OS ($p <$ 0.001) and RFS (p = 0.030) than patients without infectious

TABLE 1. Baseline demographics and clinicopathologic variables of hepatocellular carcinoma (HCC) patients with or without postoperative infectious complications

Variables	Overall (n = 734) n (%)	With infectious complications (n = 81) n (%)	Without infectious complications (n = 653) n (%)	p value
Age (years)				0.027
< 65	357 (48.6)	30 (37.0)	327 (50.1)	
≥ 65	377 (51.4)	51 (63.0)	326 (49.9)	
Gender				0.720
Male	554 (75.5)	60 (74.1)	494 (75.7)	
Female	178 (24.3)	21 (25.9)	157 (24.0)	
Missing value	2 (0.3)	0	2 (0.3)	
Obesity				0.950
Yes	121 (16.5)	11 (13.6)	110 (16.8)	
No	388 (52.9)	36 (44.4)	352 (53.9)	
Missing value	225 (30.7)	34 (42.0)	191 (29.2)	
Diabetes mellitus				0.076
Yes	232 (31.6)	33 (40.7)	199 (30.5)	
No	482 (65.7)	47 (58.0)	435 (66.6)	
Missing value	20 (2.7)	1 (1.2)	19 (2.9)	
ASA score				0.635
≤ 2	318 (43.3)	37 (45.7)	281 (43.0)	
> 2	325 (44.3)	34 (42.0)	291 (44.6)	
Missing value	91 (12.4)	10 (12.3)	81 (12.4)	
HBV infection				0.300
Yes	64 (8.7)	10 (12.3)	54 (8.3)	
No	587 (80.0)	66 (81.5)	521 (79.8)	
Missing value	83 (11.3)	5 (6.2)	78 (11.9)	
HCV infection				0.070
Yes	198 (27.0)	15 (18.5)	183 (28.0)	
No	528 (71.9)	65 (80.2)	463 (70.9)	
Missing value	8 (1.1)	1 (1.2)	7 (1.1)	
Median AFP: ng/ml (IQR)	13.0 (3.1–140.0)	16.8 (3.4–542.0)	12.8 (3.1–125.0)	0.238
Child-Pugh classification				0.352
A	456 (62.1)	57 (70.4)	399 (61.1)	
B	40 (5.4)	3 (3.7)	37 (5.7)	
Missing value	238 (32.4)	21 (25.9)	217 (33.2)	
Median tumor size: cm (IQR)	5.2 (3.2–9.0)	6.5 (4.4–9.0)	5.0 (3.0–9.0)	0.003
Laparoscopic surgery				0.073
Yes	210 (28.6)	15 (19.2)	195 (29.7)	
No	521 (71.0)	62 (79.5)	459 (70.0)	
Missing value	3 (0.4)	1 (1.3)	2 (0.3)	
Multiple lesions				0.671
Yes	89 (12.1)	11 (13.6)	78 (11.9)	
No	645 (87.9)	70 (86.4)	575 (88.1)	
Macrovascular invasion				0.658
Yes	37 (5.0)	5 (6.2)	32 (4.9)	
No	637 (86.8)	71 (87.7)	566 (86.7)	
Missing value	60 (8.2)	5 (6.2)	55 (8.4)	
BCLC stage				0.286
0/A	570 (77.7)	61 (75.3)	509 (77.9)	
B/C	105 (14.3)	15 (18.5)	90 (13.8)	

Table 1. (continued)

Variables	Overall (n = 734) n (%)	With infectious complications (n = 81) n (%)	Without infectious complications (n = 653) n (%)	p value
Missing value	59 (8.0)	5 (6.2)	54 (8.3)	
Cirrhosis				0.125
Yes	296 (40.3)	26 (32.1)	270 (41.3)	
No	436 (59.4)	54 (66.7)	382 (58.5)	
Missing value	2 (0.3)	1 (1.2)	1 (0.2)	
Major hepatectomy				0.001
Yes	269 (36.6)	44 (54.3)	225 (34.5)	
No	448 (61.0)	36 (44.4)	412 (63.1)	
Missing value	17 (2.3)	1 (1.2)	16 (2.5)	
Grade				0.068
Well-differentiated/moderate	536 (73.0)	53 (65.4)	483 (74.0)	
Poor/undifferentiated	167 (22.8)	25 (30.9)	142 (21.7)	
Missing value	31 (4.2)	3 (3.7)	28 (4.3)	
Microvascular invasion				0.137
Yes	221 (30.1)	32 (39.5)	189 (28.9)	
No	384 (52.3)	40 (49.4)	344 (52.7)	
Missing value	129 (17.6)	9 (11.1)	120 (18.4)	
Capsule involvement				0.794
Yes	114 (15.5)	15 (18.5)	99 (15.2)	
No	384 (52.3)	47 (58.0)	337 (51.6)	
Missing value	236 (32.2)	19 (23.5)	217 (33.2)	
R1 resection				0.045
Yes	86 (11.7)	15 (18.5)	71 (10.9)	
No	646 (88.0)	66 (81.5)	580 (88.8)	
Missing value	2 (0.3)	0	2 (0.3)	

ASA American Society of Anesthesiologists, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* α-fetoprotein, *IQR* interquartile range, *BCLC* Barcelona Clinic Liver Cancer

complications (Fig. 3). On multivariable analysis, after control for competing risk factors including age, tumor size larger than 5 cm, liver capsule involvement, microvascular invasion, and poor tumor differentiation, infectious complications remained associated with OS (referent, without infectious complications: HR, 1.7; 95% CI, 1.1–2.6; p = 0.016; Table 3). Similarly, infectious complications were an independent risk factor for worse RFS (referent, without infectious complications: HR, 1.6; 95% CI, 1.1–2.2; p = 0.013; Table 3).

The prognostic impact of infectious complications was analyzed according to the subtype of infection. Notably, among patients with infectious complications, individuals with non-SSI had worse OS (median: non-SSI, 19.5 vs SSI, 70.9 months [p = 0.010] vs without infectious complications, 103.9 months [$p < 0.001$]) and RFS (median: non-SSI, 12.8 vs SSI, 33.9 months [p = 0.033] vs without infectious complications, 42.3 months [$p < 0.001$]) than patients with SSI or those without infectious complications. However, long-term OS did not differ between patients with SSI versus patients without infectious complications (OS, p = 0.131; RFS, p = 0.460; Fig. 4).

DISCUSSION

Postoperative complications occur with a fair degree of frequency after liver surgery. To date, most research has focused on the association of postoperative complications with in-hospital mortality, hospital length of stay, readmission, and costs.[6–8] More recently, the potential effect of short-term complications on long-term outcomes has been a topic of increased interest. In particular, postoperative complications may result in unfavorable oncologic outcomes. For example, postoperative complications have been associated with worse long-term survival for patients undergoing resection of esophageal, lung, or colorectal cancer.[19–21] To date, the impact of postoperative complications after resection of HCC has not been well-defined.

TABLE 2. Perioperative outcomes of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) patients undergoing curative-intent resection

Variables	(n = 734) n (%)
Overall complications	269 (36.6)
Minor (Clavien–Dindo grades 1–2)	197 (26.8)
Major (Clavien–Dindo grades 3–4)	69 (9.4)
Missing value	3 (0.4)
Infectious complications	81 (11.0)
Surgical-site infection	51 (6.9)
Incisional	20 (2.7)
Intraabdominal	33 (4.5)
Systemic sepsis	3 (0.4)
Pneumonia	13 (1.8)
Urinary tract infection	15 (2.0)
Non-infectious complications	188 (25.6)
Wound dehiscence	4 (0.5)
Acute liver dysfunction	17 (2.3)
Ascites	44 (6.0)
Bile leak	26 (3.5)
Abdominal hemorrhage	11 (1.5)
Ileus	17 (2.3)
Respiratory	23 (3.1)
Pleural effusion	12 (1.6)
Cardiovascular	20 (2.7)
Acute renal dysfunction	12 (1.6)
DVT/thrombophlebitis	14 (1.9)
Others	50 (6.8)

DVT deep venous thrombosis

In addition, the specific effect of infectious complications on long-term oncologic outcomes remains largely unknown. As such, the current study was important because we used a large multi-institutional cohort of patients with HCC and noted that one in three patients (36.6%) experienced a postoperative complication after resection, and that one in ten patients (11%) had an infectious complication. Of particular interest, the patients who experienced a postoperative complication had worse long-term survival than the patients who had an uneventful postoperative course. In addition, the patients with an infectious complication had particularly worse OS and shorter RFS than the patients who had a non-infectious complication. In fact, the patients who experienced a non-infectious complication had OS and RFS compared comparable with that for the patients who had no complication. Moreover, the patients with different types of infection (non-SSI vs SSI) had distinct survival outcomes, with the negative prognostic impact of infectious complications largely due to systemic infection. Taken together, the data strongly suggest a negative oncologic effect of postoperative infection after curative resection for HCC. In turn, preventing and controlling infectious complications not only may assist with short-term recovery, but also may improve long-term oncologic outcomes.

Previous work has noted an association between complications after hepatectomy and long-term survival for patients with colorectal liver metastasis. For example, one meta-analysis of more than 10,000 patients with colorectal livers metastasis reported that postoperative complications correlated with worse prognosis.[9] In another study, the authors specifically noted that infectious complications rather than non-infectious complications independently predicted worse long-term survival for patients with colorectal liver metastasis.[11] In the current study, the incidence of postoperative complications was 36.6%, comparable with the morbidity rate reported in several

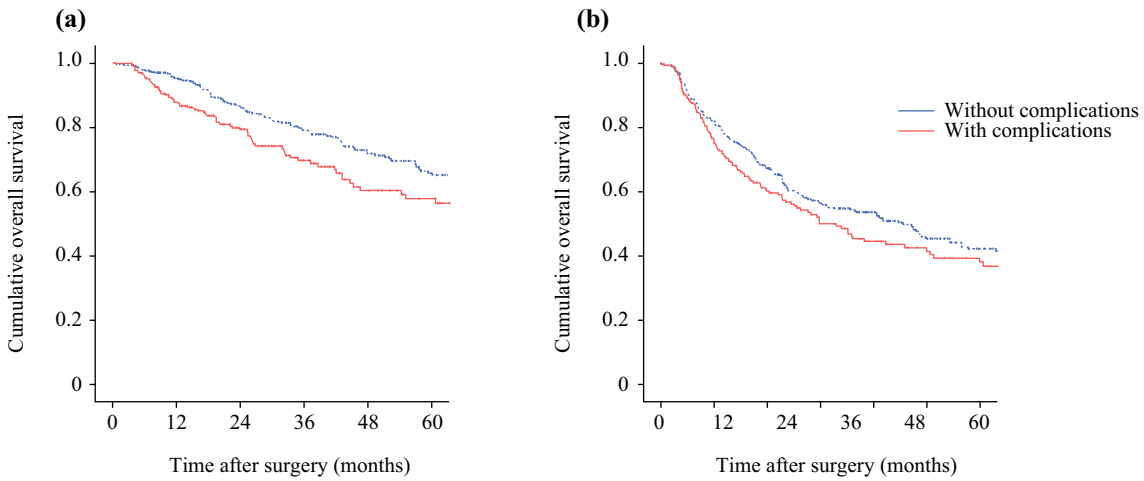

FIG. 1. (**a**) Overall survival and (**b**) recurrence-free survival of hepatocellular carcinoma (HCC) patients with or without postoperative complications after curative-intent resection

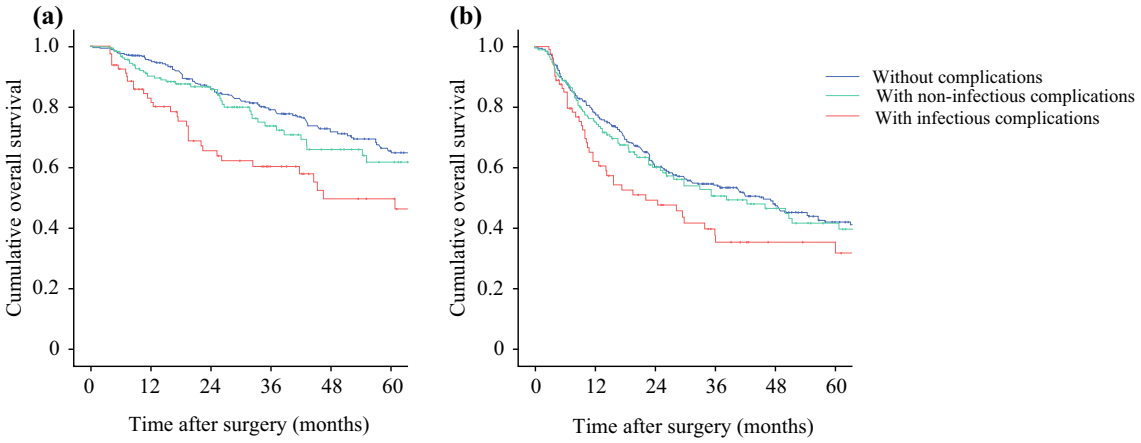

FIG. 2. (**a**) Overall survival and (**b**) recurrence-free survival of hepatocellular carcinoma (HCC) patients with infectious complications, non-infectious complications, or no complications after curative-intent resection

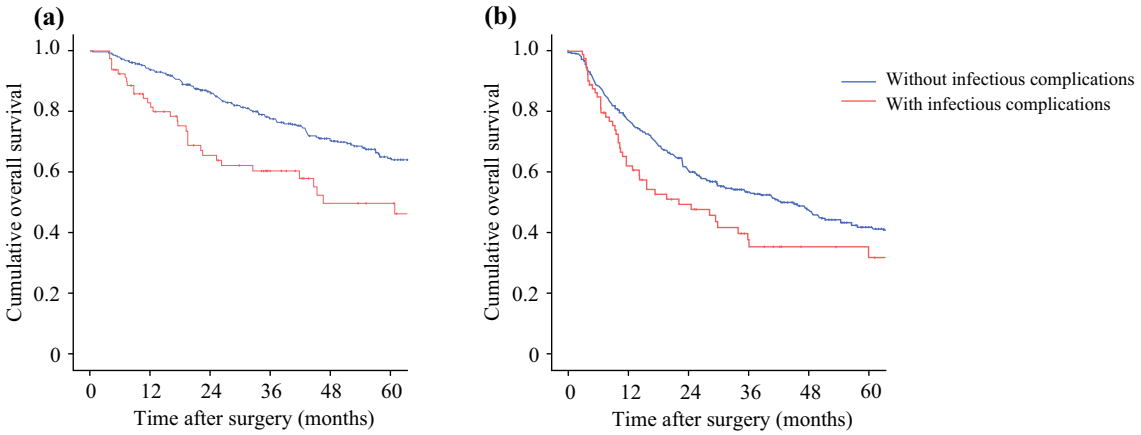

FIG. 3. (**a**) Overall survival and (**b**) recurrence-free survival of hepatocellular carcinoma (HCC) patients with infectious complications or no infectious complications after curative-intent resection

other series of patients undergoing resection of HCC (33.4–44.7%).[12,13,16,18] Of particular interest, the current study also demonstrated that postoperative complications, particularly infectious complications, had an adverse impact on the long-term survival of the patients with HCC. A previous study from China similarly noted that complications correlated with reduced OS but not RFS.[12] Other authors have suggested that intraabdominal infections may be an adverse prognostic factor.[14,15] Unlike the current study, these previous studies involved only a small cohort of patients from single centers and failed to evaluate different types of complications (infectious vs non-infectious) on long-term outcomes. One study of HCC patients from China did demonstrate infectious complications to be an independent adverse risk factor of OS and RFS after curative-intent resection, but more than 90% of the patients had HBV, and more than 75% had liver cirrhosis.[16] In contrast, the current study included patients from Western countries with a much lower incidence of HBV (8.7%) and cirrhosis (40.3%). As such, the current study cohort was more representative of HCC patients often seen in Western centers. Interestingly, infectious, but not non-infectious, complications were associated with OS after resection of HCC among patients.

Death of HCC patients after surgical resection may not be solely due to tumor recurrence because other causes, including liver disease, may contribute to mortality. Indeed, among 206 patients who died before the last follow-up evaluation, 146 (71%) had recurrence, whereas 60 (29%) patients had no recurrence. Notably, the difference in survival between the patients with infectious complications and those without infectious complications was more pronounced relative to OS than to RFS. As such, the occurrence of infectious complications may have indeed been associated with death from other causes. The underlying biologic mechanism driving the negative impact of infectious complications on prognosis is likely multifactorial. Salvans et al.[22] reported that infection promoted the

TABLE 3. Multivariate logistic regression analysis of risk factors for OS and RFS in HCC

Variables	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
OS				
Age: years (≥ 65 vs < 65)	1.5 (1.2–2.0)	0.003	1.7 (1.1–2.7)	0.011
AFP: ng/ml (≥ 400 vs < 400	1.7 (1.2–2.4)	0.003	1.3 (0.9–2.0)	0.220
Child-Pugh grade (B vs A)	1.2 (0.6–2.4)	0.536		
Multiple lesions (yes vs no)	1.3 (0.9–2.1)	0.128		
Tumor size: cm (≥ 5 vs < 5)	1.6 (1.2–2.1)	0.002	1.2 (1.1–1.2)	< 0.001
Cirrhosis (yes vs no)	1.2 (0.9–1.6)	0.223		
Macrovascular invasion (yes vs no)	2.4 (1.4–4.2)	0.003	1.7 (0.8–3.6)	0.144
Resection margin (R1 vs R0)	1.1 (0.5–2.3)	0.838		
Capsule involvement (yes vs no)	2.0 (1.4–2.8)	< 0.001	1.8 (1.2–2.6)	0.004
Microvascular invasion (yes vs no)	2.2 (1.6–3.0)	< 0.001	1.6 (1.1–2.4)	0.025
Tumor grade (3/4 vs. (1/2)	1.9 (1.4–2.5)	< 0.001	1.5 (1.0–2.1)	0.032
Infectious complications (yes vs no)	1.9 (1.3–2.7)	0.001	1.7 (1.1–2.6)	0.016
RFS				
Age: years (≥ 65 vs < 65)	1.0 (0.8–1.2)	0.894		
AFP: ng/ml (≥ 400 vs < 400)	2.2 (1.7–2.9)	< 0.001	1.9 (1.4–2.6)	< 0.001
Child-Pugh grade (B vs A)	1.1 (0.7–1.9)	0.619		
Multiple lesions (yes vs no)	1.5 (1.1–2.0)	0.009	1.2 (0.9–1.7)	0.267
Tumor size: cm (≥ 5 vs < 5)	1.6 (1.3–1.9)	< 0.001	1.3 (1.0–1.8)	0.045
Cirrhosis (yes vs no)	1.1 (0.9–1.3)	0.548		
Macrovascular invasion (yes vs no)	1.4 (0.9–2.5)	0.128		
Resection margin (R1 vs R0)	1.4 (1.0–1.9)	0.041	1.4 (0.9–2.0)	0.105
Capsule involvement (yes vs no)	1.2 (0.9–1.6)	0.296		
Microvascular invasion (yes vs no)	1.7 (1.4–2.2)	< 0.001	1.2 (0.9–1.6)	0.121
Tumor grade (3/4) vs (1/2)	1.6 (1.3–2.0)	< 0.001	1.4 (1.1–1.9)	0.018
Infectious complications (yes vs no)	1.6 (1.1–2.1)	0.006	1.6 (1.1–2.2)	0.013

OS overall survival, *RFS* recurrence-free survival, *HCC* hepatocellular carcinoma, *OR* odds ratio, *CI* confidence interval, *AFP* α-fetoprotein

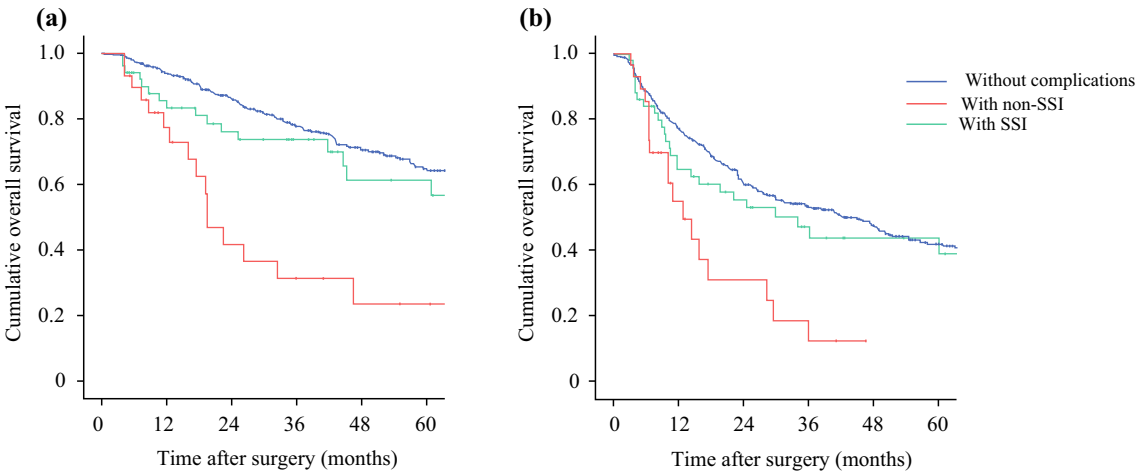

FIG. 4. (**a**) Overall survival and (**b**) recurrence-free survival of hepatocellular carcinoma (HCC) patients with surgical-site infection (SSI), non-SSI, or no infectious complications after curative-intent resection.

invasive capacity of tumor cells in vitro. Infections can lead to excessive and sustained release of inflammatory cytokines such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α), and chemokines.[23,24] The inflammatory response also may directly affect the biologic behavior of tumor cells and also impair the function of anti-tumor immune cells including cytotoxic T cells and natural killer cells.[25] In turn, immune suppression may enhance the survival of residual or spreading tumor cells and thereby worsen long-term survival. In addition, systemic inflammation and sustained use of antibiotics have been demonstrated to reshape the gut microbiota. A dysregulated microbial environment has been associated with liver cancer growth and progression.[26,27]

In contrast to tumor-associated factors, prognostic factors related to surgical and perioperative care, such as postoperative complications, may be potentially controllable and even preventable. Therefore, it is critical to identify risk factors for heightened complications such as infection. In the current study, the risk of infectious complications was associated with older age, large tumor size, and major hepatectomy, and also was correlated with preoperative diabetes mellitus. These findings were consistent with those of other studies in which patients with advanced age and diabetes as well as those undergoing major surgical procedures were more likely to experience postoperative complications, specifically infectious complications.[13,16,28,29] As such, perioperative steps to mitigate surgical infection and meticulous, technical surgical procedures, are critical. Basic infection-control approaches should be followed including smoking cessation, antiseptic shower/wash before surgery, normothermia during surgery, proper hair removal, and controlled blood sugar.[30] Drawing on experience from colorectal surgery, enhanced recovery after surgery (ERAS) approaches that include provision of preoperative free-of-charge SSI prevention kits may result in greater patient compliance with preoperative instructions and lower rates of surgical-site infections.[31] Evidence-based bundles also have been effectively used to coordinate efforts of patients, nurses, surgeons, and anesthesiologist to reduce infectious complications.[32] In turn, these types of bundles in hepato-pancreato-biliary surgery may similarly be used to decrease the risk of postoperative complications, thereby improving both short- and long-term outcomes for patients undergoing resection of HCC.

The current study should be interpreted in the light of several limitations. Although the international multi-institution-based cohort increased sample size and generalizability, patient selection, surgical procedures, and follow-up strategies may have been inconsistent among the centers. In particular, the assessment of postoperative morbidities may have varied among institutions. Only high-volume academic centers were included in the study, all of which followed a relatively standard follow-up protocol and perioperative assessment in compliance with established guidelines. Infections also may have reflected an underlying susceptibility (e.g., more advanced cancer/liver disease) as the cause of earlier death. Specifically, patients who experienced infectious complications may have had worse underlying medical conditions, chronic liver disease, or both at baseline, which may have placed these individuals at a higher risk of death from non-tumor causes.

In conclusion, postoperative complications, particularly infectious complications, were relatively common after curative-intent resection for HCC. Infectious complications were independently associated with an increased long-term risk of tumor recurrence and death. In addition, the patients with systemic versus SSI had an even worse oncologic outcome. Surgeons need to be aware that infectious complications not only have an adverse impact on short-term perioperative recovery, but also can worsen the long-term prognosis of patients undergoing curative-intent resection of HCC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1245/s10434-021-10565-2.

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