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ORIGINAL ARTICLE

Postoperative Infectious Complications Impact Long-Term Survival in Patients Who Underwent Hepatectomies for Colorectal Liver Metastases: a Propensity Score Matching Analysis

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Abstract

Objective Postoperative complications strongly impact the postoperative course and long-term outcome of patients who underwent liver resection for colorectal liver metastases (CRLM). Among them, infectious complications play a relevant role. The aim of this study was to evaluate if infectious complications still impact overall and disease-free survival after liver resection for CRLM once patients were matched with a propensity score matching analysis based on Fong's criteria.

Methods A total of 2281 hepatectomies were analyzed from a multicentric retrospective cohort of hepatectomies. Patients were matched with a 1:3 propensity score analysis in order to compare patients with (INF+) and without (INF−) postoperative infectious complications.

Results Major resection (OR = 1.69 (1.01–2.89), $p = 0.05$) and operative time (OR = 1.1 (1.1–1.3), $p = 0.05$) were identified as risk factors of infectious complications. After propensity score matching, infectious complications are associated with overall survival (OS), with 1-, 3-, 5-year OS at 94, 81, and 66% in INF− and 92, 66, and 57% in INF+ respectively ($p = 0.01$). Disease-free survival (DFS) was also different with regard to 1-, 3-, 5-year survival at 65, 41, and 22% in R0 vs. 50, 28, and 17% in INF+ ($p = 0.007$).

Conclusion Infectious complications are associated with decreased overall and disease-free survival rates.

Keywords Hepatectomy · Morbidity · Infectious · Metastases · Survival · Propensity score

Introduction

Liver resection is a potentially curative treatment for patients with colorectal liver metastases (CRLM), with a 5-year overall survival of 40%.[1] Postoperative morbidity still remains a negative factor impacting the postoperative course,[2,3] even if modern

Collaborators of the French Surgical Association (Association Française de Chirurgie) Working Group are listed in Appendix 1.

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management strategies have improved oncological results, thanks to the evolution of preoperative and perioperative management. [4,5] Recent studies have demonstrated the association of postoperative morbidity with poor long-term oncological results,[6,7] either in primary colorectal cancer or in metastasis,[8–10] with some studies stressing the influence of infectious complications on overall and disease-free survival.[11–16] Fong identified seven factors as independent predictors of poor long-term outcome: node-positive primary, disease-free interval from primary to metastases, number of hepatic tumors, largest hepatic tumor size, and carcinoembryonic antigen (CEA) level, elaborating a score which strongly predicted long-term survival. These criteria defined the concept of "tumor load." The aim of this article is to evaluate whether infectious complications strongly impact disease-free and overall survival in patients with "tumor load," in order to reduce the disturbing effect of cancer on overall and disease-free survival. Our hypothesis is that infectious complications impact overall survival as "tumor load," trying to identify factors predictive of postoperative infectious complications.

Methods

Data were obtained from a questionnaire-based survey of patients who underwent surgery for colorectal liver metastases (CRLM) in 32 French centers from January 2006 to December 2013. This study was performed under the supervision of the French National Surgical Association (Association Française de Chirurgie - AFC) after institutional approval. Medical records were submitted by surgeons of each institution. Demographic data, preoperative, intraoperative, postoperative data, and oncological results were collected and evaluated. Infectious complications were defined as any postoperative complications such as respiratory tract infection, intra-abdominal deep collection, wound infection, sepsis, catheter-related bloodstream infection, and urinary tract infection. Each site was responsible for data collection and entry. Medical records were then submitted to the AFC. Once anonymized, all questionnaires were merged to create a single database. To ensure data completeness, questionnaires were sent back to the institutions in case of missing data (> 10% per variable). Once this step was complete, patients without any long-term follow-up information or with outlying values were excluded. The authors had complete access to the final dataset.

Study Population

This study was designed to evaluate the impact of postoperative infectious complications on overall and disease-free survival. Patients who had postoperative infectious complications (INF+) and patients without infectious complications (INF−) were matched with a propensity score based on patients' characteristics and tumor recurrence prognostic factors, in order to reduce the selection bias. Infectious complications were defined as pulmonary, urinary tract infection, intra-abdominal collection, wound infection, and sepsis. The disease-free interval (DFI) was defined as the interval from the time of primary cancer resection to the diagnosis of liver metastasis. Data were corrected on medical record review and considered inpatient and outpatient settings. Synchronous metastases were defined as metastases detected via preoperative screening or during the resection of primary tumors, and occurring within 12 months of the initial colorectal cancer (CRC) diagnosis. Major hepatectomy was defined as the resection of three and more consecutive liver segments. The number of resected segments was determined by the type of surgical resection according to the Brisbane classification. In case of multiple resections, the number of segments was added.

Patients were followed up using a serum tumor marker (carcinoembryonic antigen) (CEA) and a whole-body computed tomography imaging was performed every 4 or 6 months (depending on the center). Recurrence was defined as an intrahepatic or an extrahepatic biopsy-proven recurrent adenocarcinoma, or a lesion deemed suspicious on cross-sectional imaging. Overall survival (OS) was analyzed from the date of liver resection to the date of death, and disease-free survival (DFS) to the date of recurrence. The indication for adjuvant chemotherapy was discussed in a multidisciplinary meeting.

Data Analysis

Quantitative variables were presented as a mean. Qualitative variables were presented as numbers and percentages. Comparison of quantitative variables was performed using a Mann-Whitney test. Comparison of qualitative variables was performed using Pearson's chi-squared test^2 or Fisher's exact test depending on numbers. A p value < 0.05 was considered significant. Overall and disease-free survival probabilities were calculated using the Kaplan-Meier method.

A propensity score matching (PSM) was calculated to take into account selection biases as well as confounding biases/factors between the two groups and to reduce them. Considering the Fong criteria as predictors of recurrence after liver resection for CRLM, the two populations of INF+ and INF− patients were matched in order to obtain two identical populations on preoperative prognostic factors of recurrence (Fong criteria[1]) to estimate which factor influences the impact of postoperative infections on overall and disease-free survival. After an initial comparison of unmatched INF+ and INF−, patients were matched in a 1:3 analysis with the closest estimated PS within 0.2 of the PSM standard deviation. The matching criteria and development of PSM are described in Fig. 1. For PSM, we chose variables which are known to potentially affect the outcome of interest. The propensity score was assessed using logistic regression including the following

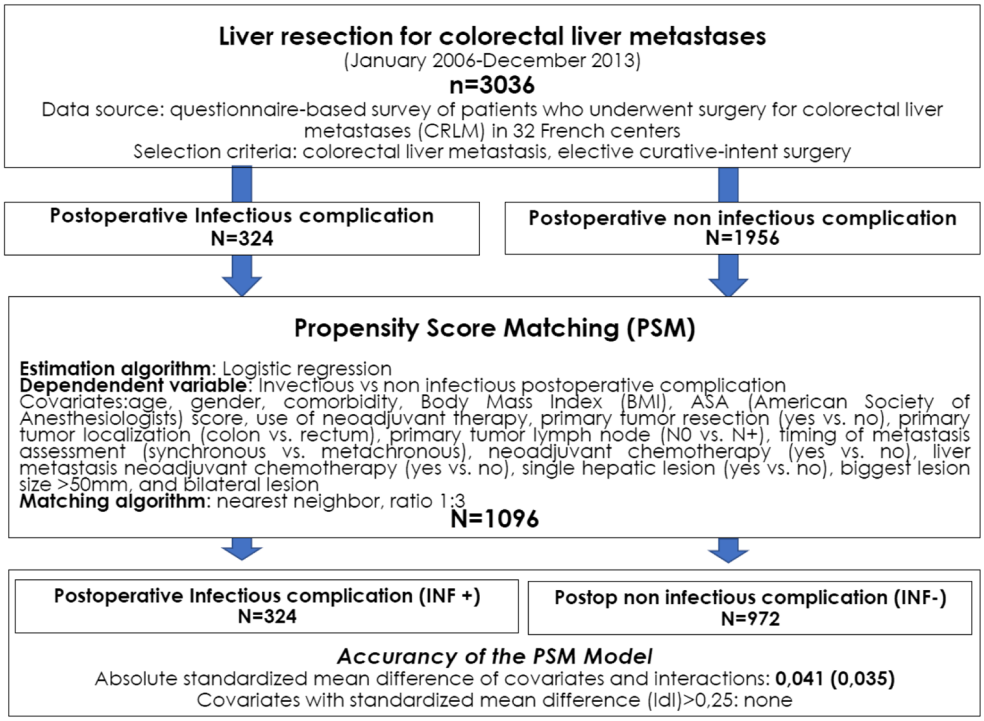

Fig. 1 Table demonstrating development of PS matching

variables: age, gender, comorbidity, body mass index (BMI), ASA (American Society of Anesthesiologists) score, use of neoadjuvant therapy, primary tumor resection (yes vs. no), primary tumor localization (colon vs. rectum), primary tumor lymph node (N0 vs. N+), timing of metastasis assessment (synchronous vs. metachronous), neoadjuvant chemotherapy (yes vs. no), liver metastasis neoadjuvant chemotherapy (yes vs. no), single hepatic lesion (yes vs. no), biggest lesion size > 50 mm, and bilateral lesion. CEA was not included due to missing data. The choice of those variables was based on the results of the univariate analysis and/or on the known influence of specific factors on the selection of the intervention type. A 1:3 ratio was used for propensity score matching, based on the nearest matching PS method. After the matching process, both groups were compared regarding their initial characteristics in order to re-evaluate the comparability of both groups. Finally, matched groups could be compared regarding the different variables of interest in the study.

For the univariate analysis, categorical variables were analyzed using Pearson's χ^2 testing. All values are expressed as a percentage of the group from which they were derived (categorical variables). On the univariate analysis, $p < 0.05$ was considered significant. Logistic regression was then performed to identify risk factors for infectious complications (INF+). Variables with a $p < 0.100$ in the univariate analysis were entered into a regular multivariate regression analysis to estimate the odds ratio (OR) of developing infection complications (INF+) (dependent variables) and the presence or absence of potential prognostic factors (independent variables). The odds ratio was defined as the coefficient with 95% confidence intervals (95% CI).

Analyses were performed using the 3.2.0 version R software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Considering our data, a total of 3036 hepatectomies were performed for CRLMs. Patients with macroscopic positive resection margins (120 patients), non-resectable liver metastasis (180 patients), extrahepatic disease (115 patients), and incomplete data (340 patients) were excluded from the study. Among them, a total of 2281 hepatectomies (324 INF+ and 1957 INF− patients) were analyzed. The median age was 58.5 years and 59% of patients were male. Infectious complications were present in 14.2% of patients. The most common ones were deep collections (7%), pulmonary complications (3%), catheter infection (2.6%), and surgical site infection (2%).

Comparison of INF+ and INF− Groups

Patients' characteristics comparing the two groups were summarized in Table 1. Patients in the INF+ group presented with more synchronous liver metastases (48 vs. 43%, $p = 0.04$), and they received less neoadjuvant

Table 1 Results of univariate and multivariate analysis on factor influencing infectious complications before PSM

	All patients ($n = 2281$)	Infection $n = 324$)	Non-infection ($n = 1956$)	Univariate analysis (p)	Multivariate analysis OR(95%CI); p
Age, years, ± STD	58.5 ± 11.5	60.8 ± 11.5	61.9 ± 11.0	0.21	
Sex, male, *n*(%)	1359 (59)	207 (64)	1152 (59)	*0.08*	
ASA score 3–4, *n*(%)	364 (15)	54 (17)	310 (16)	0.70	
Comorbidity, yes, *n*(%)	918 (40)	120 (37)	798 (41)	0.20	
BMI (kg/m^2) ± STD	25 ± 4.3	25.7 ± 3.8	25.6 ± 4.2	0.30	
Primary resected, yes, *n*(%)	1907(83)	265 (82)	1642 (84)	0.34	
Primary rectum, yes, *n*(%)	609 (26)	77 (24)	532 (27)	0.19	
Primary N+, yes, *n*(%)	1057(46)	150 (46)	907 (46)	0.98	
Primary neoadjuvant ctx, yes (%)	210 (9)	25 (8)	185 (10)	0.31	
Disease-free interval > 12 months, *n*(%)	645 (28)	85 (26)	560 (29)	0.37	
Liver metastasis synchronous, yes, *n*(%)	989 (43)	157 (48)	832 (43)	*0.04*	
Liver metastasis neoadjuvant, yes, *n*(%)	1430 (62)	193 (60)	1237 (63)	*0.0002*	
Portal vein embolization, *n*(%)	372(16)	70 (22)	302 (15)	*0.005*	
Single lesion, *n*(%)	1005 (44)	117 (36)	888 (45)	*0.002*	
Lesion size ≥50 mm, *n*(%)	446 (19)	61 (19)	385 (20)	0.72	
Bilateral lesions, *n*(%)	1040 (45)	159 (49)	881 (45)	0.17	
Number of resected segments, [median, (IQR)]	2.0 ± 1.5	2.2 ± 1.8	2.0 ± 1.7	*0.03*	
Major resection, *n*(%)	906 (36)	153 (47)	753 (38)	*0.003*	*1.69* (*1.01–2.89*); *0.05*
Re-hepatectomy, *n*(%)	490 (21)	78 (24)	412 (21)	0.22	
Two-stage hepatectomy, *n*(%)	361 (15)	56 (17)	305 (16)	0.43	
Laparoscopy, yes, *n*(%)	135(5)	12 (4)	123 (6)	*0.06*	
Pedicle clamping, yes, *n*(%)	1372 (60)	205 (63)	1167 (60)	0.21	
Hepatic vein control, *n*(%)	611 (26)	77 (24)	534 (27)	0.18	
Associated radiofrequency, *n*(%)	418 (18)	49 (15	418 (21)	0.10	
Operative time, min ± STD	257 ± 109	286 ± 121	253 ± 107	*0.001*	*1.1*(*1.01–1.3*); *0.05*
Reoperation, *n*(%)	105(4)	56 (17)	49(3)	*0.0001*	
Surgery related transfusion, *n*(%)	463 (20)	104 (32)	359 (18)	*0.00001*	
ICU stay, *n*(%)	839 (36)	162 (50)	677 (35)	*0.0002*	
ICU duration, days ± STD	4.2 ± 9.7	5.9 ± 8.1	3.8 ± 10.2	*0.001*	
Length of stay, days ± STD	12.4 ± 8.8	17.7 ± 14.3	11.5 ± 7.2	*0.0001*	
90-days morbidity, *n*(%)	619(27)	324 (100)	295 (15)	*0.00001*	
90-days, mortality, *n*(%)	26(1)	6 (2)	20 (1)	0.19	
R1 resection, *n*(%)	196(8)	36 (11)	160 (8)	*0.08*	

Values in italic are statistically significant

chemotherapy (59 vs. 63%, $p = 0.02$) and more portal vein embolization (22% vs. 15%, $p = 0.005$). Concerning liver tumor, there were fewer single nodules in the INF+ group (36 vs. 45%, $p = 0.002$), with more resected segments (2.2 vs. 2, $p = 0.03$), and a higher rate of major hepatectomies (47 vs. 38%, $p = 0.003$), with longer operative times (286 vs. 253, $p = 0.001$), more surgery related transfusion (32 vs. 18%, $p = 0.00001$), with a higher rate of postoperative transfusions (12 vs. 6%, $p = 0.001$) and reoperations (17 vs. 3%, $p = 0.0001$). Concerning hospital stay, a greater number of patients were admitted to the intensive care unit (ICU), namely the INF+ group (50 vs. 35%, $p = 0.0002$), with a longer length of stay (5.9 vs. 3.8 days, p = 0.001), and a longer length of hospital stay (17.7 vs. 11.5 days, $p = 0.0001$).

Risk Factors for Infectious Complications (INF+)

A multivariate analysis was performed on preoperative and intraoperative data in order to identify factors, which influenced INF+. Major resection (OR = 1.69 (1.01–2.89), $p =$

0.05) and operative time (OR = 1.1 (1.1–1.3), $p = 0.05$) were identified as risk factors (Table 1).

Disease-Free and Overall Survival After Propensity Score Matching

There was a difference in terms of long-term survival, with 1-, 3-, 5-year OS at 98, 80, 65% in INF− and 92, 72, 61% in INF+ respectively ($p = 0.01$) (Fig. 2). Disease-free survival (DFS) was different with 1-, 3-, 5-year survival at 63, 42, 31% in INF − vs. 43, 31, 20% in INF+ ($p = 0.007$) (Fig. 3).

Comparison of INF+ Vs. INF– Groups After Propensity Score Matching

In order to evaluate which factors influence OS, a propensity score matching based on patients' characteristics and oncological aspects were performed—324 patients in the INF+ group were matched to 972 patients in the INF− group (Table 2). Comparing the matched groups, there was a longer operative time (270 vs. 240, $p = 0.007$), more surgery related transfusions (32 vs. 19%, $p = 0.0001$), more reoperations (17 vs. 2%, $p = 0.0002$), more postoperative transfusions (12 vs. 5%, $p = 0.004$), a longer ICU stay (3.8 vs. 2 days, $p = 0.001$), and a longer hospital stay (13 vs. 10 days, $p = 0.05$).

Risk Factors for Infectious Complications After Propensity Score Matching

No factor was evidenced with a multivariate analysis.

Disease-Free and Overall Survival After Propensity Score Matching

There was a difference in terms of long-term survival, with 1-, 3-, 5-year OS at 94, 81, and 66% in the INF− group and 92, 66, and 57% in the INF+ group respectively ($p = 0.01$) (Fig. 4). DFS was different with 1-, 3-, 5-year survival at 65, 41, and 22% in the INF− group vs. 50, 28, and 17% in the INF+ group ($p = 0.007$) (Fig. 5).

Discussion

Postoperative infectious complications are associated with the worst overall and disease-free survival after major surgery as evidenced in the literature.[4,16,17] Even if the association of infectious complications with poor oncological prognosis is obvious, no study demonstrates how infectious complications have influenced oncological outcomes in patients with equal oncological prognostic factors. In the literature, it is unclear whether infectious

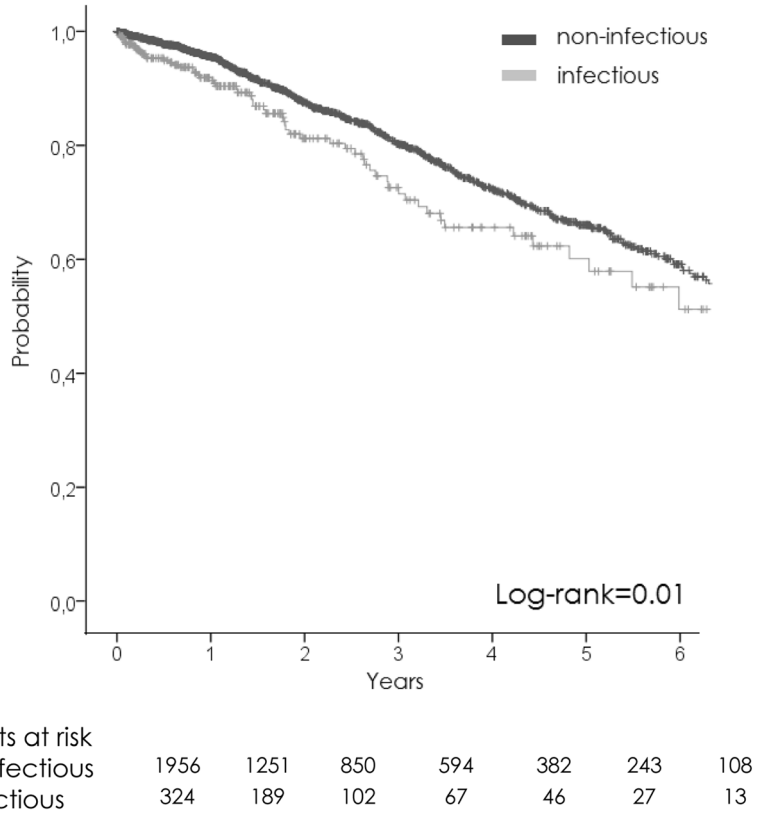

Fig. 2 Relation between infectious and non-infectious complications on overall survival before PSM

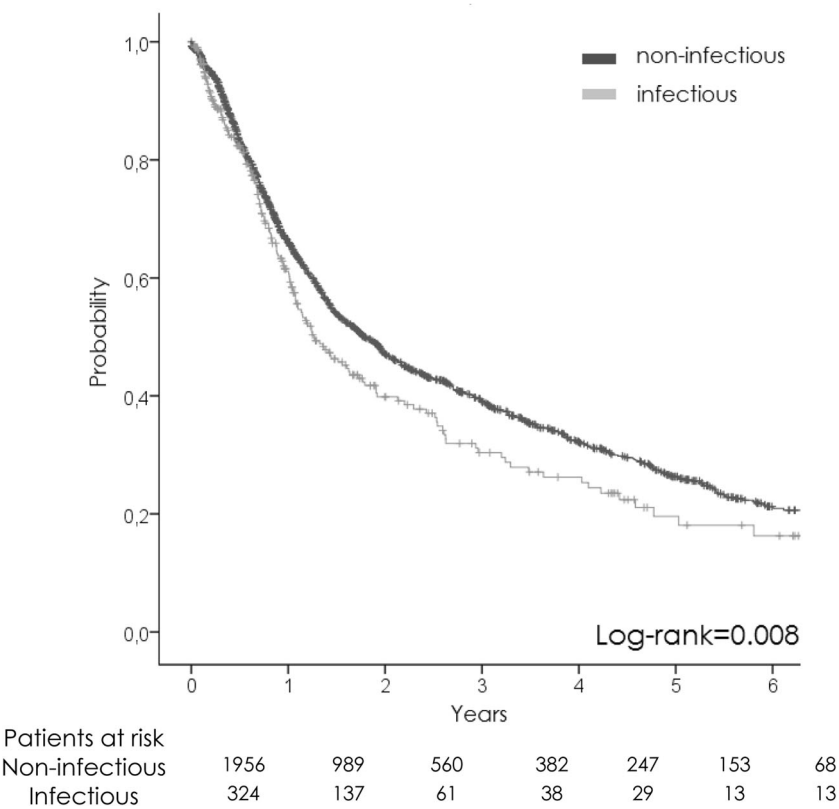

Fig. 3 Relation between infectious and non-infectious complications on disease-free survival before PSM

complications increase the risk of recurrence irrespective of tumor load. Some articles[18–20] demonstrated how effectively postoperative infectious complications negatively impact overall and disease-free survival in patients who underwent curative resection for colorectal cancer, increasing the rate of local recurrence.[18–21]

To our knowledge, this is the only series which analyzed the impact of infectious complications on OS and DFS in patients who underwent liver resection for CLM matched with oncological prognostic factors. This series demonstrated that infectious complications impact overall and disease-free survival negatively.

Our study demonstrated that infectious complications were present in almost 14.2% of patients who underwent liver resection for colorectal liver metastases. As previously described in the literature, tumor progression is a process, which is not only depending on tumor properties but it is also influenced by the interaction of cells present in host cells, an excessive level of proinflammatory cytokines by IL-1, IL-6, and IL-8, and tumor necrosis factor. This high level reduces the number and function of T lymphocytes, natural killer cells,[22] reducing prognosis in cancer patients, increasing inflammation and immunosuppression which may contribute to metastatic proliferation,[23] and accelerating the growth of residual cancer cells. Inflammation also increases vascular endothelial growth factor (VEGF)[24] production, which is associated with tumor growth and poor prognosis in patients with cancer.[24,25] In order to obtain two comparable groups to evaluate the real value of infectious complications on tumor recurrence and survival, we compared INF+ and INF− groups. As evidenced in the comparison between INF+ and INF− patients, infectious complications strongly impact overall and disease-free survival in unmatched populations. Comparing the unmatched populations, some preoperative confounding factors were different among groups, namely the presence of synchronous liver metastasis, differences in neoadjuvant chemotherapy, portal vein embolization, and the presence of single nodules. Concerning intraoperative data, a larger presence of major hepatectomies with longer operative times, a longer ICU and hospital stay, and a higher 90-day morbidity were more present in INF+ patients. In multivariate analysis on factors influencing infectious complications, operative time and the presence of major resection were identified as influencing factors. Such data could be considered essential in patients who undergo major resection as they are exposed to a higher risk of infectious complications, due to the complexity of surgery and to the longer operative time required to complete surgery. After propensity score matching with preoperative factors which could influence overall and disease-free survival following the Fong criteria, the only differences evidenced were longer operative times, the presence of transfusion, and the rate of reoperations, all factors considered accountable for immunosuppression and indirectly responsible for recurrence,[8,26,27] a longer ICU and hospital stay, always associated with a higher postoperative morbidity in the INF+

Table 2 Results of univariate and multivariate analysis on factor influencing infectious complications after PSM

	All patients ($n = 1296$)	Infection ($n = 324$)	Non-infection ($n = 972$)	Univariate analysis (p)	Multivariate analysis OR(95%CI); p
Age, years, ± STD	62.1 ± 11.3	62.1 ± 11.5	62.1 ± 11.2	0.57	
Sex, male, *n*(%)	778 (60)	207 (64)	571 (59)	0.10	
ASA score 3–4, *n*(%)	216 (17)	54 (17)	162 (17)	0.99	
Comorbidity, yes, *n*(%)	500 (39)	120 (37)	380 (39)	0.51	
BMI (kg/m^2) ± STD	25.6 ± 4.1	25.7 ± 3.8	25.6 ± 4.3	0.56	
Primary resected, yes, *n*(%)	1094 (84)	265 (82)	829 (85)	0.13	
Primary rectum, yes, *n*(%)	328 (25)	77 (24)	251 (26)	0.46	
Primary N+, yes, *n*(%)	614 (47)	150 (46)	464 (48)	0.65	
Primary neoadjuvant ctx, yes (%)	119 (9)	25 (8)	94 (10)	0.29	
Disease-free interval > 12 months, *n*(%)	353(27)	85 (26)	268 (28)	0.64	
Liver metastasis synchronous, yes, *n*(%)	628 (48)	157 (48)	471 (48)	0.99	
Liver metastasis neoadjuvant, yes, *n*(%)	792 (61)	193 (60)	599(62)	0.51	
Portal vein embolization, *n*(%)	249 (19)	70 (22)	179 (18)	0.20	
Single lesion, *n*(%)	469 (36)	117 (36)	352 (36)	0.97	
Lesion size ≥ 50 mm, *n*(%)	268 (21)	61 (19)	207 (21)	0.34	
Bilateral lesions, *n*(%)	627 (48)	159 (49)	468 (48)	0.77	
Number of resected segments [median, (IQR)]	2 ± 1.8	2 ± 1.7	2 ± 1.8	0.91	
Major resection, *n*(%)	610 (47)	153 (47)	457 (47)	0.94	
Re-hepatectomy, *n*(%)	287 (22)	78 (24)	209 (22)	0.33	
Two-stage hepatectomy, *n*(%)	223 (17)	56 (24)	167 (17)	0.99	
Laparoscopy, yes, *n*(%)	51 (4)	12 (4)	39 (4)	0.80	
Pedicle clamping, yes, *n*(%)	819 (63)	205 (63)	614 (63)	0.97	
Hepatic vein control, *n*(%)	356 (27)	77 (24)	279 (29)	0.08	
Associated radiofrequency, *n*(%)	831 (64)	49 (15)	182 (19)	0.14	
Operative time, min ± STD	250 ± 114	270 ± 121	240 ± 112	*0.007*	
Surgery related transfusion, *n*(%)	292 (22)	104 (32)	188 (19)	*0.0001*	
Reoperation, *n*(%)	77 (6)	56 (17)	21 (2)	*0.00002*	
ICU stay, *n*(%)	522 (40)	162 (50)	360 (37)	*0.00001*	
ICU duration, days ± STD	2.5 ± 6.8	3 ± 8.1	2 ± 12	*0.001*	
Length of stay, days ± STD	11.5 ± 8.2	13 ± 14	10 ± 6.6	*0.05*	
90-day morbidity, *n*(%)	480 (37)	324 (100)	156 (16)	*0.0003*	
90-day mortality, *n*(%)	16 (1)	6 (2)	10 (1)	0.24	
R1 resection, *n*(%)	117 (9)	36 (11)	81 (8)	0.13	

Values in italic are statistically significant

group. Even if 17% of patients were reoperated on in the INF+ group, the distribution of reoperation causes was similar among INF+ and INF− patients, even after PSM. This could well be the clear demonstration that major hepatectomies could be a risk factor of infection, as previously confirmed by Lundy et al.[28] Even after PSM, a difference in overall and disease-free survival was still present, corroborating the influence of infectious complications irrespective of tumor-related factors.

In the modern era of liver surgery, the postoperative management of patients with CRLM plays an important role in the prevention of factors which could influence postoperative course, especially duration of stay. In our postoperative management, we should reduce any unnecessary act to a minimum and should follow enhanced recovery after surgery environment programs. In fact, as demonstrated by Pessaux et al.[29] the use of a nasogastric tube after liver surgery is unnecessary as it may bring about a risk of pulmonary complications. Likewise, a recent article by Wong-Lun-Hing et al.[30] demonstrated how prophylactic abdominal drainage had no impact on intra-abdominal infection and reoperation rates. All this could positively impact the postoperative course, reducing the risk of infectious complications.

In conclusion, even if tumor load is comparable among the two populations, infectious complications still strongly impact overall and disease-free survival. The main bias of this study is

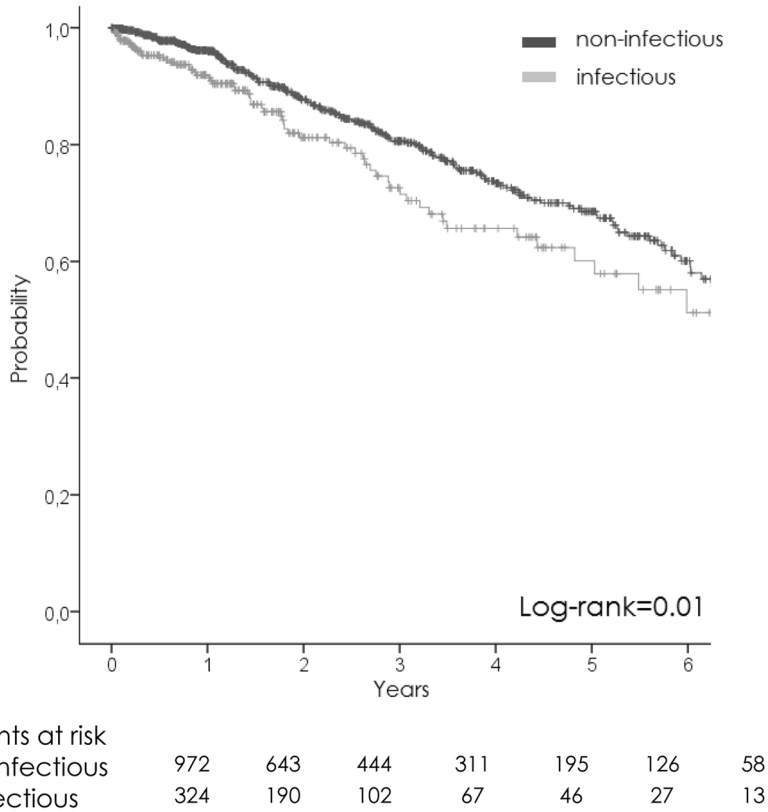

Fig. 4 : Relation between infectious and non-infectious complication on overall survival after PSM

related to the presence of many confounding factors which could impact overall and disease-free survival, such as immunosuppressive conditions which could not easily be estimated in our series. Another major limitation of the paper is its retrospective characteristic of the study. For this reason, it was impossible to establish a more detailed about postoperative

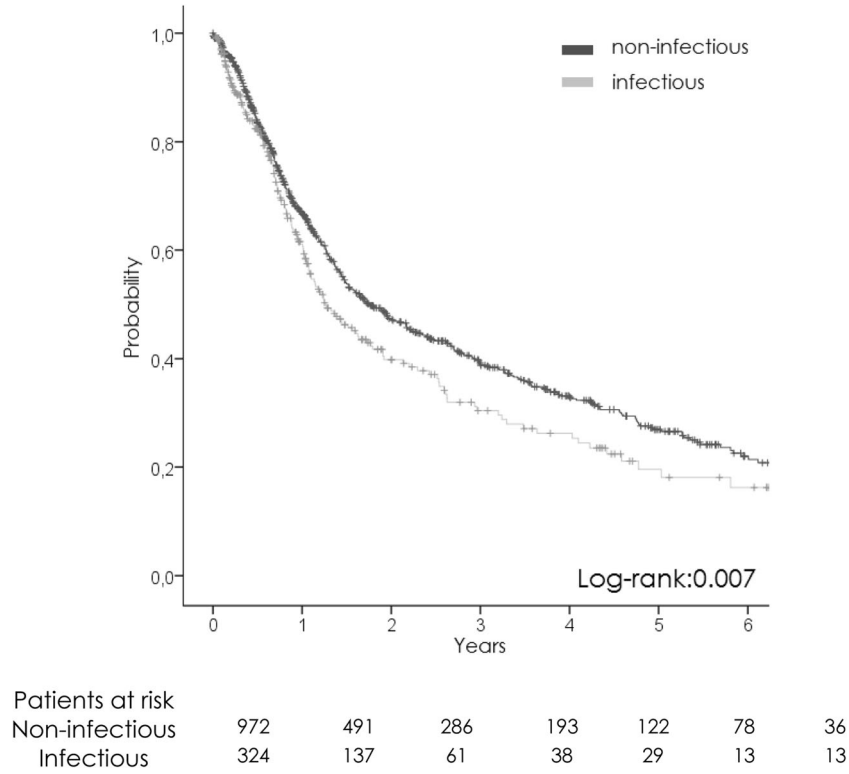

Fig. 5 : Relation between infectious and non-infectious complication on disease-free survival after PSM

infection-related complications or precise data on duration and starting of adjuvant chemotherapy. However, considering available data, we could conclude that infectious complications, in case of comparable oncological load among groups, are associated with poorer overall and disease-free survival. Even if we have a high volume of patients in the study, it is based on a multicentric retrospective comparison, with different management modalities in each center depending on patient characteristics and local practices and expertise, with non-unique strategies. Further investigations are required to clarify and identify the role of factors which predict postoperative infectious complications, and further progress should be made in surgical techniques in order to reduce postoperative morbidity and the risk of recurrence and to improve therapeutic outcomes. Even if it is clear that infectious complications impact postoperative outcomes, up to now it is difficult to anticipate which factors predict infectious complications, even in our large patient population study. Our data tend to suggest caution and a better selection of patients in case of major resection.

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