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## LAPAROSCOPIC VERSUS OPEN LIVER RESECTION FOR INTRAHEPATIC CHOLANGIOCARCINOMA: REPORT OF AN INTERNATIONAL MULTICENTER COHORT STUDY WITH PROPENSITY SCORE MATCHING.

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Part of the results of this research study was presented as an oral communication to the AFC 2020 French congresses in Paris, France.

## **ABSTRACT**

### **BACKGROUND**

Intrahepatic cholangiocarcinoma (ICC) is a rare disease with a poor prognosis. In patients where surgical resection is possible, outcome is influenced by peri-operative morbidity and lymph node status. Laparoscopic liver resection (LLR) is associated with improved clinical and oncological outcomes in primary and metastatic liver cancer compared to open liver resection (OLR), but evidence on ICC is still insufficient.

The primary aim of this study was to compare overall survival (OS) for large series of patients treated for ICC. Secondary objectives were to compare disease free survival (DFS), predictors of death and recurrence.

### **METHODS**

Patients treated with LLR or OLR for ICC from 2000 to 2018 from three large international databases were analyzed retrospectively. Each patient in the LLR group (case) was matched with one OLR control (1:1 ratio), through a propensity score calculated on clinically relevant pre-operative covariates. Overall and disease-free survival were compared between the matched cohorts. Predictors of mortality and recurrence were analyzed with COX regression, and the TO were described.

### **RESULTS**

During the study period, 855 patients met the inclusion criteria (OLR=709, 82.9%; LLR=146, 17.1%). Two groups of 89 patients each were analyzed after propensity score matching, with no significant difference regarding pre- and post-operative variables.

Overall survival at 1, 3 and 5 years was 92%, 75% and 63% in LLR group versus 92%, 58% and 49% in OLR group ( $p=0.0043$ ). Adjusted Cox regression revealed severe post-operative complications (HR: 10.5, 95%CI (1.01, 109)  $p=0.049$ ) and steatosis (HR: 13.8, 95%CI (1.23, 154)  $p=0.033$ ) as predictors of death, while transfusion (HR: 19.2, 95%CI (4.04, 91.4)  $p<0.001$ ) and severe post-operative complications (HR: 4.07, 95%CI (1.15, 14.4)  $p=0.030$ ) as predictors of recurrence

### **CONCLUSION**

The survival advantage of LLR over OLR for ICC is equivocal, given historical bias and missing data.

## INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a rare disease with a poor prognosis<sup>1,2</sup> and its incidence is increasing in Western countries<sup>1,3</sup>. Surgical resection plays a pivotal role in curative treatment<sup>4</sup>, but except for some subgroups with good prognostic features<sup>5</sup>, morbidity<sup>6,7</sup> and mortality<sup>2,8,9</sup> outcomes are disappointing.

Laparoscopic liver resection (LLR) is gaining momentum for malignant liver disease<sup>10</sup>, including hepatocellular carcinoma (HCC)<sup>11,12</sup> and colorectal liver metastasis (CLM)<sup>13,14</sup>. The laparoscopic approach is often associated with reduced blood loss and lower complication rates<sup>15,16</sup>, even if no difference in survival outcomes was observed within two randomized clinical trials (RCT) comparing LLR to open approach (OLR) in CLM<sup>17</sup> or HCC<sup>18</sup>.

Data on LLR and ICC are scarce, but combined analysis of small-volume, unmatched series indicate that LLR appears to have similar oncological efficacy compared to OLR, except for lymph node dissection<sup>19</sup>.

Textbook outcome (TO) is a recently proposed composite-outcome metric, composed of post-operative outcomes that represent the ideal (i.e. textbook) hospitalization. It has been evaluated in the setting of ICC and HCC. The TO Achievement rate for ICC is around 25%<sup>20,21</sup>. For HCC, a laparoscopic approach has been shown to achieve the TO more often and to significantly improve overall (OS) and disease free survival (DFS)<sup>20,21</sup>.

The aim of this study was to compare the morbidity, lymph node dissection rate, TO, and long-term survival of LLR versus OLR in a large, international multicenter series of patients treated for ICC.

## **METHODS**

This study was an international, multicenter cohort study to compare the outcomes of laparoscopic (LLR) and open liver resection (OLR) within the target population of patients affected by ICC. To minimize historical bias due evolving clinical and surgical practice, only patients treated by LLR or OLR from January 2000 up to June 2018 were included, while patients with a minimum follow-up period of less than 6 months were excluded. Given the limited experience of individual centers, three existing independent multicenter databases were repurposed, and data were merged.

- 1) The AFC-LLR-2018 study group was created in 2018 under the auspices of the French Association of Surgery (AFC) to produce a retrospective registry of LLR. Data on 4215 consecutive patients undergoing LLR from 1995 to 2018 were retrospectively collected from 29 institutions. Data were extracted from the nested cohort of patients treated for ICC.
- 2) The Preoperative Risk Score (PRS) study group was organized to externally validate a published score for prediction of long-term outcomes after surgery for ICC. Eleven international HPB centers provided data on 355 patients resected from 2001 to 2018 for ICC, by open or laparoscopic approach<sup>5</sup>.
- 3) The AFC-ICC-2009 study group was created in 2009 to produce a registry of patients operated for ICC. Data on all consecutive patients undergoing resection with curative intent for ICC from 1989 to 2009 were collected from a dedicated multi-institutional database from 24 university hospitals, as reported elsewhere<sup>22</sup>.

This study was designed in November 2019 in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement* and guidelines<sup>23</sup>.

### **Participants and study size**

Patients from each database were screened for duplicates and data completeness, then sequentially merged into a raw dataframe including n=1215 patients.

These were further screened according to the following inclusion criteria:

- Patients underwent LLR or OLR with curative intent (R0 or R1) by hepatectomy, with or without an associated procedure.
- the biliary origin of the tumor was histopathologically confirmed.

- the tumor was a typical ICC. (gallbladder cancer, hepatocholangiocarcinomas, cystadenocarcinomas and hilar cholangiocarcinomas were excluded)

This resulted in exclusion of n=360 patients (flowchart with reasons in Fig. 1), leaving n=855 patients in the final (unmatched) study cohort (time trend in suppl. Fig 1). Patients undergoing LLR were considered as cases and compared with a 1:1 matched OLR control group.

## **Variables**

Peri-operative variables reported in each database were reconciled in a single dataset for analysis. Each patient was anonymized and assigned a unique alphanumeric code. The dataset worksheet was hosted on a secure computer with limited access and password protection. Data management was compliant with the reference methodology on personal data processing and protection (MR003), as dictated by the French data protection authority (*Commission Nationale de l'Informatique et des Libertés*).

Textbook Outcome<sup>24</sup>, a composite-outcome metric, was defined by the presence of (all) the following six parameters: negative margins (R0), no peri-operative transfusion, no postoperative surgical complications, no prolonged length of stay (defined by  $\leq 50^{\text{th}}$  percentile of the general and matched cohort), no readmissions within 30 days after discharge and no postoperative mortality within 30 days after surgery.

The extent of LS was considered as major when involving more than three segments, and further classified according to the Institut Mutualiste Montsouris (IMM) Difficulty classification, published by Kawaguchi and coll<sup>25,26</sup>, with three increasing levels of difficulty according to the number, location and difficulty of resected liver segments, irrespective of a laparoscopic or open approach. LLR was analyzed on an intention-to-treat basis.

Regional node dissection (or lymphadenectomy) should be considered as the removal of station 12 (hepatoduodenal), station 8 (common hepatic artery) and station 13 (posterior to pancreas). For left-sided tumors, station 7 (left gastric artery) and station 1 (right oesophageal crus) should also be considered. Nevertheless, the recommendation for disease-specific staging for ICC was introduced only in 2010 by the 7<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) manual, followed by the guidelines of the European Association for the Study of the Liver<sup>27</sup>. Moreover, the consensus on the number of nodes harvested (n=4 and more recently n=6) was defined only within the 8<sup>th</sup> AJCC

manual<sup>28</sup> in 2017, and a recent multicenter study reported how even in tertiary centers the use of lymphadenectomy and the proportion of nodes retrieved increased over time from 2000 to 2015<sup>29</sup>.

Last, given the nature of data source with data from over 40 centers, the investigators had no access to individual patient data and in particular to the number of nodes retrieved.

On the basis of these considerations, and to minimize any historical bias, "node dissection" (or lymphadenectomy) was considered to be performed according to the presence of nodes (N1 or N0) on the pathological report (node dissection = Y). In the event of absence of nodes (Nx) or missing variable (NA), the worst case-scenario "no lymphadenectomy" was considered (node dissection = N).

Given the oncological role of N status, as well as the anticipated missing data, a subgroup analysis of patients with the same oncologic approach and available N status was realized. Hospital stay was defined as the time spent in hospital during the primary admission from day of operation to discharge.

Complications were described according to the Clavien-Dindo classification<sup>30</sup> and collected within 90 days after surgery. Complications were designated severe if superior or equal to ( $\geq$ ) Grade III, including postoperative death.

### **Study objectives:**

The primary objective was to compare overall survival (OS) between LLR and OLR after propensity score matching. Variables required to measure the primary endpoint were the event (death) and time until the event (OS), the latter defined as the time from surgical intervention to the date of death or last follow-up.

Secondary objectives were to compare disease free survival (DFS) between LLR and OLR after propensity score matching, as well as risk factors for mortality, recurrence and the description of textbook outcomes.

### **Missing data**

The 89 variables included in the final dataset were inspected with the `vis_miss` function of the `visdat` package. After exclusion of 28 variables with a missing rate  $> 80\%$ , the whole database was 84.1% complete (missing data = 15.9%).



A multiple imputation through the package `mice` was used for preoperative variables only, and only when <5% of observations *per* variable were missing.

## **Statistical analysis methods**

### *Statistical software*

Data managing, statistical evaluation and analysis were performed with R software (version 4.0.2 or higher. The R Foundation for Statistical Computing. [www.cran.r-project.org](http://www.cran.r-project.org), Vienna, Austria). All the packages, libraries and functions refer to the R Software.

### *Descriptive statistics*

Categorical variables were reported as percentages, while continuous variables were summarized as means and standard deviation (SD) or median and range for discrete variables, as appropriate. The Student's *t*-test or Mann-Whitney U test were used for comparisons of quantitative variables as appropriate, whereas a  $\chi^2$  test or Fisher's exact test was used to compare categorical data. Data were compared before and after matching.

### *Propensity score matching*

Potential biases due to the different distribution of covariates among patients who underwent LLR and OLR, were controlled by matching based on a propensity score (MatchIt package), which included five pre-operative covariates: difficulty classification (IMM classification, as defined above<sup>25,26</sup>), patient's age (<50 y,  $\leq 50y < 70$ ,  $\geq 70y$ ), the year of surgery (from 2000 to 2018), number of lesions and tumor size (max.diameter). Each patient in the LLR group (case) was matched with one OLR control (1:1 ratio), without replacement, to minimize conditional bias. For each patient treated with LLR, a nearest score neighbour treated with OLR was matched. Multiple caliper widths were tested. A caliper width of 0.02 resulted in the best trade-off between homogeneity and retained sample size. Finally, patients were compared with respect to propensity score.

### *Survival analyses.*

Kaplan–Meier curves for OS and DFS before and after matching were created through `survfit` and `ggsurvplot` functions from `survminer` and `survival` packages, with two strata corresponding to both LLR and OLR groups.

### *Definition of variables predicting death or recurrence within the whole cohort.*

Unadjusted hazard ratios (HRs) and 95% confidence intervals (95% CI) were calculated by Cox proportional hazards regression analysis for peri-operative variables associated with death

or recurrence. Variables with a p value <0.1 (as well as those considered clinically relevant) were entered in a multivariate Cox model to identify factors independently associated with death or recurrence. The final model expressed the adjusted HRs and 95%CI.

## **RESULTS**

### **Participants**

A total of 855 patients undergoing liver resection for ICC from 30 participating centers were included during the study period (2000 – 2018) and represented the study cohort (Figure 1), with 82.9% treated by OLR (n=709) and 17.1% treated by LLR (n=146). Among them 51.2% (n=437) were male. The cohort had a median BMI of 25.66±4.69 Kg/m<sup>2</sup> and was affected by metabolic syndrome in 29.3% (n=135) of cases. Major hepatectomy was required in 71.8% (n=614) of cases (LLR 41.8%, n=61 vs OLR 78.0%, n=553; p<0.001). No differences were observed in the rate of R1 resections and severe post-operative complications (Clavien-Dindo≥Grade III). Textbook outcomes were achieved in 15.8%(n=135) of patients, significantly more often after LLR than OLR (30.8%(n=45) vs 12.7%(n=90) respectively; p<0.001).

The rate of node dissection was significantly lower in the LLR vs OLR group (17.4% n=25) vs 46.2% n=328) respectively; p<0.001) (Table 1).

### **Propensity score model**

After propensity score adjustment (suppl. Fig 2), the demographic and preoperative variables of matched patients (n=178) (LLR n=89; OLR n=89) were similar (Table 1), except for the presence of metabolic syndrome (LLR 32.5%, n=26 vs OLR 13.6%, n=11; p=0.008) and underlying liver disease (LLR 44.9%, n=40 vs OLR 22.7%, n=20; p=0.001). In particular, no differences were observed in the rates of portal vein embolization, major hepatectomy, rates of R1 resection or lymph node dissection either. The time-trend distribution of cases and controls after matching is represented within the supplementary figure 3.

### **Overall survival, before and after matching**

Within the whole cohort, Kaplan–Meier OS estimation at 1, 3 and 5 years was 93%, 74% and 65% in LLR group versus 83%, 53% and 39% in OLR group, respectively (p<0.001) (Figure 2).

After matching, Kaplan–Meier OS estimation at 1, 3 and 5 years was 92%, 75% and 63% in LLR group versus 92%, 58% and 49% in OLR group, respectively ( $p=0.0043$ ) (Figure 3).

#### **Predictors of mortality within the matched cohort.**

A univariate Cox model was analyzed to determine predictors of death within the matched cohort: OLR (HR: 1.94, 95%CI (1.01, 3.74)  $p=0.048$ ), tumor diameter (HR: 1.12, 95%CI (1.01, 1.23)  $p=0.025$ ), R1 status (HR: 3.2, 95%CI (1.27, 8.1)  $p=0.014$ ) node dissection (HR: 6.51, 95%CI (1.44, 29.4)  $p=0.015$ ) and positive node (N) status (OR: 2.31, 95%CI (1.00, 5.33)  $p=0.049$ ) were associated with long term mortality.

Multivariable analysis (including steatosis) revealed that severe post-operative complications (HR: 10.5, 95%CI (1.01, 109)  $p=0.049$ ) and steatosis (HR: 13.8, 95%CI (1.23, 154)  $p=0.033$ ) were significantly associated with mortality (Table 2).

#### **Disease free survival, before and after matching**

Within the whole cohort, Kaplan–Meier DFS estimation at 1, 3 and 5 years was 70%, 37% and 32% for LLR versus 48%, 22% and 19% in the OLR group, respectively ( $p<0.001$ ) (Figure 4).

Figure 5 displays the Kaplan–Meier DFS estimation after matching at 1, 3 and 5 years (71%, 41% and 41% LLR versus 61%, 37% and 29% OLR, respectively ( $p=0.22$ )).

#### **Predictors of recurrence within the matched cohort.**

A univariate Cox model was used to investigate predictors of recurrence within the matched cohort: ASA score (ASA\_II HR: 0.24, 95%CI (0.08, 0.77)  $p=0.016$ ; ASA\_III HR: 0.28, 95%CI(0.08, 0.93)  $p=0.038$ ) tumor diameter (HR: 1.15, 95%CI (1.05, 1.25)  $p=0.001$ ), RBC transfusion (HR: 3.08, 95%CI(1.65, 5.74)  $p<0.001$ ), R1 status (HR: 2.63, 95%CI (1.20, 5.75)  $p=0.016$ ), node dissection (HR: 3.17, 95%CI(1.42, 7.11)  $p=0.005$ ) and positive node (N1) status (HR: 2.77, 95%CI(1.41, 5.46)  $p=0.003$ ), .92, 95%CI (1.06, 3.49)  $p=0.032$ ) were associated with recurrence.

Adjustment by multivariable analysis showed that RBC transfusion (HR: 19.2, 95%CI (4.04, 91.4)  $p<0.001$ ) and severe post-operative complications (HR: 4.07, 95%CI (1.15, 14.4)  $p=0.030$ ) were significantly associated with recurrence (Table 3).

### **Textbook outcome and survival.**

Textbook Outcome (TO), which defined the quality of surgical care, was achieved in 15.8% (n=135) and 36.5% (n=65) of cases before and after matching, respectively.

The details of post-operative outcomes defining TO within the matched cohort are summarized in Table 4 and supplementary Figure 4. With reference to surgical approach, 42.3% (n= 38) and 30.3% (n=27) of patients treated by LLR and OLR achieved a TO, respectively.

Neither OS, nor DFS were different between the groups with or without TO achievement.

### **Subgroup analysis of patients with complete N status.**

From the cohort of n=855 patients, 39.6% (n=339) with missing data on N status were removed, resulting in n=516 patients left for analysis in the subgroup. Among them 79.6% were treated by OLR (n=411) and 20.3% treated by LLR (n=105).

After propensity score adjustment, the demographic and preoperative variables of matched patients (n=102) (LLR n=51; OLR n=51) were similar (Supplementary Table 1), except for the higher rate of metabolic syndrome and underlying liver disease in the LLR group. Notably, the N1 rate was significantly lower in the LLR compared to OLR group, (n=5, 9.8% vs n=14, 27.5%; p=0.042).

Within the subgroup cohort before matching, Kaplan–Meier OS estimation at 1, 3 and 5 years was 91%, 74% and 62% in LLR group versus 84%, 51% and 37% in OLR group, respectively (p=0.0016) (Figure 6A). After matching, Kaplan–Meier OS estimation at 1, 3 and 5 years was 89%, 71% and 62% in LLR group versus 94%, 64% and 46% in OLR group, respectively (p=0.55) (Figure 6B).

About DFS, Kaplan–Meier DFS estimation before matching at 1, 3 and 5 years was 73%, 40% and 32% for LLR versus 50%, 27% and 23% in the OLR group, respectively (p<0.001) (Figure 7A). Figure 7B displays the Kaplan–Meier DFS estimation after matching at 1, 3 and 5 years (74%, 44% and 44% LLR versus 66%, 39% and 39% OLR, respectively (p=0.47).

## DISCUSSION

This large multicenter study of ICC, treated by LLR versus OLR, made three significant findings: a benefit in OS for the laparoscopic group, a similar DFS and rate of textbook outcomes between the two approaches.

This is the first data to suggest an advantage for laparoscopic resection of ICC over open surgery. Published single center case-control studies and a large meta-analysis which included 2531 patients failed to report a difference<sup>19,31</sup> between the two approaches. In the setting of CLM, one single RCT<sup>17</sup> and one high-quality metanalysis<sup>16</sup> comparing LLR versus OLR for oncological outcomes found no difference in survival. Similarly, for HCC, the existing literature reports conflicting results on the effect of LLR on survival: some in favor of LLR<sup>15,32</sup> and others - including one RCT<sup>18</sup> - no difference<sup>33,34</sup> between LLR and OLR. The reason often cited is the low incidence of post-operative complications after LLR, which are associated with poorer survival<sup>35,36</sup>. The observations of this study are consistent with these reports on severe post-operative complications, predictors of death and recurrence, even if their distribution was similar between LLR and OLR groups before and after matching.

Univariable Cox regression analysis confirmed N1 status as a predictor of mortality and recurrence, but not on the multivariable regression. This can be explained by the high rate of missing observations within the “N” variable, together with the lack of “node dissection” definition in the original dataframes. This represents clearly one of the main limitations of this study: given the wide time span (2000-2018) and the three merged datasets (with data from over 30 centers and no access to individual patient data), we had to deal with some data “granularity”. In particular no information either on the nodal station retrieved, or on the number of nodes found on each specimen.

In the subset of patients with available data on node dissection, the overall rate within both the unmatched (n=353, 41.3%) and matched cohort (n=35, 19.6%) was disappointing. These rates were even lower in the unmatched and matched LLR groups (17.4% and 17.9%, respectively). Literature reports suggest that node dissection for ICC in both Eastern and Western centers is increasingly performed<sup>29</sup> for accurate staging, long-term prognostic stratification<sup>5,37</sup>, as well as adequate clearance of the locoregional nodal basin. A large National Cancer Database study of more than 2300 patients who underwent resection of ICC found a higher rate of nodal evaluation (58%)<sup>38</sup> than the present study, but also revealed

reduced quality of node dissection during LLR compared to OLR, given the inadequate number of nodes resected<sup>38</sup>.

In this study, and when data were available, the observed node dissection rate was higher in the OLR group; this might suggest some underlying bias, such as the greater skills needed (to perform node dissection during LLR), the possible selection bias of patients with preoperative workup negative for enlarged/suspect nodes, or high preoperative CA 19-9 values. Of note, given the significant number of missing information on N status (n=289, 33.8% in the unmatched cohort), a statistical imputation to replace missing variables was not considered, preventing from any meaningful conclusion and suggesting careful interpretation of this finding.

Given these limitations, a subgroup analysis was realized including patients with complete N status, representing some 60% of the initial cohort. After PS matching, no difference in OS and DFS was observed between LLR and OLR, similarly to what reported by Kang S and colleagues<sup>31</sup>.

The recommendation for disease-specific staging for ICC was introduced after 2010<sup>27</sup> and the consensus on the number of nodes harvested was defined only within the 8<sup>th</sup> AJCC manual<sup>28</sup> in 2017 (n=6): given the study period from 2000 to 2018, this study suffers from a secular bias. Despite the findings of a retrospective study<sup>39</sup>, regional lymphadenectomy is unlikely to offer a survival advantage but may prevent locoregional recurrence, which can be a particular challenge when it occurs at the hepatic hilum<sup>29</sup>.

All these observations argue that routine lymphadenectomy should be considered even for node-negative intrahepatic cholangiocarcinoma, with the objective of improving prognostic stratification. On the other hand, our study also exposed a lower rate of lymph node dissection to be the main limitation of the laparoscopic approach. The ability of LLR for ICC to comply with oncological standards should be examined further<sup>38</sup>.

It is possible that robotic surgery might help to overcome this issue in the future, by facilitating precise lymph node dissection through improved visualization and instrument dexterity in narrow and deep spaces<sup>40-45</sup>.

Finally, this study revealed how severe postoperative complications were associated with ICC survival and recurrence, in line with reports on HCC and liver metastases<sup>35,36,46,47</sup>. The type of approach, open or laparoscopic, had no influence on survival or recurrence.

Enhanced recovery after surgery was not the focus of this study, but a minimally invasive approach is recommended in guidelines<sup>48,49</sup>, including those for liver surgery. The reduced trauma induced by minimally invasive surgery is associated with improved recovery and a reduced rate of post-operative complications. The present study found that the lower complication rate observed in the LLR group translated into improved survival. TO achievement, which includes the absence of postoperative complications, has been shown to be associated with improved DFS in studies concerning HCC<sup>20,21</sup>. Although we found a higher rate of some of the six TO variables in the LLR group, TO was not shown to significantly improve OS or DFS. This may be explained by the collinearity of variables included within the TO, which were also considered individually elsewhere in the analysis (Clavien  $\geq$  III, Transfusion), as well as the small sample gathered over a long accrual period.

This study highlights the importance of repurposing existing clinical databases. Even though RCT generate the highest level of evidence, a randomized trial is unlikely to be a realistic proposition for a rare disease such as ICC. In fact, the low case-volume per center, together with a lower rate of lymph node dissection by LLR, implying a learning curve even in expert centers, translates into poor feasibility for the design of a RCT comparing LLR to OLR. It follows that alternative study designs deserve consideration, so that the best evidence can be produced from the often limited resources available in clinical research. The reuse of existing clinical databases is a promising solution in these circumstances, more focused than larger administrative databases. We strongly believe in a more responsible, honest and somehow “sustainable” research: time and money are limited, and the “3R” concept (Reduce, Reuse, Recycle) may apply in clinical research to reduce the avoidable burden of waste<sup>50</sup>. A rigorous methodology<sup>51</sup> together with the availability of free-of-charge statistical programs hold tremendous potential for the new generation of surgeon scientists<sup>52</sup>.

At the same time, the collaborative design of this study suffers from the classical limits that influence multicenter retrospective series, viz. different case-mix, hospital case-load, surgical expertise, long accrual period (18 years) as well as the evolution of standards (on LLR) and

recommendations (on node dissection). The dataset obtained is both comprehensive (large number of cases) but limited: many of the variables were missing (N status) or not collected at all (CA 19-9, number of nodes).

Together with the aforementioned limitations, the key findings of improved overall survival advantage (but not DFS) at 1, 3 and 5 years for ICC treated with LLR compared to OLR, should be tempered by overlapping Kaplan-Meier confidence intervals around 0-24 months and 36-60 months. In particular, the LLR survival advantage is no more observed when the subset of patients with complete N status is analyzed.

In conclusion and based on the findings of the present study, LLR for ICC seems feasible with similar rates of morbidity, compared to OLR. Nevertheless, the survival advantage of LLR over OLR is equivocal.



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## **TABLES**

**TABLE 1. Clinical characteristics of the study cohort, before and after matching.**

**TABLE 2. Results of univariable and multivariable Cox analysis predicting death in the matched cohort.**

**TABLE 3. Results of univariable and multivariable Cox analysis predicting recurrence in the matched cohort.**

**TABLE 4. Distribution of Textbook Outcome (TO).**

## **FIGURES**

**FIGURE 1. Flowchart of the patients included in the cohort.**

**FIGURE 2. Overall survival (OS) before matching at 1, 3 and 5 years was 93%, 74% and 65% in LLR group versus 83%, 53% and 39% in OLR group, respectively ( $p<0.001$ ).**

**FIGURE 3. Overall survival (OS) after matching at 1, 3 and 5 years was 92%, 75% and 63% in LLR group versus 92%, 58% and 49% in OLR group, respectively ( $p=0.0043$ ).**

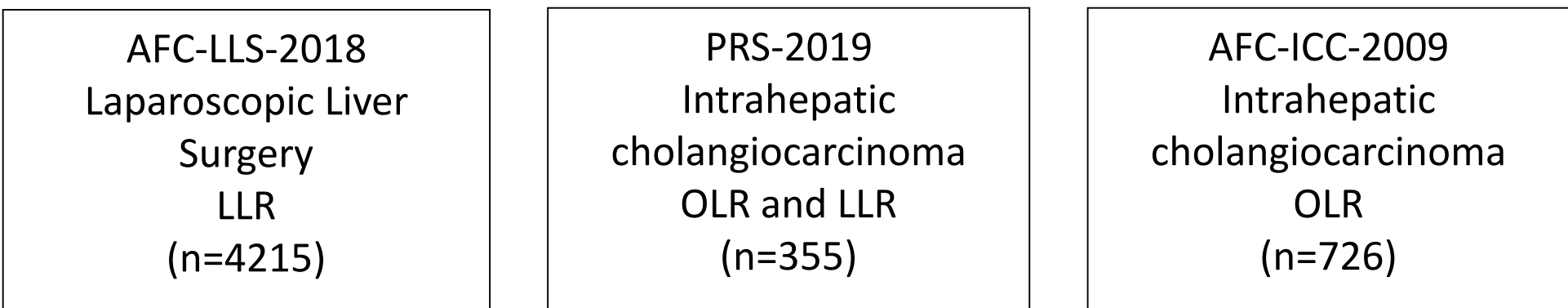
**FIGURE 4. Disease free survival (DFS) before matching at 1, 3 and 5 years was 70%, 37% and 32% in LLR group versus 48%, 22% and 19% in OLR group, respectively ( $p<0.001$ ).**

**FIGURE 5. Disease free survival (DFS) after matching at 1, 3 and 5 years was 71%, 41% and 41% in LLR group versus 61%, 37% and 29% in OLR group, respectively ( $p=0.22$ ).**

**FIGURE 6. Subgroup analysis of patients with complete N status. Overall survival (OS) before (A) and after (B) matching at 1, 3 and 5 years.**

**FIGURE 7. Subgroup analysis of patients with complete N status. Disease free survival (DFS) before (A) and after (B) matching at 1, 3 and 5 years.**

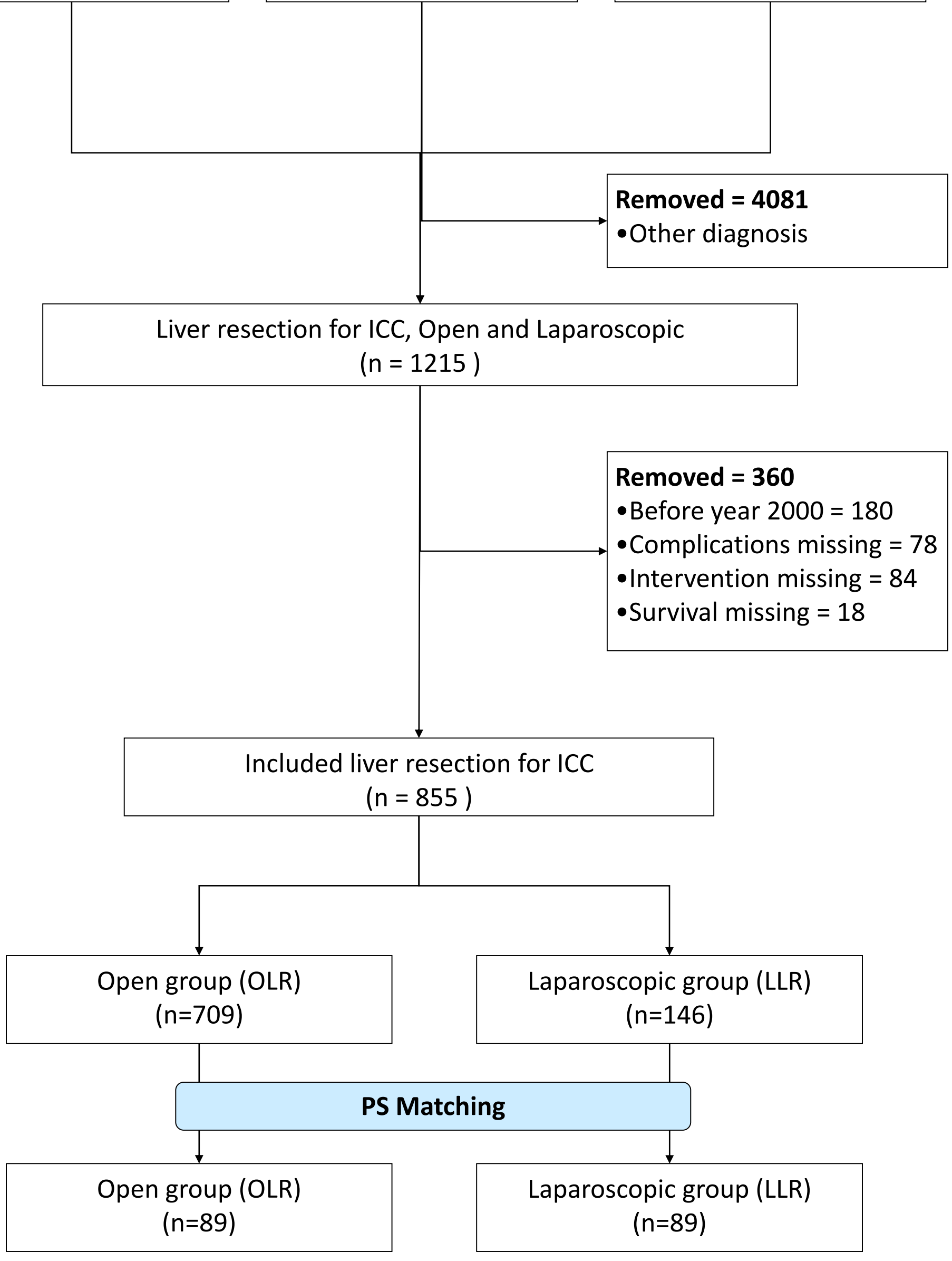
Identification



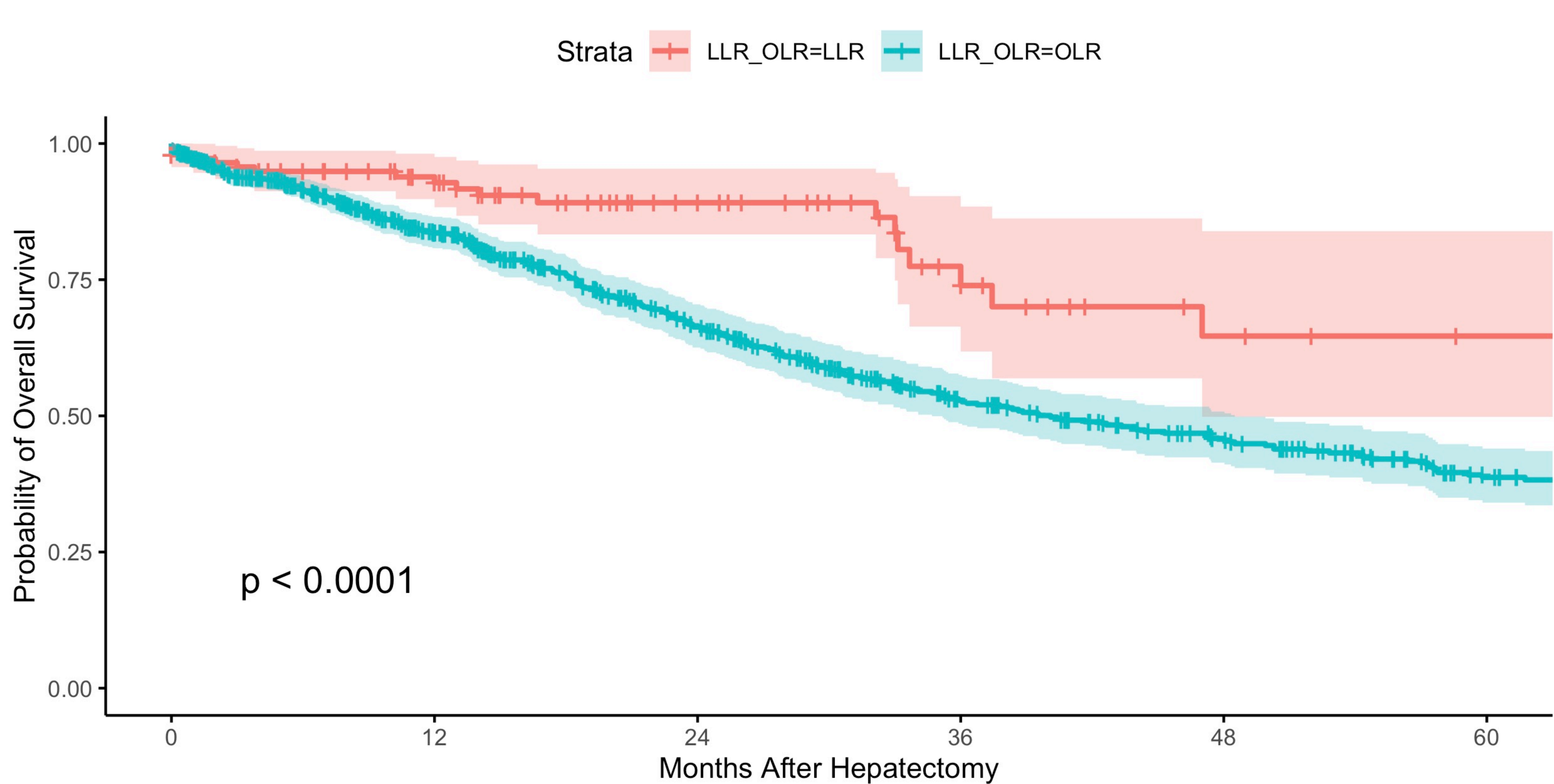
Screening

Inclusion

After Matching





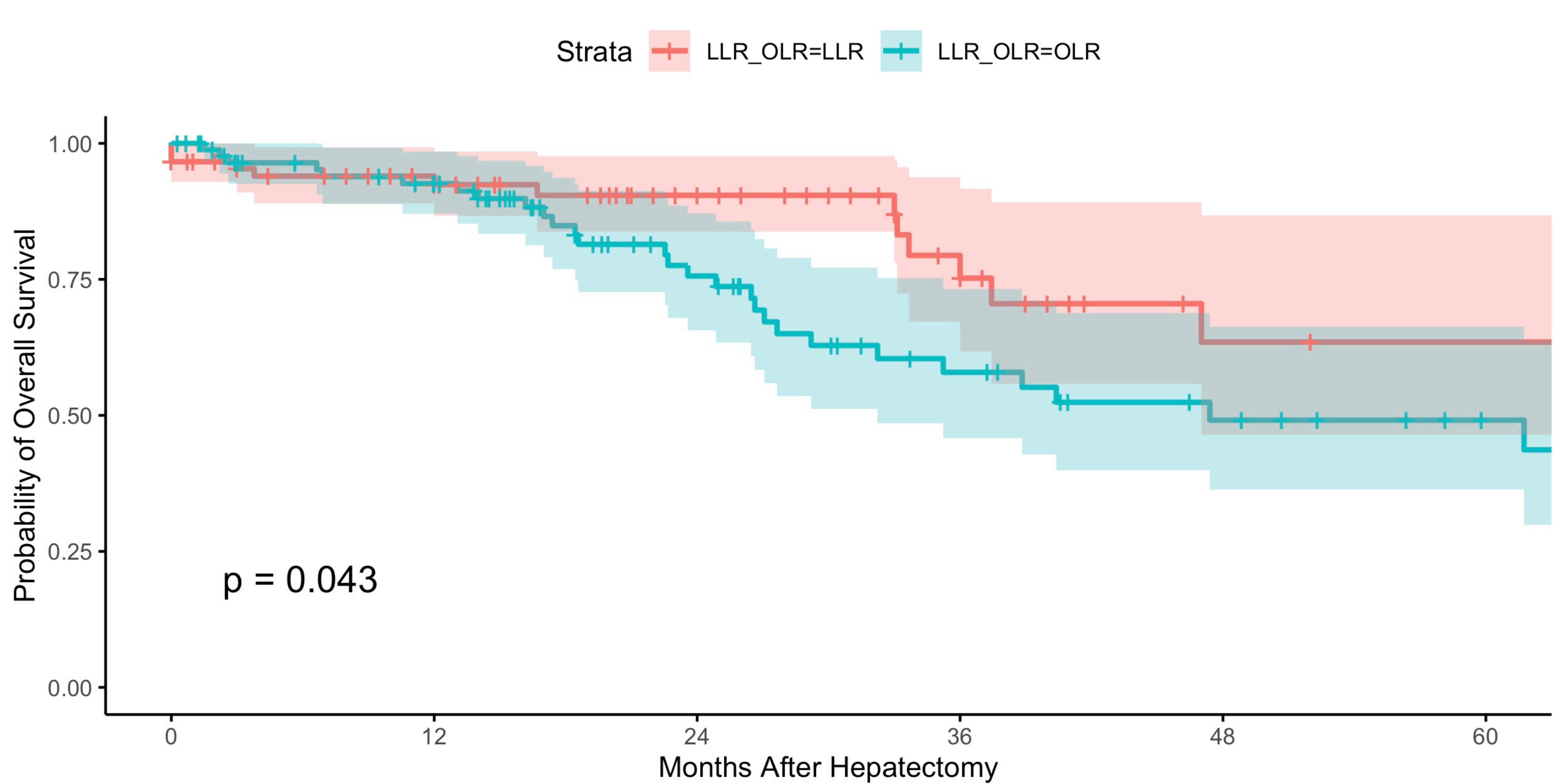


Number at risk

Strata	0	12	24	36	48	60
LLR_OLR=LLR (Red)	146	88	47	22	12	9
LLR_OLR=OLR (Teal)	709	472	311	194	143	87

Months After Hepatectomy



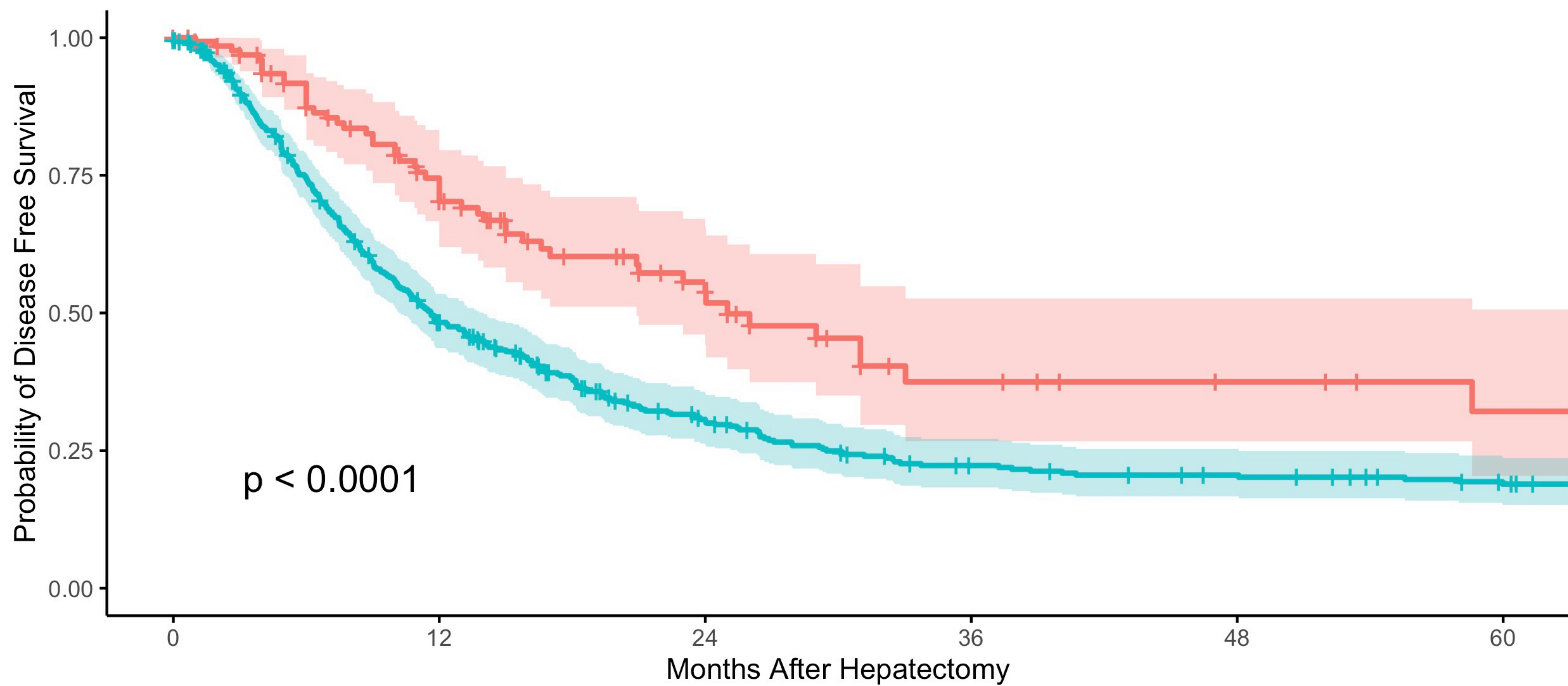


Number at risk

Strata	0	12	24	36	48	60
LLR_OLR=LLR	89	60	36	19	9	8
LLR_OLR=OLR	89	70	39	23	15	9

Months After Hepatectomy

Strata LLR\_OLR=LLR LLR\_OLR=OLR

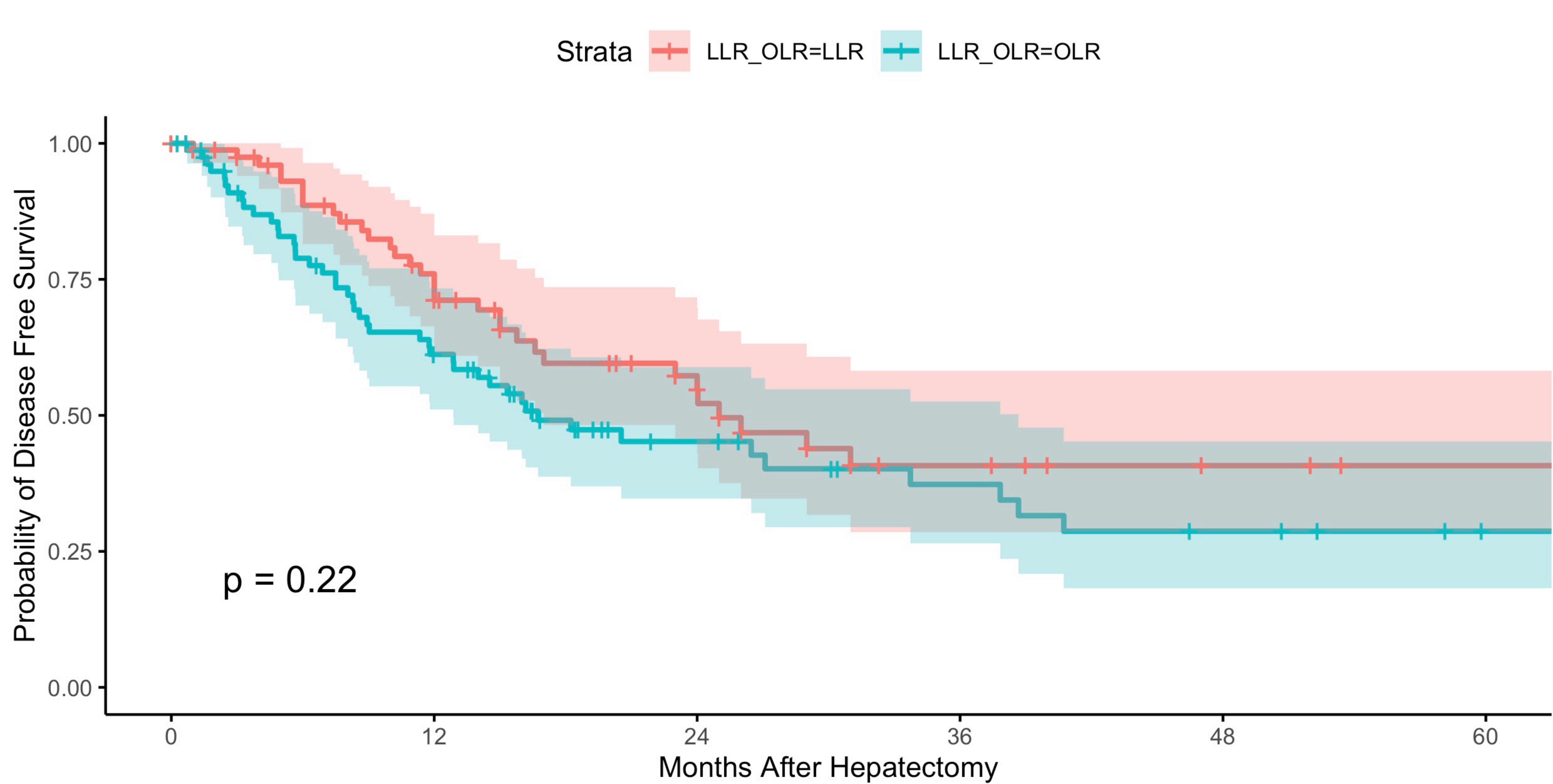


Number at risk

Strata	0	12	24	36	48	60
LLR_OLR=LLR	141	70	31	13	9	6
LLR_OLR=OLR	414	187	99	64	55	44

Months After Hepatectomy

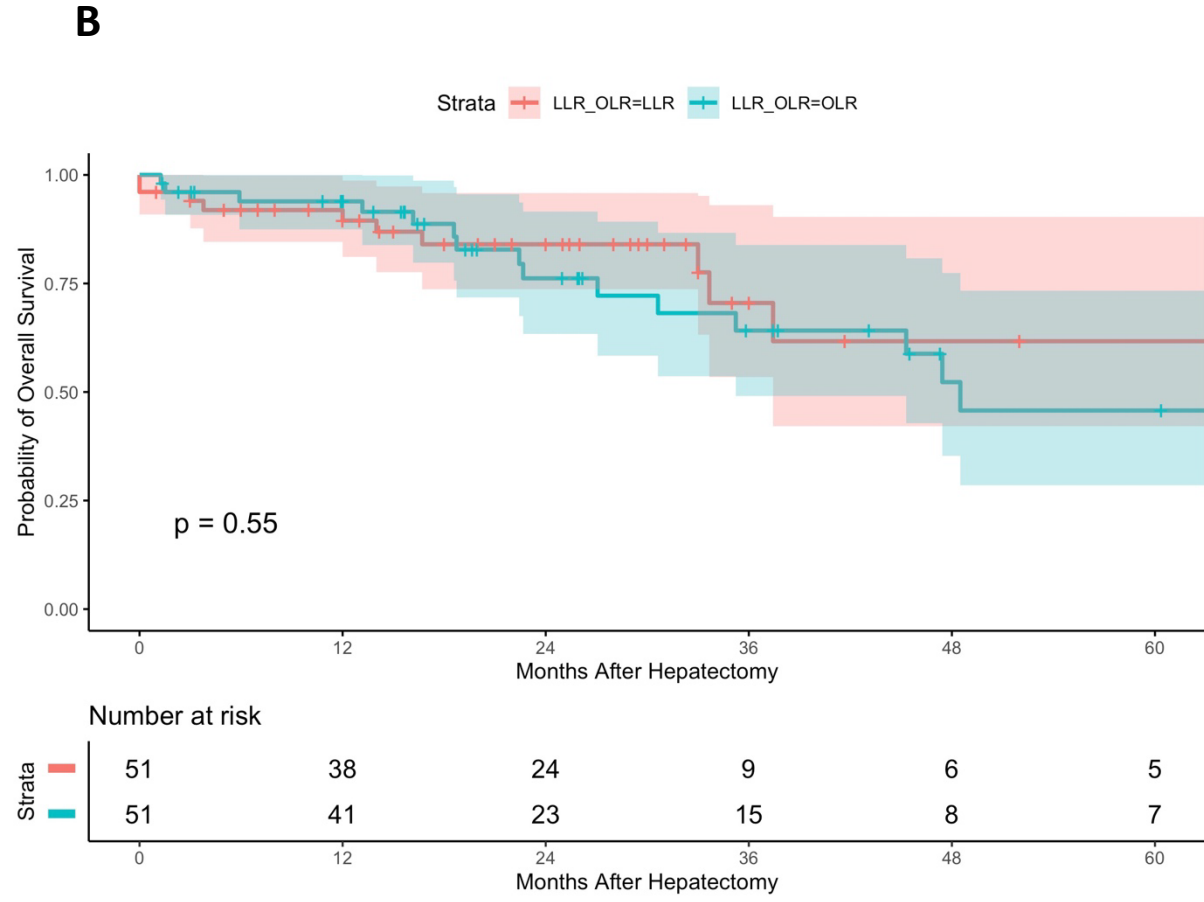
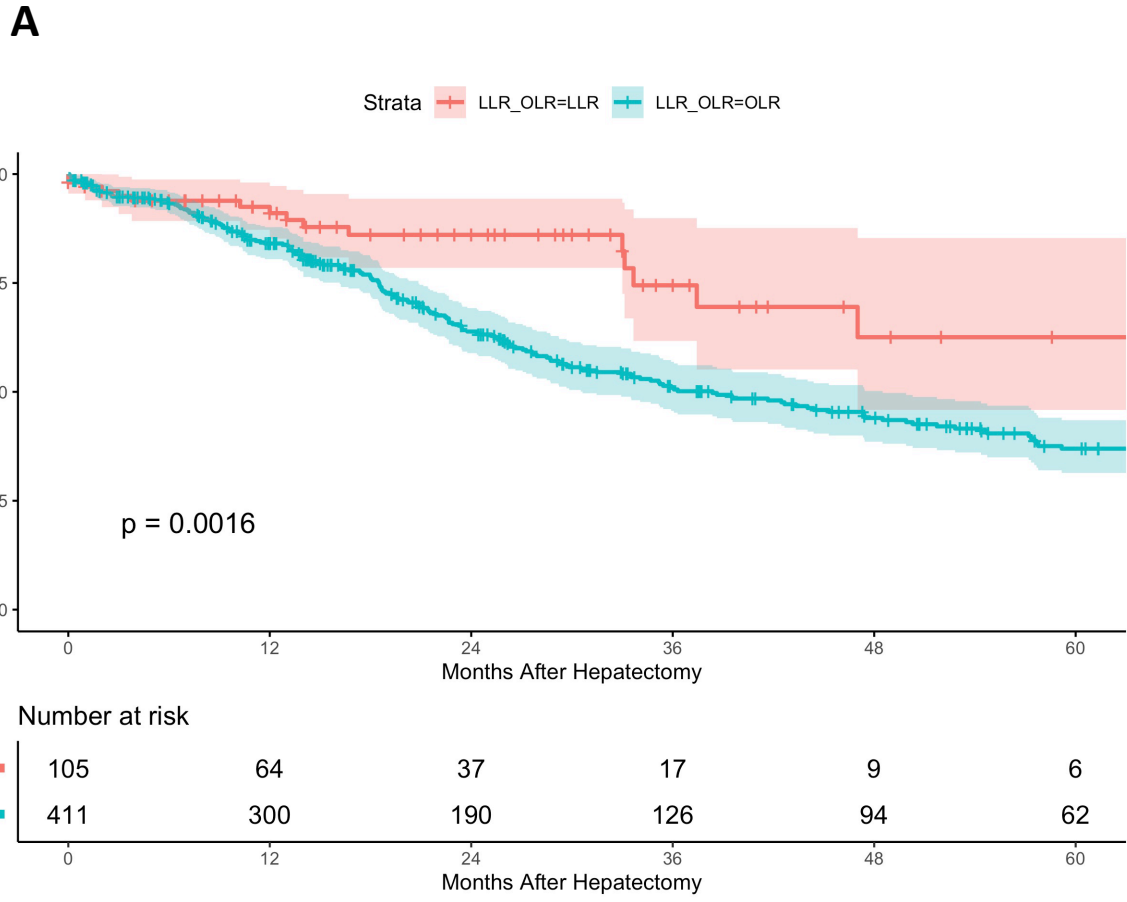


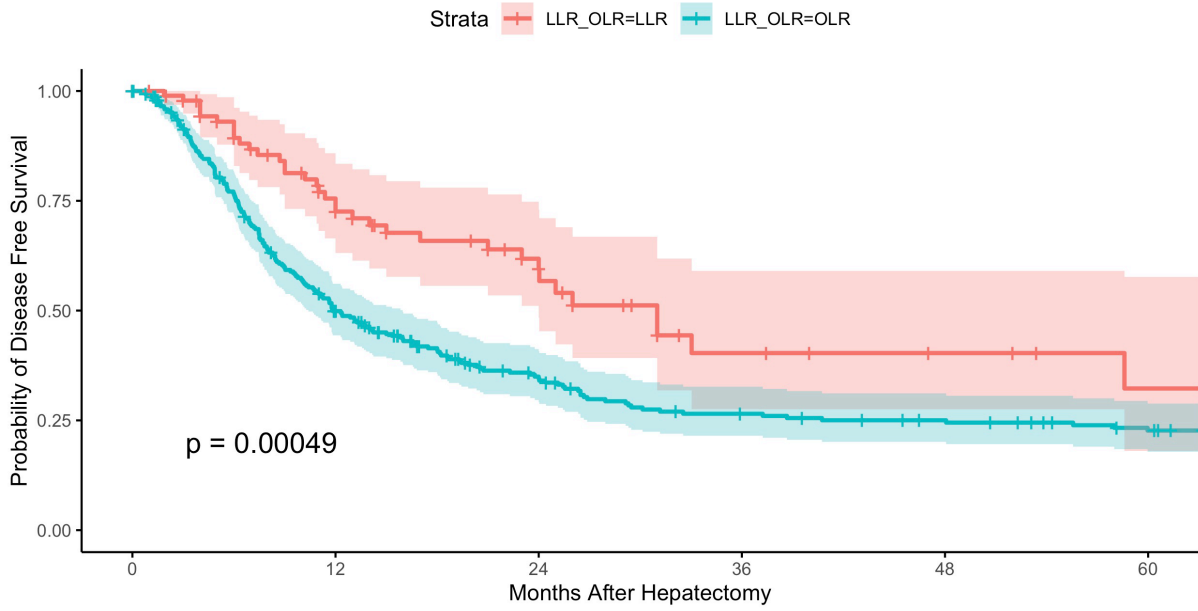


Number at risk

Strata	0	12	24	36	48	60
LLR_OLR=LLR	85	47	23	11	7	5
LLR_OLR=OLR	81	44	20	13	9	5

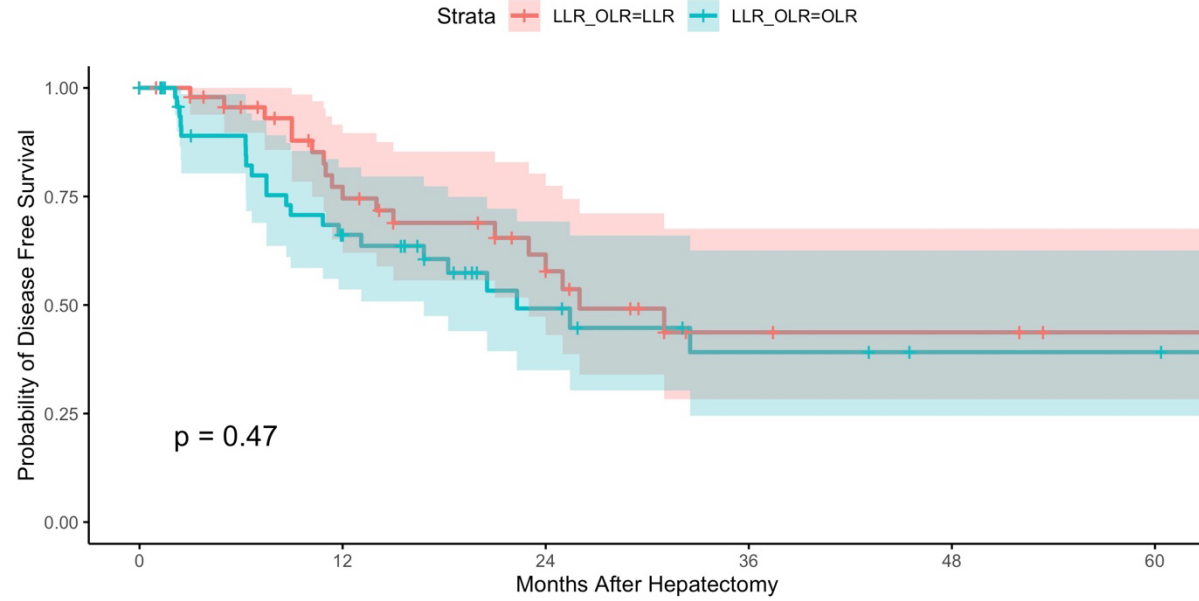
Months After Hepatectomy



**A**

Number at risk

Strata	0	12	24	36	48	60
LLR_OLR=LLR	103	51	26	10	7	4
LLR_OLR=OLR	293	136	77	54	47	37

**B**

Number at risk

Strata	0	12	24	36	48	60
LLR_OLR=LLR	50	29	16	6	5	3
LLR_OLR=OLR	50	27	12	7	5	5

Table 1	BEFORE MATCHING				AFTER MATCHING			
	Overall	LLR	OLR		Overall	LLR	OLR	
	(n=855)	(n=146)	(n=709)	p	(n=178)	(n=89)	(n=89)	p
<b>Cohort of origin</b>				<0.001				<0.001
AFC_CC_2008	428 ( 50.1)	0 ( 0.0)	428 ( 60.4)		7 ( 3.9)	0 ( 0.0)	7 ( 7.9)	
AFC_LLS_2018	110 ( 12.9)	110 ( 75.3)	0 ( 0.0)		70 ( 39.3)	70 ( 78.7)	0 ( 0.0)	
PRS_2019	317 ( 37.1)	36 ( 24.7)	281 ( 39.6)		101 ( 56.7)	19 ( 21.3)	82 ( 92.1)	
<b>Age (mean (SD))</b>	64.96 (11.35)	64.64 (12.81)	65.02 (11.03)	0.716	66.58 (10.31)	65.24 (11.40)	67.92 (8.97)	0.082
<b>Age, classes (%)</b>				0.441				0.070
<50y	89 ( 10.4)	17 ( 11.6)	72 ( 10.2)		11 ( 6.2)	8 ( 9.0)	3 ( 3.4)	
50-70y	463 ( 54.2)	84 ( 57.5)	379 ( 53.5)		96 ( 53.9)	52 ( 58.4)	44 ( 49.4)	
≥70	302 ( 35.4)	45 ( 30.8)	257 ( 36.3)		71 ( 39.9)	29 ( 32.6)	42 ( 47.2)	
<b>Gender = M (%)</b>	437 ( 51.2)	83 ( 56.8)	354 ( 50.0)	0.157	90 ( 50.6)	52 ( 58.4)	38 ( 42.7)	0.051
<b>BMI (mean (SD))</b>	25.66 (4.69)	26.65 (5.08)	25.36 (4.52)	0.005	25.54 (4.47)	25.82 (4.55)	25.28 (4.40)	0.437
NA	331	22	309		5	2	3	
<b>ASA (%)</b>				0.016				0.123
I	61 ( 11.6)	12 ( 9.7)	49 ( 12.2)		9 ( 6.8)	8 ( 8.9)	1 ( 1.7)	
II	293 ( 55.9)	59 ( 47.6)	234 ( 58.5)		68 ( 51.1)	36 ( 49.3)	32 ( 53.3)	
III	156 ( 29.8)	51 ( 41.1)	105 ( 26.2)		52 ( 39.1)	28 ( 38.4)	24 ( 40.0)	
<b>Metabolic syndrome = 1 (%)</b>	135 ( 29.3)	50 ( 37.3)	85 ( 26.1)	0.022	37 ( 23.0)	26 ( 32.5)	11 ( 13.6)	0.008
NA	395	12	383		6	3	3	
<b>Underlying liver disease = 1 (%)</b>	169 ( 23.8)	64 ( 47.1)	105 ( 18.3)	<0.001	60 ( 34.9)	40 ( 44.9)	20 ( 22.7)	0.001
NA	146	10	136		2	2	0	
<b>Number of lesions, preoperative (%)</b>				0.218				0.487
1	696 ( 85.8)	127 ( 87.0)	569 ( 85.6)		152 ( 85.4)	77 ( 86.5)	75 ( 84.3)	
2	43 ( 5.3)	12 ( 8.2)	31 ( 4.7)		14 ( 7.9)	8 ( 9.0)	6 ( 6.7)	
3	27 ( 3.3)	4 ( 2.7)	23 ( 3.5)		7 ( 3.9)	3 ( 3.4)	4 ( 4.5)	

4	16 ( 2.0)	2 ( 1.4)	14 ( 2.1)		-	-	-	
5	9 ( 1.1)	0 ( 0.0)	9 ( 1.4)		2 ( 1.1)	0 ( 0.0)	2 ( 2.2)	
6	10 ( 1.2)	0 ( 0.0)	10 ( 1.5)		1 ( 0.6)	0 ( 0.0)	1 ( 1.1)	
8	2 ( 0.2)	1 ( 0.7)	1 ( 0.2)		1 ( 0.6)	1 ( 1.1)	0 ( 0.0)	
9	3 ( 0.4)	0 ( 0.0)	3 ( 0.5)					
10	5 ( 0.6)	0 ( 0.0)	5 ( 0.8)		1 ( 0.6)	0 ( 0.0)	1 ( 1.1)	
<b>Tumoral diameter, cm (mean (SD))</b>	6.28 (4.94)	5.49 (7.31)	6.45 (4.28)	0.034	4.99 (3.20)	4.67 (2.56)	5.32 (3.73)	0.173
<b>PVE = 1 (%)</b>	65 ( 8.8)	4 ( 3.3)	61 ( 10.0)	0.027	11 ( 7.6)	4 ( 5.3)	7 ( 10.0)	0.455
NA	119	23	96		17	4	13	
<b>Major hepatectomy (%)</b>	614 ( 71.8)	61 ( 41.8)	553 ( 78.0)	<0.001	109 ( 61.2)	48 ( 53.9)	61 ( 68.5)	0.065
<b>IMM Difficulty classification (%)</b>				<0.001				0.818
I	122 ( 14.3)	50 ( 34.2)	72 ( 10.2)		31 ( 17.4)	14 ( 15.7)	17 ( 19.1)	
II	187 ( 21.9)	51 ( 34.9)	136 ( 19.2)		66 ( 37.1)	33 ( 37.1)	33 ( 37.1)	
III	546 ( 63.9)	45 ( 30.8)	501 ( 70.7)		81 ( 45.5)	42 ( 47.2)	39 ( 43.8)	
<b>Number of resected segments (%)</b>				<0.001				0.025
1	95 ( 11.1)	35 ( 24.0)	60 ( 8.5)		29 ( 16.3)	17 ( 19.1)	12 ( 13.5)	
2	143 ( 16.7)	51 ( 34.9)	92 ( 13.0)		40 ( 22.5)	25 ( 28.1)	15 ( 16.9)	
3	138 ( 16.1)	28 ( 19.2)	110 ( 15.5)		41 ( 23.0)	19 ( 21.3)	22 ( 24.7)	
4	250 ( 29.2)	25 ( 17.1)	225 ( 31.7)		41 ( 23.0)	22 ( 24.7)	19 ( 21.3)	
5	137 ( 16.0)	5 ( 3.4)	132 ( 18.6)		13 ( 7.3)	4 ( 4.5)	9 ( 10.1)	
6	84 ( 9.8)	2 ( 1.4)	82 ( 11.6)		14 ( 7.9)	2 ( 2.2)	12 ( 13.5)	
<b>Hepaticojejunostomy = 1 (%)</b>	109 ( 14.9)	4 ( 3.0)	105 ( 17.6)	<0.001	10 ( 6.4)	4 ( 4.8)	6 ( 8.3)	0.562
NA	124	12	112		16	3	13	
<b>Node dissection = 1 (%)</b>	353 ( 41.3)	25 ( 17.4)	328 ( 46.2)	<0.001	35 ( 19.6)	16 ( 17.9)	19 ( 21.3)	0.571
NA	289	47	242		45	9	36	
<b>Conversion to open = 1 (%)</b>	21 ( 2.5)	21 ( 14.7)	unrelated		16 ( 9.1)	16 ( 17.9)	unrelated	
<b>Packed RBC transfusion = 1 (%)</b>	330 ( 38.6)	19 ( 13.0)	311 ( 43.9)	<0.001	42 ( 23.6)	13 ( 14.6)	29 ( 32.6)	0.008
<b>Packed RBC transfused, units (mean (SD))</b>	1.76 (3.53)	0.24 (0.94)	2.26 (3.91)	<0.001	0.41 (1.21)	0.24 (1.14)	0.59 (1.26)	0.125
<b>Clavien-Dindo<math>\geq</math>III = 1 (%)</b>	141 ( 21.2)	28 ( 20.1)	113 ( 21.5)	0.821	24 ( 15.8)	16 ( 17.9)	8 ( 8.9)	0.352



NA	190	7	183		17	3	14	
<b>Nodules on specimen, n (mean (SD))</b>	3.23 (8.57)	1.22 (0.77)	3.73 (9.48)	0.002	2.32 (1.04)	2.23 (0.78)	2.42 (1.25)	0.227
<b>R1 = 1 (%)</b>	147 ( 20.5)	20 ( 15.7)	127 ( 21.6)	0.177	33 ( 22.8)	12 ( 16.0)	21 ( 30.0)	0.070
NA	139	19	120		22	9	13	
<b>Surgical margins, mm (mean (SD))</b>	5.81 (9.27)	9.62 (11.44)	4.83 (8.36)	<0.001	7.69 (9.17)	9.93 (10.58)	5.45 (6.87)	0.004
<b>N1 (%)</b>	136 ( 26.4)	9 ( 8.6)	127 ( 30.9)	<0.001	23 ( 18.3)	6 ( 9.7)	17 ( 26.6)	0.026
NA	339	41	298		0	0	0	
<b>F3-F4 = 1 (%)</b>	80 ( 15.7)	39 ( 27.9)	41 ( 11.1)	<0.001	27 ( 16.9)	21 ( 24.7)	6 ( 8.0)	0.009
NA	346	6	340		5	3	2	
<b>Steatosis = 1 (%)</b>	231 ( 41.8)	27 ( 20.8)	204 ( 48.2)	<0.001	36 ( 24.7)	12 ( 14.8)	24 ( 26.9)	0.004
NA	302	16	286		18	4	14	
<b>Recurrence = 1 (%)</b>	395 ( 47.2)	54 ( 38.0)	341 ( 49.1)	0.020	80 ( 45.7)	34 ( 39.5)	46 ( 51.7)	0.144
<b>Death = 1 (%)</b>	330 ( 38.6)	19 ( 13.0)	311 ( 43.9)	<0.001	42 ( 23.6)	13 ( 14.6)	29 ( 32.6)	0.008
<b>Textbook Outcomes = 1 (%)</b>	135 (15.8)	45 (30.8)	90 (12.7)	<0.001	65 (36.5)	38 (42.3)	27 (30.3)	0.258

AFC\_CC\_2008=Cohort Cholangiocarcinoma 2008 from Association Francaise de Chirurgie, AFC\_LLS\_2018=Cohort Laparoscopic Liver Surgery 2018 from Association Francaise de Chirurgie, PRS\_2019= Cohort from Preoperatiive Risk Score study 2019, BMI=body mass index, PVE=portal vein embolisation, IMM=Institut Mutualiste Montsouris, RBC=Red blood cell, F=Fibrosis, N=node, M=Male, ASA=American Society of Anesthesiology

Table 2

Results of univariable and multivariable Cox analysis predicting death in the matched cohort

Patients = 178	Univariate Analysis			Multivariate Analysis		
	HR <sup>1</sup>	95% CI <sup>1</sup>	p-value	HR <sup>1</sup>	95% CI <sup>1</sup>	p-value
<b>Approach</b>						
Laparoscopy	—	—		—	—	
Open	1.94	1.01, 3.74	0.048	1.43	0.12, 16.5	0.8
<b>Gender</b>						
F	—	—				
M	1.08	0.58, 1.99	0.8			
<b>Age, class</b>						
<50y	—	—				
50-70y	1.22	0.35, 4.25	0.7			
>70	2.24	0.67, 7.50	0.2			
<b>ASA</b>						
I	—	—				
II	1.61	0.21, 12.2	0.6			
III	1.62	0.21, 12.6	0.6			
IV	1.24	0.08, 20.0	0.9			
<b>Metabolic syndrome</b>						
0	—	—				
1	1.01	0.34, 3.03	>0.9			
<b>Underlying liver disease = 1 (%)</b>						
0	—	—				
1	1.68	0.75, 3.77	0.2			
<b>Tumoral diameter (cm)</b>	1.12	1.01, 1.23	0.025	1.03	0.86, 1.23	0.8
<b>IMM Difficulty classification</b>						

1	—	—			
2	1.22	0.38, 3.89	0.7		
3	1.89	0.67, 5.39	0.2		
<b>Extent of hepatectomy</b>					
Minor	—	—			
Major	1.17	0.53, 2.57	0.7		
<b>Portal vein Embolization</b>					
0	—	—			
1	4.14	0.52, 33.2	0.2		
<b>R1</b>					
0	—	—			
1	3.20	1.27, 8.10	0.014	1.82	0.25, 13.3 0.6
<b>Clavien-Dindo≥III</b>					
0	—	—		—	—
1	1.37	0.50, 3.73	0.5	10.5	1.01, 109 0.049
<b>Node dissection</b>					
0	—	—		—	—
1	6.51	1.44, 29.4	0.015	10.5	0.90, 123 0.061
<b>N status</b>					
0	—	—		—	—
1	2.31	1.00, 5.33	0.049	0.54	0.05, 5.30 0.6
<b>Fibrosis (F3 or F4)</b>					
0	—	—			
1	0.95	0.32, 2.78	>0.9		
<b>Steatosis</b>					
0	—	—		—	—

1	2.45	0.97, 6.18	0.058	13.8	1.23, 154	0.033
<b>Textbook Outcomes</b>						
0	—	—				
1	0.98	0.55, 1.75	>0.9			

<sup>1</sup>HR = Hazard Ratio, CI = Confidence Interval, F=Female, M=Male, ASA=American Society of Anesthesiology

Table 3

Results of univariable and multivariable Cox analysis predicting recurrence in the matched cohort

Patients = 178	Univariate Analysis			Multivariate Analysis		
	HR <sup>1</sup>	95% CI <sup>1</sup>	p-value	HR <sup>1</sup>	95% CI <sup>1</sup>	p-value
<b>Approach</b>						
Laparoscopy	—	—				
Open	1.46	0.80, 2.66	0.2			
<b>Gender</b>						
F	—	—				
M	0.71	0.39, 1.30	0.3			
<b>Age, class</b>						
<50y	—	—		—	—	
50-70y	2.43	0.98, 6.00	0.055	0.76	0.16, 3.62	0.7
>70	1.43	0.50, 4.09	0.5	0.24	0.03, 1.73	0.2
<b>ASA</b>						
I	—	—		—	—	
II	0.24	0.08, 0.77	0.016	0.64	0.06, 7.02	0.7
III	0.28	0.08, 0.93	0.038	1.05	0.08, 13.8	>0.9
IV	0.00	0.00, Inf	>0.9	0.00	0.00, Inf	>0.9
<b>Metabolic syndrome</b>						
0	—	—		—	—	
1	0.43	0.17, 1.10	0.078	2.68	0.60, 11.9	0.2
<b>Underlying liver disease</b>						
0	—	—				
1	1.00	0.52, 1.92	>0.9			
<b>Tumoral diameter</b>	1.15	1.05, 1.25	0.001	1.11	0.98, 1.26	0.090
<b>IMM Difficulty classification</b>						

1	—	—			
2	0.94	0.43, 2.06	0.9		
3	0.90	0.42, 1.93	0.8		
<b>Extent of hepatectomy</b>					
Minor	—	—			
Major	1.64	0.88, 3.06	0.12		
<b>Portal vein Embolization</b>					
0	—	—			
1	0.00	0.00, Inf	>0.9		
<b>RBC transfusion</b>					
0	—	—		—	—
1	3.08	1.65, 5.74	<0.001	19.2	4.04, 91.4 <0.001
<b>R1</b>					
0	—	—		—	—
1	2.63	1.20, 5.75	0.016	0.68	0.23, 2.01 0.5
<b>Clavien-Dindo≥III</b>					
0	—	—		—	—
1	1.36	0.61, 3.00	0.4	4.07	1.15, 14.4 0.030
<b>Node dissection</b>					
0	—	—			
1	1.44	0.86, 2.44	0.2		
<b>N status</b>					
0	—	—		—	—
1	2.77	1.41, 5.46	0.003	1.48	0.43, 5.08 0.5
<b>Fibrosis (F3 or F4)</b>					
0	—	—			

1	1.09	0.48, 2.47	0.8
<b>Steatosis</b>			
0	—	—	
1	1.15	0.51, 2.60	0.7
<b>Textbook Outcomes</b>			
0	—	—	
1	0.92	0.59, 1.45	0.7

<sup>1</sup>HR = Hazard Ratio, CI = Confidence Interval, F=Female, M=Male, ASA=American Society of Anesthesiology

<b>Table 4</b>	<b>Overall (n=178)</b>	<b>LLS (n=89)</b>	<b>OLS (n=89)</b>	<b>p</b>
Textbook Outcomes achieved	65 (36.5)	38 (42.3)	27 (30.3)	0.258
Negative margins	145 ( 77.2)	77 ( 84.0)	68 ( 70.0)	0.195
No perioperative transfusion	136 (76.4)	76 (85.4)	60 (67.4)	0.008
No complications	154 ( 84.2)	73 (82.1)	81 (91.1)	0.352
No prolonged hospital stay (<50percentile)	133 (74.7)	70 (78.6)	63 (70.4)	0.359
No 30-d readmission	138 (77.5)	71 (80.0)	67 (75.3)	1.000
No 30-d mortality	154 ( 84.2)	85 (95.0)	69 (77.5)	<0.001