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Lymphocyte-to-monocyte ratio and clinical outcomes in Cholangiocarcinoma: A systematic review and meta-analysis

TESIS

Para optar el título profesional de Médico Cirujano

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RESUMEN

Antecedentes y objetivos: La relación de linfocitos a monocitos (LMR) ha demostrado una asociación con los resultados de supervivencia en varias enfermedades oncológicas. Este estudio tuvo como objetivo evaluar la asociación entre LMR y los resultados clínicos para pacientes con colangiocarcinoma.

Material y métodos: Se realizó una revisión sistemática y un metaanálisis para evaluar la asociación entre los valores de LMR y la supervivencia general (SG), la supervivencia libre de enfermedad (DFS), la supervivencia libre de recurrencia (RFS) y el tiempo hasta la recurrencia (TTR) en pacientes con colangiocarcinoma. Utilizamos el cociente de riesgos (HR) y el intervalo de confianza (IC) del 95 % como medida del efecto para el metaanálisis del modelo de efectos aleatorios. Se utilizó la escala de Newcastle-Ottawa para la evaluación de la calidad. La prueba de Egger y el gráfico en embudo se desarrollaron para abordar el sesgo de publicación.

Resultados: En este estudio se incluyeron un total de 19 estudios (n = 3860). El metaanálisis mostró que los pacientes con colangiocarcinoma con valores bajos de LMR se asociaron con peor SG (HR: 0,82; IC 95 %: 0,71–0,96; I2 = 86 %) y peor TTR (HR: 0,71; IC 95 %: 0,58-0,86; I2 = 0%). También se evaluaron DFS y RFS; sin embargo, no mostraron asociaciones estadísticamente significativas.

Conclusión: Los valores bajos de LMR se asociaron con una peor SG y TTR.

Palabras clave: Colangiocarcinoma; Linfocito-monocito; Supervivencia; Metaanálisis

ABSTRACT

Background and aims: Lymphocyte-to-Monocyte Ratio (LMR) has shown an association with survival outcomes in several oncological diseases. This study aimed to evaluate the association between LMR and survival outcomes for cholangiocarcinoma patients.

Materials and Methods: A systematic review and meta-analysis was performed to assess the association between LMR and overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) and time to recurrence (TTR) in cholangiocarcinoma patients. We used hazard ratios (HRs) and their 95% confidence intervals (CIs) as a measure of effect for the random effect model meta-analysis. The Newcastle-Ottawa Scale was used for quality assessment. The Egger test and funnel plot were developed for approaching publication bias.

Results: A total of 19 studies were included in this study (n=3860). The meta-analysis showed that cholangiocarcinoma patients with low values of LMR were associated with worse OS (HR: 0.82; 95% CI: 0.71-0.96; I2=86%) and TTR (HR: 0.71; 95% CI: 0.58-0.86; I2=0%). DFS and RFS also were evaluated; however, they did not show statistically significant associations.

Conclusion: Low LMR values were associated with worse OS and TTR.

Keywords: Cholangiocarcinoma; Lymphocyte-monocyte ratio; Survival; Meta-analysis

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1. INTRODUCTION

Cancer refers to cells that grow out of control and invade other tissues[1]. Cholangiocarcinoma (CCA), or bile duct cancer, is a malignant and lethal adenocarcinoma of the hepatobiliary system that can be divided into three anatomical regions: intrahepatic, perihilar (extrahepatic) and distal. Each anatomical subtype has a clinical presentation and therapeutic approach[2]. The most frequent cancer found in the bile duct bifurcation is called perihilar cholangiocarcinoma or Klatskin tumor. However, intrahepatic cholangiocarcinoma (ICC) is the second most common liver malignancy characterized by its late diagnosis and fatal outcome, ranking behind hepatocellular carcinoma (HCC)[3]. Cholangiocarcinoma represents 3% of all gastrointestinal tumors and 10-15% of all hepatobiliary tumors[4]. This cancer is common in Asian countries such as Thailand[5] and South Korea but rare in countries like Brazil and Costa Rica[6]. However, despite its low prevalence and incidence, recent studies have shown that ICC's incidence and mortality rates are increasing[7].

The etiology remains uncertain, but it is known that there is an association with chronic inflammation of the bile ducts, such as primary sclerosing cholangitis, chronic hepatitis, and cirrhosis[8]. Most patients are asymptomatic in the early stages of the disease until advanced stages; therefore, their diagnosis is late. Most people receive a cholangiocarcinoma diagnosis after cancer has already spread to other organs. The life expectancy is usually poor, and it will depend on the location of cancer and its stage. Bile duct cancer survival is 50% at one year, 20% at two years, and 10% at three years[1].

Because of the suggested role of inflammation in the genesis and prognosis of cancer, several inflammatory response markers have been studied, such as the neutrophil-to-lymphocyte

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ratio (NLR), which is associated with the prognosis of different types of cancers[9,10]. Lymphocyte-to-monocyte ratio (LMR) is another inflammatory marker that has shown prognostic value in different types of cancers and may have a prognostic value in patients with cholangiocarcinoma[11-13]. Although studies have been published that have evaluated the role of LMR in the prognosis of patients with cholangiocarcinoma, the available evidence has not been systematized to the best of our knowledge. Therefore, the purpose of this research is to evaluate the role of lymphocyte-to-monocyte ratio (LMR) as a prognostic indicator in cholangiocarcinoma.

2. METHODS

2.1 Research question and study design

This systematic review was conducted for answering the research question based on Population, Exposure, Comparison and Outcome (PECO) strategy: Do patients with cholangiocarcinoma (P) and low values of LMR (E) have worse overall survival (O) than patients with cholangiocarcinoma and high values of LMR (C)?

2.2 Register and report guideline

This study was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with code CRD42021290302, and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement was used for reporting[14].

2.3 Search strategy and data sources

The search strategy for this systematic review was built following the Peer Review of Electronic Search Strategies (PRESS) checklist with no language or date restriction[15]. At

first, it was built for Pubmed with MeSH and free terms and afterwards, it was adapted to the other databases. On November 30 2021, an advanced search was performed for retrieving studies assessing the association between LMR and overall survival (OS) in patients with cholangiocarcinoma through the following peer review databases: PubMed, Scopus, Web of Science, Embase and The Cochrane Library. In addition, a hand-search was carried out in preprint databases (Medrixv and ResearchSquare).

2.4 Eligibility criteria, study selection and data extraction

Inclusion criteria were studies: (i) with case-control or cohort design, (ii) conducted in adult patients (≥ 18 years old) with a confirmed diagnosis of cholangiocarcinoma, and (iii) that assessed the association between LMR and OS in cholangiocarcinoma patients. Studies without all eligibility criteria and duplicates were excluded. The primary outcome was OS, and Disease-Free Survival (DFS), Recurrence Free Survival (RFS) and Time to Recurrence (TTR) were secondary outcomes (see definitions of the outcomes for each study in Supplementary Table S1). RFS and TTR were considered secondary outcomes in patients who underwent curative resection. Rayyan QCRI software was used for study selection and removing duplicates[16]. First, two authors (GD-V, AKV-A) screened the retrieved records independently by titles and abstracts. Then, these authors assessed the remaining records independently by full-text. Any conflicts in the screening process were resolved by consensus of all authors. Finally, two authors' sheets (GD-V, AKV-A) collected data from included studies in a preset data extraction Microsoft Excel ©. Collected data were: first author, study title, publication date, study design, study location, population baseline characteristics (number of participants, age, sex, comorbidities, stratified sample data), Hazard Ratio (HR)

and corresponding 95% confidence interval (CI) as association measure between LMR and OS, RFS, DFS or TTR.

2.5 Quality assessment

Quality assessment was evaluated independently with the Newcastle-Ottawa Scale (NOS) by two authors (GD-V and AKV-A), and scores were categorized as: low risk of bias (≥ 7 stars) and moderate risk of bias (4-6 stars), and high risk of bias (≤ 3 stars)[17].

2.6 Data synthesis and publication bias

Statistical analysis was performed using Review Manager 5.4 (RevMan 5.4). Estimates for HRs and their 95% CI were pooled and weighted by generic inverse variance, and due to anticipated heterogeneity, a random-effects meta-analysis was performed. Heterogeneity analysis was assessed using the I^2 test and Cochran's Q-statistic. Test values were categorized as: severe heterogeneity (≥ 60%) and mild heterogeneity (< 60%). A p-value of < 0.05 was considered statistically significant. Additionally, a subgroup analysis was developed by study location and treatment (non-surgery vs surgery), and the interaction test p-value per subgroup analysis was reported. Finally, sensitivity analyses were performed using the low risk of bias studies only. Publication bias was assessed through funnel plots and Egger's test, and a p-value < 0.1 was considered indicative of publication bias.

3. RESULTS

3.1 Study Selection

We identified 215 articles, leaving 162 studies after eliminating duplicates. Next, the screening by titles and abstracts excluded 132 studies because of lack of relevance and left

30 studies for the full-text review. Then, 11 full-text articles were excluded because of wrong exposure. Finally, a total of 19 articles were included in the meta-analysis[18-36]. A flow diagram of the literature search is shown in Figure 1.

3.2 Study characteristics

We included 19 articles, giving us a total of 21 cohort studies because two articles analyzed data from two different cohorts. All studies evaluated OS, four evaluated RFS, and three evaluated DFS and TTR. These were studies carried out in four countries, 15 studies in China, four in Japan, one in South Korea and one in Italy. There was a total of 3860 participants, of which 2333 were men. The age ranges of the participants were between 20 and 87 years old. However, three studies did not provide us with the participants' ages. In addition, the range of medians was provided by 18 studies having a range of 42 to 70. According to the TNM stage, it was found that 1441 patients were in stages I and II, while 744 were in stages III and IV. Finally, most studies focused on patients with intrahepatic cholangiocarcinoma (17 studies). On the other hand, 16 studies evaluated optimal LMR cut-off values for OS, RFS, DFS and TTR, ranging from 2.1 to 8. The NOS identified that eight studies had a moderate risk of bias, and only 13 had a low risk of bias (Table 2).

3.3 Association between LMR and OS in cholangiocarcinoma patients

This association was evaluated by 21 studies (n=3860), and meta-analysis showed that cholangiocarcinoma patients with low values of LMR were associated with a worse OS (HR: 0.82; 95% CI: 0.71-0.96; I^2=86%) (Figure 2A). Due to high heterogeneity, subgroup analyses were carried out according to cut-off values, study location and treatment. In the subgroups analysis by cut-off values, we found thar LMR values lower than 3.5 showed a statistically

significant association with a worse OS (HR: 0,58; 95% CI: 0.46-0.74; I^2=57%). On the other hand, LMR values greater than or equal to 3.5 did not show a statistically significant association with OS (HR: 1.07; 95% CI:0.73-1.55; I^2=87%) (Figure 2B). The curative resection subgroup remained the association for OS (HR: 0.72; 95% CI: 0.56-0.93; I^2=85%) and curative surgery subgroup lost the statistically significant association (HR: 1.02; 95% CI: 0.81-1.30; I^2=80%) (Figure 2C). Regarding subgroup analysis by study location, just the Chinese studies subgroup (HR: 0.68; 95% CI: 0.57-0.81; I^2=87%) remained the statistically significant association with OS (Figure 2D). The sensitivity analysis showed a significant decrease of heterogeneity in the association of low values of LMR and worse OS (HR: 0.64; 95% CI: 0.55-0.74; I^2=41%) (Figure 2E).

3.4 Association between LMR and DFS in cholangiocarcinoma patients

The association between LMR and DFS was evaluated by three cohort studies (n=227), and the meta-analysis did not show statistically significant results for this association in cholangiocarcinoma patients (HR: 0.81; 95% CI: 0.33-1.97; I^2=71%) (Figure 3).

3.5 Association between LMR and RFS in cholangiocarcinoma patients

The association between LMR and RFS was evaluated by four cohort studies (n=551), and the meta-analysis did not show statistically significant results for this association in cholangiocarcinoma patients (HR: 0.79; 95% CI: 0.61-1.03; I^2=82%) (Figure 4).

3.6 Association between LMR and TTR in cholangiocarcinoma patients

The association between LMR and TTR was evaluated by three cohort studies (n=748), and the meta-analysis showed that cholangiocarcinoma patients with low values of LMR were associated with worse TTR (HR: 0.71; 95% CI: 0.58-0.86; I^2=0%) (Figure 5).

3.7 Publication bias

Publication bias was not found for the association between LMR values and OS in funnel plot and Egger test (p=0.4495) (Figure 6)

4. DISCUSSION

The main results of our study show that patients with cholangiocarcinoma who have low LMR values were associated with worse OS and TTR. Inflammation is one of the main contributors to the malignant transformation of cells by creating reactive oxygen species and activating cell signalling pathways that promote cell proliferation and limit the degree of apoptosis[37,38]. It also influences cancer progression through its effect on the cellular components of the immune system. Additionally, although the overall effects of cellular immunity on cancer progression are still debated, a chronic state of immune stimulation is associated with a poor prognosis[39]. In that sense, different markers associated with inflammation have been studied as prognostic inflammatory markers of different types of cancers, such as neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR), which have shown usefulness in urogenital and gastrointestinal cancers[9,10,40].

The LMR is composed of two important factors in tumor progression. The first is the immune response to the tumor shown by the number of lymphocytes, potentially including tumor-infiltrating lymphocytes[41]. These induce a DNA damage response, leading to apoptosis or excessive autophagy[42]. In contrast, monocytes associated with malignant tissue, commonly

called tumour-associated macrophages, are drivers of cancer progression due to their contribution to angiogenesis and lymphangiogenesis[43,44]. This mechanism results in increased tumor cell proliferation capacity, increased intravascular fluid flow and increased rates of distant metastasis[45]. In this regard, several systematic reviews have shown that a high LMR value was associated with longer disease-free days and recurrence-free survival in patients with hepatocellular carcinoma and pancreatic cancer[11]. Likewise, a high value was associated with a better prognosis in head and neck cancer[46]. Similarly, a low value was associated with worse OS in patients with esophageal cancer[47], lower OS and progression-free survival in patients with lung cancer[13], and worse prognosis in patients with renal[48] and breast cancer[49].

In patients with cholangiocarcinoma, inflammation has been shown to play an essential role in both genesis and progression. Regardless of its etiology, most risk factors for cholangiocarcinoma cause inflammation or cholestasis[50]. Chronic inflammation leads to increased exposure of cholangiocytes to inflammatory mediators, causing progressive mutations in tumor suppressor genes, proto-oncogenes and DNA mismatch repair genes[50]. The accumulation of bile acids from cholestasis leads to a reduced pH, increased apoptosis, and activation of mediators that stimulate cell proliferation, migration, and survival[50]. Additionally, the presence and maintenance of an inflammatory microenvironment at the primary tumor site plays a vital role in the development and metastasis through mechanisms that activate tumor vasculature and improve angiogenesis and lymphangiogenesis[51].

Although our results are promising, significance was not found in all the outcomes evaluated, as occurred in other types of cancers. For example, in patients with hepatocarcinoma[11], LMR was not associated with OS, and in patients with renal carcinoma[48], a low LMR values were

not associated with OS and DFS. Although our study does not assess the reasons, it is likely to be related to some of the patient's characteristics that influence the outcomes of other types of cancers. Similarly, in patients with pancreatic and breast cancer, the prognostic value of LMR was observed in **s**ubgroups such as ethnicity, surgery treatment, stage of the disease, and LMR cut-off value <3[12], or Asian populations, triple negative patients and patients with non-metastatic disease, and mixed stage, respectively[49].

In contrast, the prognostic value appeared to be influenced by histologic type in lung cancer[13] or some histopathologic features in renal carcinoma[48]. These findings suggest that some patient characteristics may influence the association depending on the clinical outcome assessed.

Our results show enough evidence to recommend a low LMR value as a prognostic marker associated with worse OS and TTR in patients with cholangiocarcinoma. Our study is the first systematic review and meta-analyses that evaluate these associations. Furthermore, we perform sensitivity analyses considering the biases, which robustness our results. Our findings allow us to suggest a potential prognostic marker of low-cost cholangiocarcinoma that will allow health workers to prioritize or individualize management strategies in patients with low LMR values. However, since some characteristics of patients or cancer may affect the prognostic value in some clinical outcomes, it is suggested to design studies that consider different subgroups of patients[13,48].

4.1 Limitations

This study has several limitations, which should be considered for future research. First, most of the studies found in this systemic review were developed on the Asian continent,

preventing us from good comparisons between different ethnic groups. Secondly, the studies did not adjust LMR values with confounding variables that influenced the result of the study. Sociodemographic and clinical factors must be adjusted to improve accuracy in different populations. In the third place, due to lack of information in the included studies, the values of specificity, sensitivity and an optimal cut-off point could not be estimated in a meta-analysis to predict different outcomes in patients with cholangiocarcinoma. Finally, we found a high heterogeneity between the included studies, which is attributed to the high risk of bias of several studies.

5. CONCLUSIONS

Low LMR values are associated with a worse OS and TTR. In addition, no statistically significant association was found between LMR values and the risk of DFS and RFS.

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7. ANNEX

APPENDIX 1:

SEARCH ESTRATEGY

PUBMED

Lymphocyte (#1)

Lymphocytes [MH] OR Lymphocyte [MH] OR Lymphoid Cells [MH] OR Cell, Lymphoid [MH] OR Cells, Lymphoid [MH] OR Lymphoid Cell [MH] OR Lymphocytes [TIAB] OR Lymphocyte [TIAB] OR "Lymphoid Cells" [TIAB] OR "Lymphoid Cell" [TIAB] OR Lymphocytes [OT] OR Lymphocyte [OT] OR "Lymphoid Cells" [OT] OR "Lymphoid Cell" [OT]

Monocyte (#2)

Monocyte [MH] OR Monocytes [MH] OR Monocyte [OT] OR Monocytes [OT] OR Monocyte [TIAB] OR Monocytes [TIAB]

Lymphocyte to monocyte ratio (#3)

"Lymphocyte/Monocite ratio" [OT] OR "Lymphocyte/Monocite index" [OT] OR "Ratio Lymphocyte/Monocite" [OT] OR "Index Lymphocyte/Monocite" [OT] OR "Lymphocyte to Monocite ratio" [OT] OR "Lymphocyte-to Monocite ratio" [OT] OR "Lymphocyte

to-Monocite ratio" [OT] OR "Lymphocyte-to-Monocite ratio" [OT] OR "Lymphocyte to Monocite index" [OT] OR "Lymphocyte-to Monocite index" [OT] OR "Lymphocyte to-Monocite index" [OT] OR "Lymphocyte-to-Monocite index" [OT] OR "Ratio Lymphocyte to Monocite" [OT] OR "Ratio Lymphocyte-to Monocite" [OT] OR "Ratio Lymphocyte to-Monocite" [OT] OR "Ratio Lymphocyte-to-Monocite" [OT] OR "Index Lymphocyte to Monocite" [OT] OR "Index Lymphocyte-to Monocite" [OT] OR "Index Lymphocyte to-Monocite" [OT] OR "Index Lymphocyte-to-Monocite" [OT] OR "Lymphocyte-monocyte ratio" [OT] OR "Lymphocyte-monocyte index" [OT] OR "Ratio Lymphocyte-monocyte" [OT] OR "Index Lymphocyte-monocyte" [OT] OR LMR [OT]

Cholangiocarcinoma (#4)

Cholangiocarcinoma [MH] OR Cholangiocarcinomas [MH] OR Cholangiocellular Carcinoma [MH] OR Carcinoma, Cholangiocellular [MH] OR Carcinomas, Cholangiocellular [MH] OR Cholangiocellular Carcinomas [MH] OR Extrahepatic Cholangiocarcinoma [MH] OR Cholangiocarcinoma, Extrahepatic [MH] OR Cholangiocarcinomas, Extrahepatic [MH] OR Extrahepatic Cholangiocarcinomas [MH] OR Intrahepatic Cholangiocarcinoma [MH] OR Cholangiocarcinoma, Intrahepatic [MH] OR Cholangiocarcinomas, Intrahepatic [MH] OR Intrahepatic Cholangiocarcinomas [MH] OR Cholangiocarcinoma [TIAB] OR Cholangiocarcinomas [TIAB] OR Cholangiocellular Carcinoma [TIAB] OR "Cholangiocellular Carcinomas" [TIAB] OR "Extrahepatic Cholangiocarcinoma" [TIAB] OR "Extrahepatic Cholangiocarcinomas" [TIAB] OR "Intrahepatic Cholangiocarcinoma" [TIAB] OR "Intrahepatic Cholangiocarcinomas" [TIAB] OR Cholangiocarcinoma [OT] OR Cholangiocarcinomas [OT] OR Cholangiocellular Carcinoma [OT] OR "Cholangiocellular

Carcinomas” [OT] OR “Extrahepatic Cholangiocarcinoma” [OT] OR “Extrahepatic Cholangiocarcinomas” [OT] OR “Intrahepatic Cholangiocarcinoma” [OT] OR “Intrahepatic Cholangiocarcinomas” [OT]

Search Formula :

((#1 AND #2) OR #3) AND #4

SCOPUS

(((TITLE-ABS-KEY ("Lymphocytes" OR "Lymphocyte" OR "Lymphoid Cells" OR "Cell, Lymphoid" OR "Cells, Lymphoid" OR "Lymphoid Cell" OR "Lymphocytes" OR "Lymphocyte" OR "Lymphoid Cells" OR "Lymphoid Cell" OR "Lymphocytes" OR "Lymphocyte" OR "Lymphoid Cells" OR "Lymphoid Cell")) AND (TITLE-ABS-KEY ("Monocyte" OR "Monocytes" OR "Monocyte" OR "Monocytes" OR "Monocyte" OR "Monocytes"))) OR (ALL ("Lymphocyte/Monocite ratio" OR "Lymphocyte/Monocite index" OR "Ratio Lymphocyte/Monocite" OR "Index Lymphocyte/Monocite" OR "Lymphocyte to Monocite ratio" OR "Lymphocyte-to Monocite ratio" OR "Lymphocyte to-Monocite ratio" OR "Lymphocyte-to-Monocite ratio" OR "Lymphocyte to Monocite index" OR "Lymphocyte-to Monocite index" OR "Lymphocyte to-Monocite index" OR "Lymphocyte-to-Monocite index" OR "Ratio Lymphocyte to Monocite" OR "Ratio Lymphocyte-to Monocite" OR "Ratio Lymphocyte to-Monocite" OR "Ratio Lymphocyte-to-Monocite" OR "Index Lymphocyte to Monocite" OR "Index Lymphocyte-to Monocite" OR "Index Lymphocyte to-Monocite" OR "Index Lymphocyte-to-Monocite" OR "Lymphocyte-monocyte ratio" OR "Lymphocyte-monocyte

index" OR "Ratio Lymphocyte-monocyte" OR "Index Lymphocyte-monocyte" OR "LMR"))) AND (TITLE-ABS-KEY ("Cholangiocarcinoma" OR "Cholangiocarcinomas" OR "Cholangiocellular Carcinoma" OR "Carcinoma, Cholangiocellular" OR "Carcinomas, Cholangiocellular" OR "Cholangiocellular Carcinomas" OR "Extrahepatic Cholangiocarcinoma" OR "Cholangiocarcinoma, Extrahepatic" OR "Cholangiocarcinomas, Extrahepatic" OR "Extrahepatic Cholangiocarcinomas" OR "Intrahepatic Cholangiocarcinoma" OR "Cholangiocarcinoma, Intrahepatic" OR "Cholangiocarcinomas, Intrahepatic" OR "Intrahepatic Cholangiocarcinomas" OR "Cholangiocarcinoma" OR "Cholangiocarcinomas" OR "Cholangiocellular Carcinoma" OR "Cholangiocellular Carcinomas" OR "Extrahepatic Cholangiocarcinoma" OR "Extrahepatic Cholangiocarcinomas" OR "Intrahepatic Cholangiocarcinoma" OR "Intrahepatic Cholangiocarcinomas" OR "Cholangiocarcinoma" OR "Cholangiocarcinomas" OR "Cholangiocellular Carcinoma" OR "Cholangiocellular Carcinomas" OR "Extrahepatic Cholangiocarcinoma" OR "Extrahepatic Cholangiocarcinomas" OR "Intrahepatic Cholangiocarcinoma" OR "Intrahepatic Cholangiocarcinomas"))

WEB OF SCIENCE

(((ALL=(“Lymphocytes” OR “Lymphocyte” OR “Lymphoid Cells” OR “Cell, Lymphoid” OR “Cells, Lymphoid” OR “Lymphoid Cell” OR “Lymphocytes” OR “Lymphocyte” OR “Lymphoid Cells” OR “Lymphoid Cell” OR “Lymphocytes” OR “Lymphocyte” OR “Lymphoid Cells” OR “Lymphoid Cell”)) AND ALL=(“Monocyte” OR “Monocytes” OR “Monocyte” OR “Monocytes” OR “Monocyte” OR “Monocytes”)) OR ALL=(“Lymphocyte/Monocite ratio” OR “Lymphocyte/Monocite index” OR “Ratio

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("Lymphocytes" OR "Lymphocyte" OR "Lymphoid Cells" OR "Cell, Lymphoid" OR "Cells, Lymphoid" OR "Lymphoid Cell" OR "Lymphocytes" OR "Lymphocyte" OR "Lymphoid Cells" OR "Lymphoid Cell" OR "Lymphocytes" OR "Lymphocyte" OR "Lymphoid Cells" OR "Lymphoid Cell"):ti,ab,kw AND ("Monocyte" OR "Monocytes" OR "Monocyte" OR "Monocytes" OR "Monocyte" OR "Monocytes"):ti,ab,kw OR ("Lymphocyte to Monocite ratio" OR "Lymphocyte-to Monocite ratio" OR "Lymphocyte to-Monocite ratio" OR "Lymphocyte-to-Monocite ratio" OR "Lymphocyte to Monocite index" OR "Lymphocyte-to Monocite index" OR "Lymphocyte to-Monocite index" OR "Lymphocyte-to-Monocite index" OR "Ratio Lymphocyte to Monocite" OR "Ratio Lymphocyte-to Monocite" OR "Ratio Lymphocyte to-Monocite" OR "Ratio Lymphocyte-to-Monocite" OR "Index Lymphocyte to Monocite" OR "Index Lymphocyte-to Monocite" OR "Index Lymphocyte to-Monocite" OR "Index Lymphocyte-to-Monocite" OR "Lymphocyte-monocyte ratio" OR "Lymphocyte-monocyte index" OR "Ratio Lymphocyte-monocyte" OR "Index Lymphocyte-monocyte" OR "LMR") AND ("Cholangiocarcinoma" OR "Cholangiocarcinomas" OR "Cholangiocellular Carcinoma" OR "Carcinoma, Cholangiocellular" OR "Carcinomas, Cholangiocellular" OR "Cholangiocellular Carcinomas" OR "Extrahepatic Cholangiocarcinoma" OR "Cholangiocarcinoma, Extrahepatic" OR "Cholangiocarcinomas, Extrahepatic" OR "Extrahepatic Cholangiocarcinomas" OR "Intrahepatic Cholangiocarcinoma" OR "Cholangiocarcinoma, Intrahepatic" OR "Cholangiocarcinomas, Intrahepatic" OR "Intrahepatic Cholangiocarcinomas" OR "Cholangiocarcinoma" OR "Cholangiocarcinomas" OR "Cholangiocellular Carcinoma" OR "Cholangiocellular Carcinomas" OR "Extrahepatic Cholangiocarcinoma" OR "Extrahepatic Cholangiocarcinomas" OR "Intrahepatic

Cholangiocarcinoma" OR "Intrahepatic Cholangiocarcinomas" OR "Cholangiocarcinoma" OR "Cholangiocarcinomas" OR "Cholangiocellular Carcinoma" OR "Cholangiocellular Carcinomas" OR "Extrahepatic Cholangiocarcinoma" OR "Extrahepatic Cholangiocarcinomas" OR "Intrahepatic Cholangiocarcinoma" OR "Intrahepatic Cholangiocarcinomas"):ti,ab,kw

OVID MEDLINE

("Lymphocytes" OR "Lymphocyte" OR "Lymphoid Cells" OR "Cell, Lymphoid" OR "Cells, Lymphoid" OR "Lymphoid Cell" OR "Lymphocytes" OR "Lymphocyte" OR "Lymphoid Cells" OR "Lymphoid Cell" OR "Lymphocytes" OR "Lymphocyte" OR "Lymphoid Cells" OR "Lymphoid Cell").af. AND ("Monocyte" OR "Monocytes" OR "Monocyte" OR "Monocytes" OR "Monocyte" OR "Monocytes").af. OR ("Lymphocyte to Monocite ratio" OR "Lymphocyte-to Monocite ratio" OR "Lymphocyte to-Monocite ratio" OR "Lymphocyte-to-Monocite ratio" OR "Lymphocyte to Monocite index" OR "Lymphocyte-to Monocite index" OR "Lymphocyte to-Monocite index" OR "Lymphocyte-to-Monocite index" OR "Ratio Lymphocyte to Monocite" OR "Ratio Lymphocyte-to Monocite" OR "Ratio Lymphocyte to-Monocite" OR "Ratio Lymphocyte-to-Monocite" OR "Index Lymphocyte to Monocite" OR "Index Lymphocyte-to Monocite" OR "Index Lymphocyte to-Monocite" OR "Index Lymphocyte-to-Monocite" OR "Lymphocyte-monocyte ratio" OR "Lymphocyte-monocyte index" OR "Ratio Lymphocyte-monocyte" OR "Index Lymphocyte-monocyte" OR "LMR").af. AND ("Cholangiocarcinoma" OR "Cholangiocarcinomas" OR "Cholangiocellular Carcinoma" OR "Carcinoma, Cholangiocellular" OR "Carcinomas, Cholangiocellular" OR "Cholangiocellular Carcinomas" OR "Extrahepatic Cholangiocarcinoma" OR

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Figure 1: PRISMA Flow Diagram

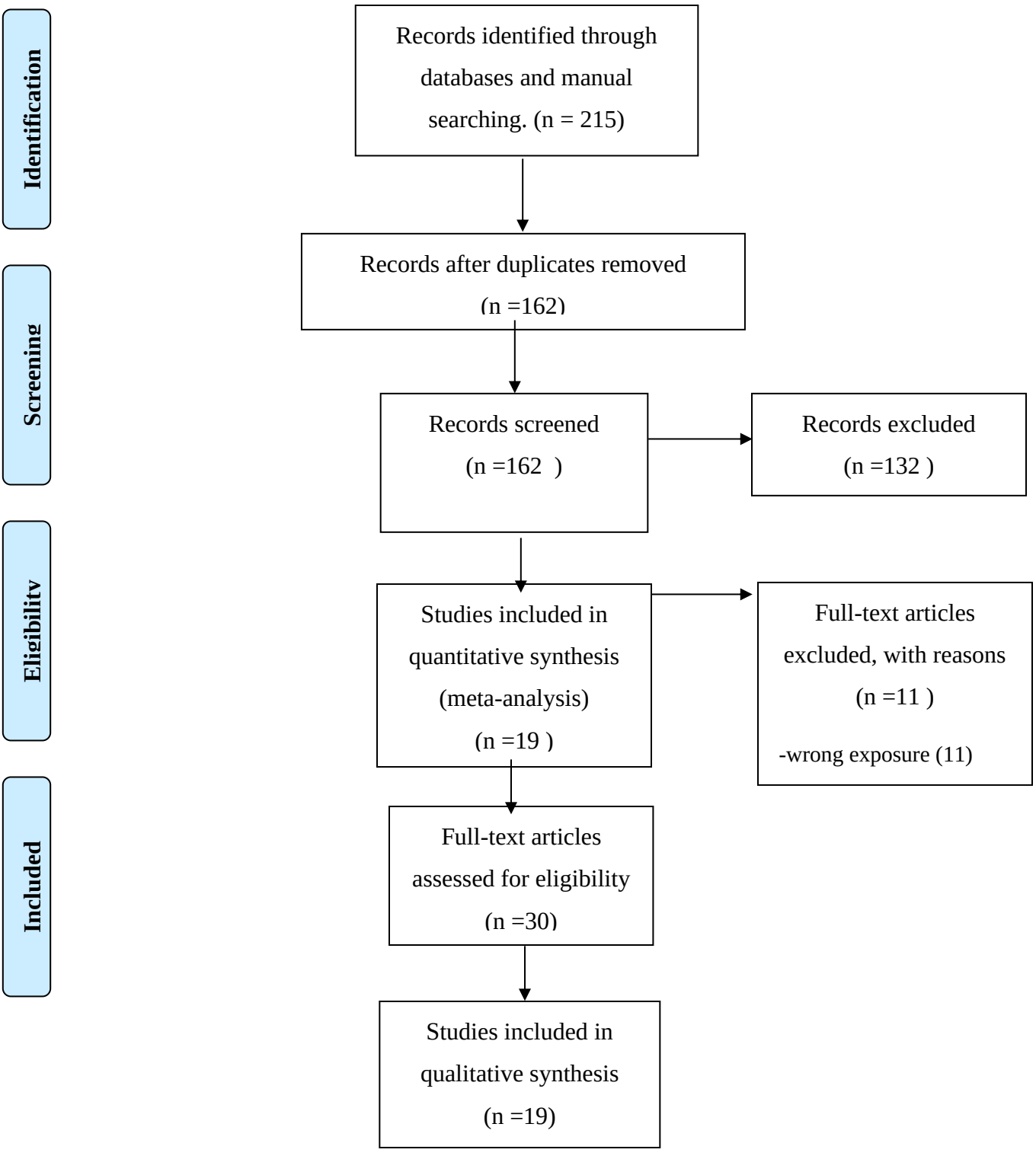

Figure 2A: Association of LMR and OS in patients with cholangiocarcinoma

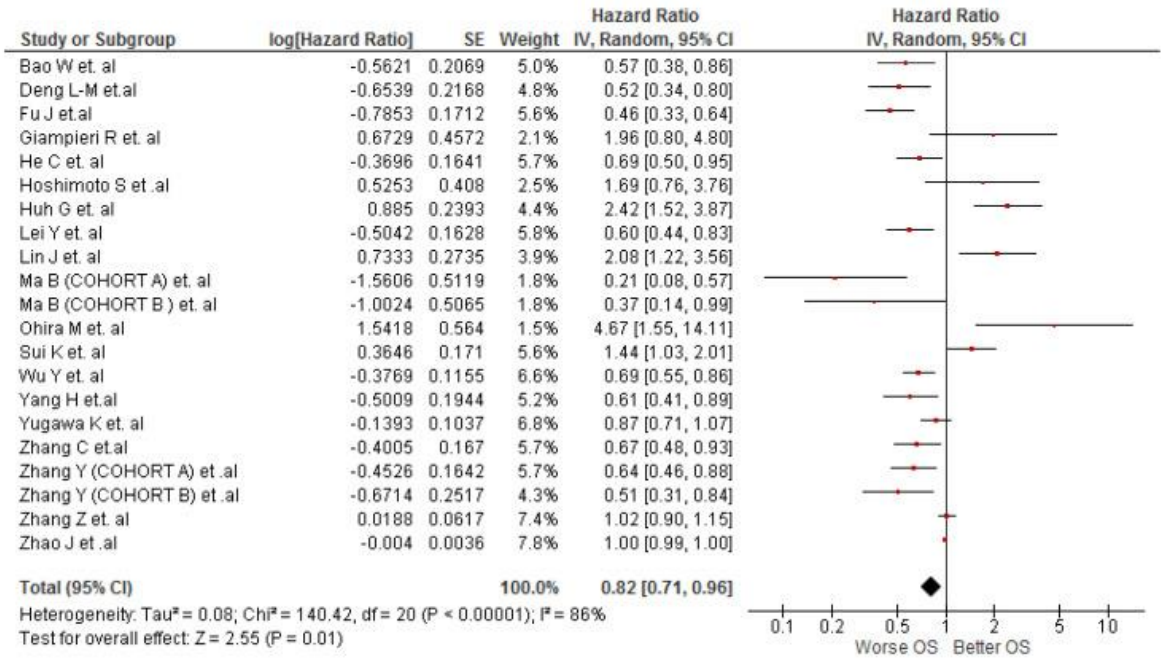

Figure 2B: Subgroup analysis according to the cut-off values (≥3.5 vs <3.5) of the association between LMR and OS in patients with cholangiocarcinoma

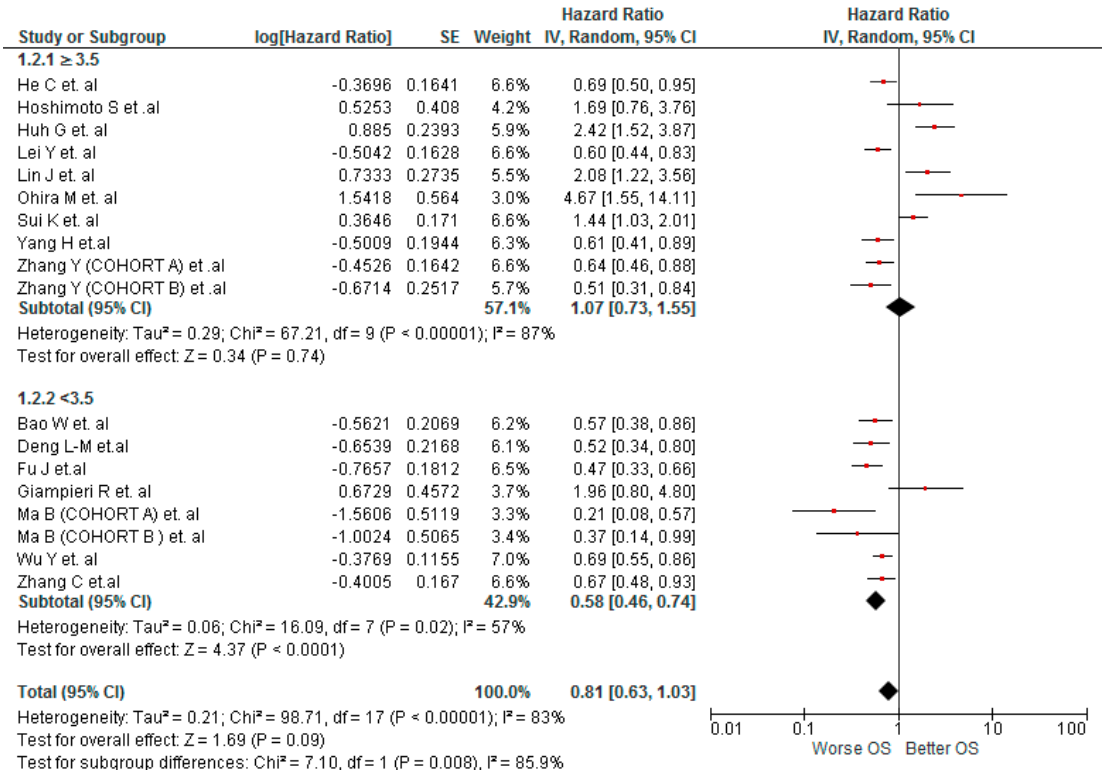

Figure 2C: Subgroup analysis according to the treatment of the association between LMR and OS in patients with cholangiocarcinoma

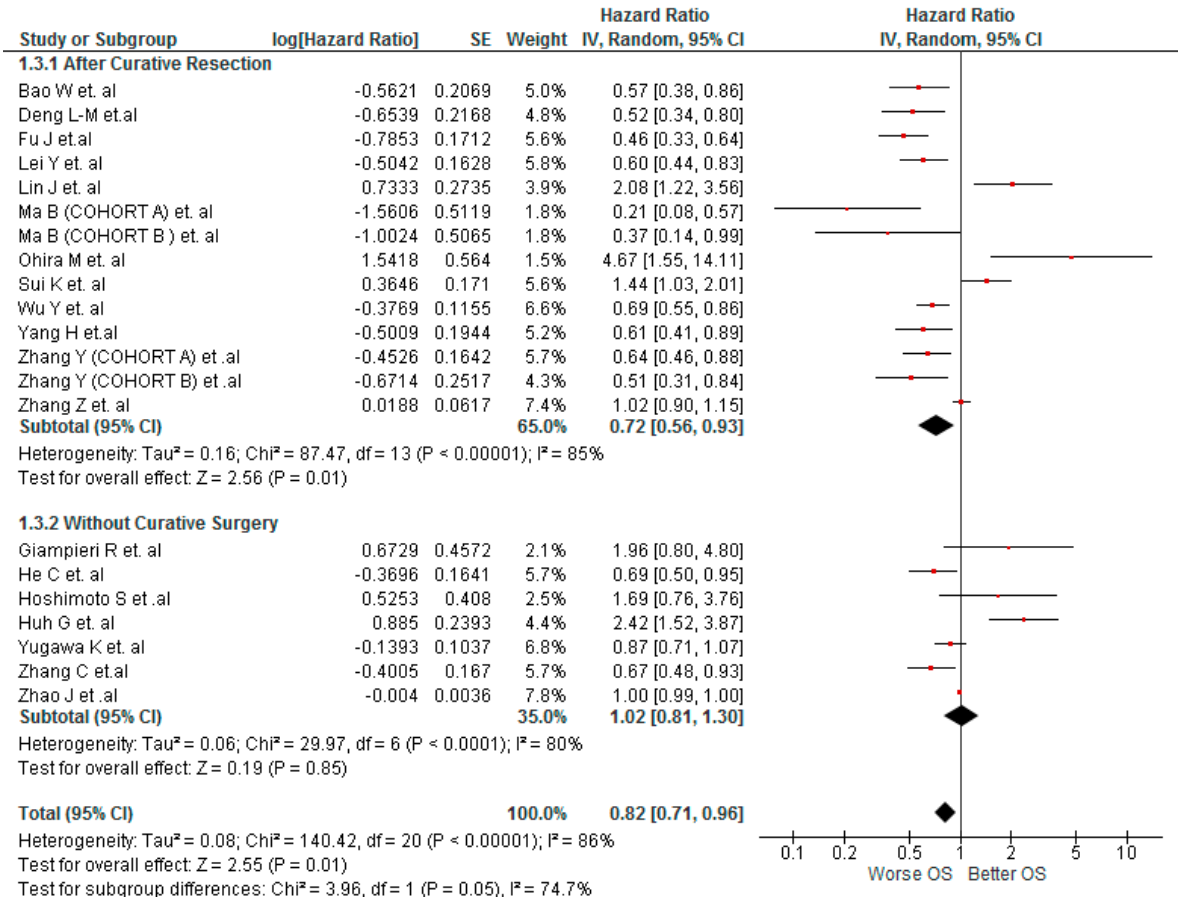

Figure 2D: Subgroup analysis according to the origin country of the association between LMR and OS in patients with cholangiocarcinoma

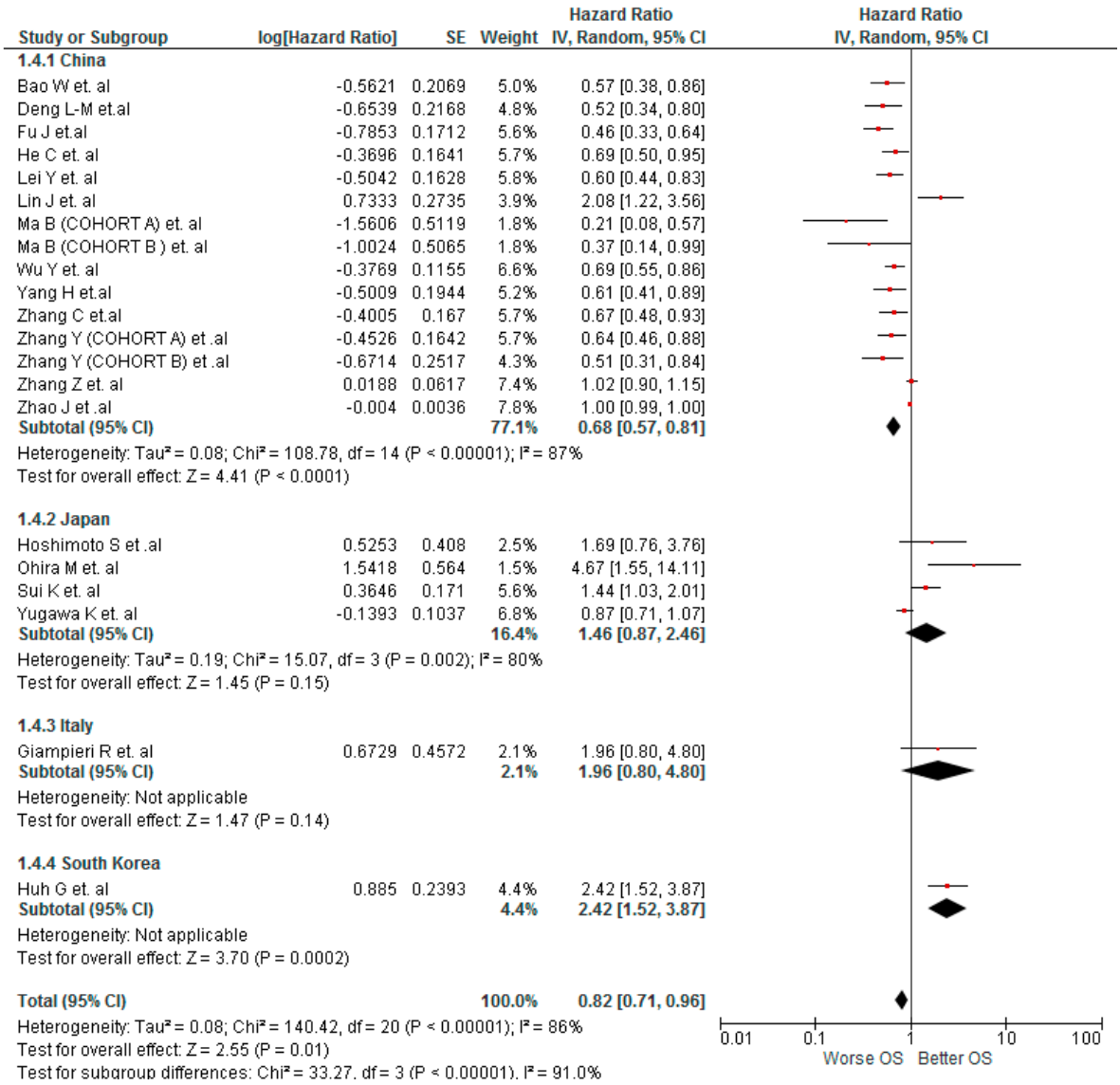
Study or Subgroup
log[Hazard Ratio]
SE
Weight
Hazard Ratio
IV, Random, 95% CI
Hazard Ratio
IV, Random, 95% CI
1.4.1 China
Bao W et. al -0.5621 0.2069 5.0% 0.57 [0.38, 0.86]
Deng L-M et.al -0.6539 0.2168 4.8% 0.52 [0.34, 0.80]
Fu J et.al -0.7853 0.1712 5.6% 0.46 [0.33, 0.64]
He C et. al -0.3696 0.1641 5.7% 0.69 [0.50, 0.95]
Lei Y et. al -0.5042 0.1628 5.8% 0.60 [0.44, 0.83]
Lin J et. al 0.7333 0.2735 3.9% 2.08 [1.22, 3.56]
Ma B (COHORT A) et. al -1.5606 0.5119 1.8% 0.21 [0.08, 0.57]
Ma B (COHORT B) et. al -1.0024 0.5065 1.8% 0.37 [0.14, 0.99]
Wu Y et. al -0.3769 0.1155 6.6% 0.69 [0.55, 0.86]
Yang H et.al -0.5009 0.1944 5.2% 0.61 [0.41, 0.89]
Zhang C et.al -0.4005 0.167 5.7% 0.67 [0.48, 0.93]
Zhang Y (COHORT A) et .al -0.4526 0.1642 5.7% 0.64 [0.46, 0.88]
Zhang Y (COHORT B) et .al -0.6714 0.2517 4.3% 0.51 [0.31, 0.84]
Zhang Z et. al 0.0188 0.0617 7.4% 1.02 [0.90, 1.15]
Zhao J et .al -0.004 0.0036 7.8% 1.00 [0.99, 1.00]
Subtotal (95% CI) 77.1% 0.68 [0.57, 0.81]
Heterogeneity: Tau² = 0.08; Chi² = 108.78, df = 14 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.41 (P < 0.0001)
1.4.2 Japan
Hoshimoto S et .al 0.5253 0.408 2.5% 1.69 [0.76, 3.76]
Ohira M et. al 1.5418 0.564 1.5% 4.67 [1.55, 14.11]
Sui K et. al 0.3646 0.171 5.6% 1.44 [1.03, 2.01]
Yugawa K et. al -0.1393 0.1037 6.8% 0.87 [0.71, 1.07]
Subtotal (95% CI) 16.4% 1.46 [0.87, 2.46]
Heterogeneity: Tau² = 0.19; Chi² = 15.07, df = 3 (P = 0.002); I² = 80%
Test for overall effect: Z = 1.45 (P = 0.15)
1.4.3 Italy
Giampieri R et. al 0.6729 0.4572 2.1% 1.96 [0.80, 4.80]
Subtotal (95% CI) 2.1% 1.96 [0.80, 4.80]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)
1.4.4 South Korea
Huh G et. al 0.885 0.2393 4.4% 2.42 [1.52, 3.87]
Subtotal (95% CI) 4.4% 2.42 [1.52, 3.87]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.70 (P = 0.0002)
Total (95% CI) 100.0% 0.82 [0.71, 0.96]
Heterogeneity: Tau² = 0.08; Chi² = 140.42, df = 20 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.55 (P = 0.01)
Test for subgroup differences: Chi² = 33.27, df = 3 (P < 0.00001), I² = 91.0%
0.01
0.1
1
10
100
Worse OS
Better OS

Figure 2E: Sensitivity analysis according to risk of bias of the association between LMR and OS in patients with cholangiocarcinoma

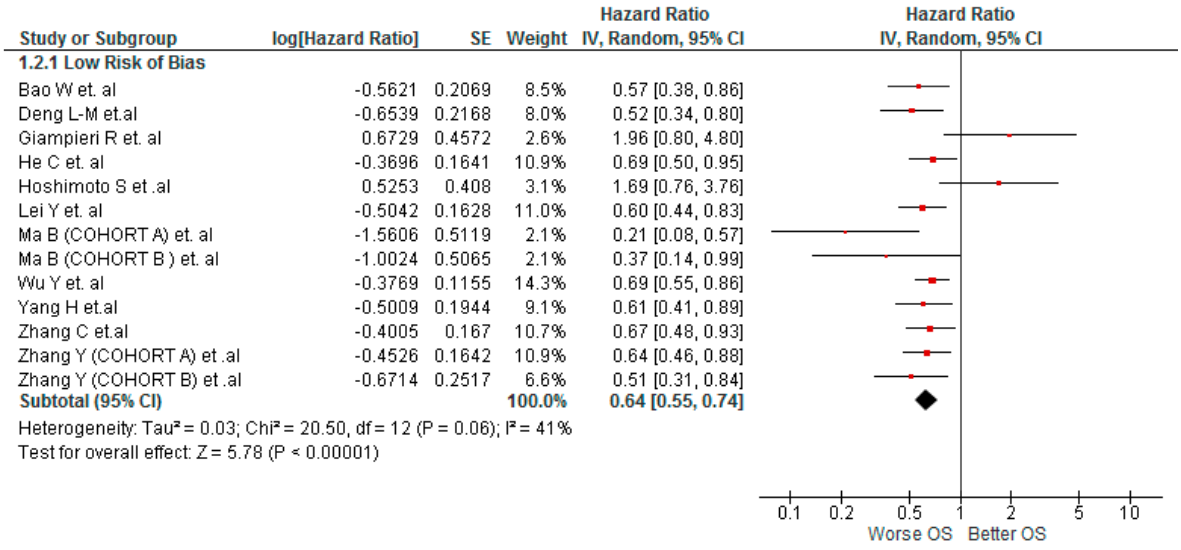

Figure 3: Association of LMR and DFS in patients with cholangiocarcinoma

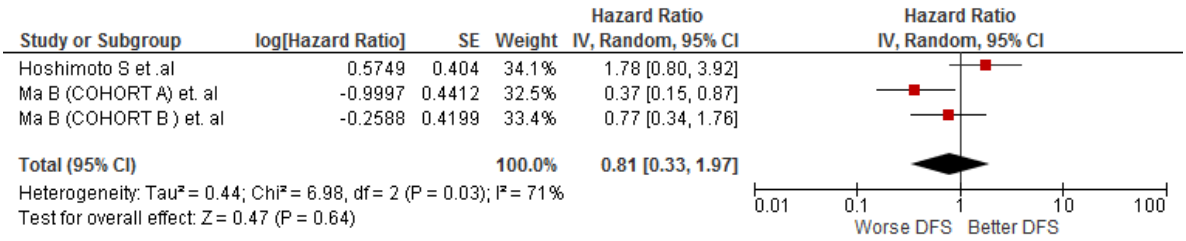

Figure 4: Association of LMR and RFS in patients with cholangiocarcinoma

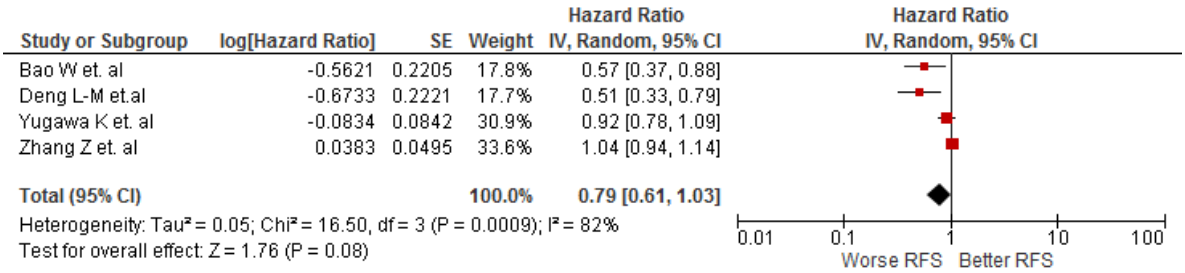

Figure 5: Association of LMR and TTR in patients with cholangiocarcinoma

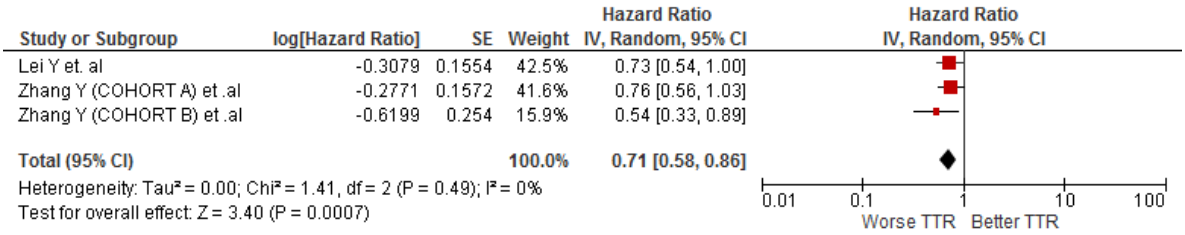

Figure 6: Funnel Plot of the studies that evaluated the association between LMR values and OS

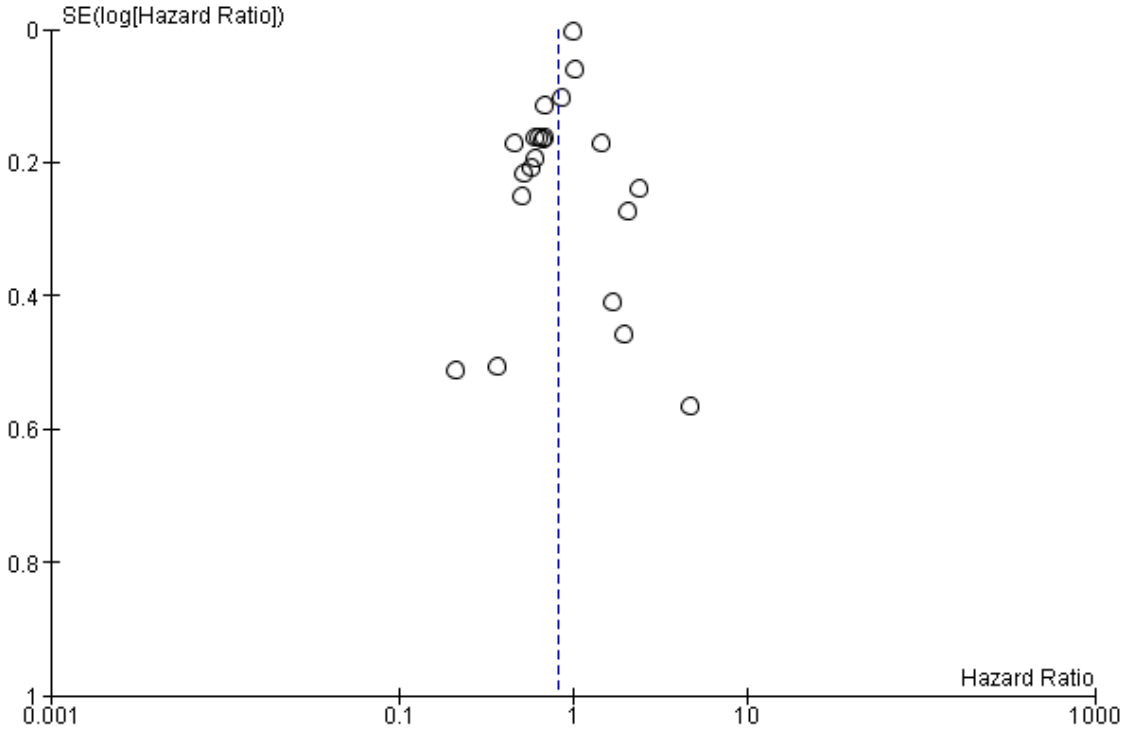

Table 1: Characteristics of the included studies

Author	*Year*	*Study Location*	*Median follow-up time*	*Participants (Male)*	*Median/mean Age (IQR/SD)*	*Type of Cholangiocarcinoma evaluated*	*Outcome*	*HR(95% CI), p-value*	*Cut-off*	*TNM Stage (I-II/III-IV)*
Wu Y et. al	2019	China	29.1 months	123(67)	57 (11)	Intrahepatic	Overall Survival	0.686(0.547–0.819), p<0.05	3.42	38/85

He C et. al	2021	China	NR	292(181)	56 (20–77)	Intrahepatic	Overall Survival	0.691 (0.501–0.953) , p<0.05	4.06	107/185
Lin J et. al	2019	China	NR	123(65)	60 (31–85)	Intrahepatic	Overall Survival	2.082(1.218–3.558), p<0.05	3.62	99/24
Huh G et. al	2020	South Korea	35.4 months	137(83)	64 (57-72)	Intrahepatic	Overall Survival	2.423 (1.516–3.875), p<0.05	3.5	NR/NR
Ohira M et. al	2021	Japan	NR	52(41)	61 (39–82)	Intrahepatic	Overall Survival	4.673(1.547–20.165), p<0.05	4.36	35/17

Yang H et.al	2019	China	44 months	299(181)	NR	Intrahepatic	Overall Survival	0.606(0.414–0.885), p<0.05	4.45	226/73
Fu J et.al	2021	China	NR	446(295)	54.36 (10.71)	Intrahepatic	Overall Survival	0.465(0.326-0.663), p<0.005	2.48	NR/NR
Sui K et. al	2020	Japan	27.6 months	273(164)	70 (9.4)	Intrahepatic	Overall Survival	1.44 (1.03–2.43), p<0.05	3.7	NR/NR
Giampieri R et. al	2021	Italy	NR	45(NR)	NR	Mixed	Overall Survival	1.96(0.80–4.8) , p=0.138	2.1	NR/NR
Zhao J et .al	2021	China	NR	468(282)	58 (51–65)	Intrahepatic	Overall Survival	0.996(0.989–1.003), p=0.302	NR	NR/NR

Zhang C et.al	2016	China	NR	187(117)	58(12)	Intrahepatic	Overall Survival	0.67 (0.483–0.931), p<0.05	3	NR/NR
Bao W et. al	2021	China	28.7 months	178(85)	64 (10)	Intrahepatic	Overall Survival	0.57(0.38–0.87), p<0.05	3	126/52
							Recurrence-free survival	0.57(0.37–0.86), p<0.05		
Zhang Z et. al	2020	China	NR	128(70)	56 (10)	Intrahepatic	Overall Survival	1.019 (0.903–1.151), p=0.757	NR	53/75
							Recurrence-free survival	1.039 (0.943–1.146), p =0.435		

Yugawa K et. al	2021	Japan	NR	78(55)	66 (39–87)	Intrahepatic	Overall Survival	0.87 (0.71–1.71), p=0.1354	NR	NR/NR
							Recurrence-free survival	0.92 (0.78–1.06), p=0.2414		
Ma B (COHORT A) et. al	2021	Tianjin, China	NR	72(41)	59(32-76)	Intrahepatic	Overall Survival	0.21 (0.077–0.569), p<0.05	2.65	NR/NR
							Disease Free Survival	0.368 (0.155-0.874), p<0.05		
Ma B (COHORT B) et. al	2021	Weifang, China	25.1 months	102(57)	49(28-77)	Intrahepatic	Overall Survival	0.367(0.136-0.993), p<0.05	2.7	

							Disease Free Survival	0.772(0.339-1.758), p=0.537		NR/NR
Hoshimoto S et .al	2019	Japan	NR	53(31)	70(50–87)	Distal	Overall Survival	1.691(0.760–3.764), p=0.198	4.633	50/3
							Disease Free Survival	1.777(0.805–3.925), p=0.155	3.208	
Deng L-M et.al	2021	China	29.3 months	167(83)	63(9)	Intrahepatic	Overall Survival	0.52(0.34-0.8), p<0.05	3.13	116/51
							Recurrence-free survival	0.51(0.33-0.78), p<0.05		

Lei Y et. al	2020	China	44 months	322(194)	NR	Intrahepatic	Overall Survival	0.604 (0.439-0.831), p<0.05	4.45	248/74
							Time to recurrence	0.735 (0.542-0.997), p<0.05		
Zhang Y (COHORT A) et .al	2019	China	44 months	322(194)	58 (27–81)	Intrahepatic	Overall Survival	0.636 (0.461-0.878), p<0.05	4.45	248/74
							Time to recurrence	0.758 (0.557-1.032), p=0.079		
Zhang Y (COHORT B) et .al	2019	China	38.3 months	104(47)	42(33-56)	Intrahepatic	Overall Survival	0.511 (0.312-0.837), p<0.05	4.45	95/31

	Time to recurrence	0.538 (0.327-0.884), p<0.05

NR : Not Reported

Table 2: Newcastle Ottawa Quality Assessment Scale for included studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES										
STUDY	**SELECTION**				**COMPARABILITY**	**OUTCOME**				
	Representativeness of the exposed cohort	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of Cohorts on the Basis of the Design or Analysis Maximum : ☆☆**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**SCORE**	**Evidence quality**

Wu Y et. al	☆	☆	☆	☆	☆	☆	☆	☆	*8*	Low Risk of bias
He C et. al		☆	☆	☆	☆	☆	☆	☆	*7*	Low Risk of bias
Lin J et. al	☆		☆	☆	☆	☆		☆	*6*	Moderate risk of bias
Huh G et. al		☆	☆	☆	☆	☆	☆		*6*	Moderate risk of bias
Ohira M et. al	☆		☆	☆	☆			☆	*5*	Moderate risk of bias

Yang H et.al	☆	☆	☆	☆	☆☆	☆	☆	☆	*9*	Low Risk of bias
Sui K et. al	☆			☆		☆	☆		*4*	Moder ate risk of bias
Giampieri R et. al	☆	☆	☆	☆	☆	☆	☆	☆	*8*	Low Risk of bias
Zhao J et .al	☆	☆	☆	☆			☆		*5*	Moder ate risk of bias
Zhang C et.al	☆	☆	☆		☆	☆	☆	☆	*7*	Low Risk of bias

Bao W et. al	☆	☆	☆	☆	☆		☆	☆	*7*	Low Risk of bias
Zhang Z et. al	☆	☆	☆			☆	☆	☆	*6*	Moder ate risk of bias
Yugawa K et. al	☆	☆		☆		☆	☆		*5*	Moder ate risk of bias
Ma B (COHO RT A) et. al	☆	☆	☆	☆	☆	☆		☆	*7*	Low Risk of bias

Ma B (COHORT B) et. al	☆	☆	☆	☆	☆	☆		☆	*7*	Low Risk of bias
Fu J et.al	☆		☆	☆	☆			☆	*5*	Moderate risk of bias
Hoshimoto S et .al	☆	☆	☆	☆	☆☆	☆	☆	☆	*9*	Low Risk of bias
Deng L-M et.al	☆	☆	☆	☆	☆	☆	☆	☆	*8*	Low Risk of bias

Lei Y et. al	☆	☆	☆		☆	☆	☆	☆	*7*	Low Risk of bias
Zhang Y (COHORT A) et .al	☆	☆	☆		☆☆	☆	☆	☆	*8*	Low Risk of bias

Zhang Y (COHORT B) et .al	☆	☆	☆		☆☆	☆	☆	☆	*8*	Low Risk of bias

NR: Not Reported

Table 3: Outcome definitions for each study

Author	Outcome	Definition
Wu Y et. al	OS	The time between radical surgery and mortality.
He C et. al	OS	The date of surgery to the date of death and tumor progression, respectively, or the last follow-up.
Lin J et. al	OS	The interval between the date of resection and the date of death or the last follow-up.
Huh G et. al	OS	The time from chemotherapy initiation until death or the last follow-up.
Ohira M et. al	OS	NR
Yang H et. al	OS	The interval between the dates of partial hepatectomy and death or between the dates of partial hepatectomy and the last observation.
Fu J et. al	OS	The interval between the date of LR to the date censored, the date of the patient's death, or last follow-up.
Sui K et. al	OS	The surgery date until death related to ICC.
Giampieri et. al	OS	NR
Zhao J et. al	OS	NR
Zhang C et. al	OS	The interval between the date of a definitive diagnosis and death or between the date of a definitive diagnosis and the last observation of surviving patients
Bao W et. al	OS	The date of surgery to the date of patient's death or the last follow-up date
	RFS	The date of surgery to the date of the first recurrence or last follow-up
	OS	The first day after hepatectomy to the ICC-related death.

Zhang Z et. al	RFS	The first day after hepatectomy to the recurrence of ICC- or ICC-related death
Yugawa K et. al	OS	The time from the date of surgery to the date of the last follow-up or death.
	RFS	NR
Ma B et. al	OS	The date of first diagnosis of ICC to the date of death or last follow-up
	DFS	The period between the date of surgery and the date of first recurrence or last follow-up
Hoshimoto S et. al	OS	The time period from the date of surgery to either the date of death or the date of the last follow-up, whichever occurred first
	DFS	The time period from the date of surgery to the date of recurrence, last follow-up, or death, whichever occurred first.
Deng L-M et. al	OS	The date of surgery to the date of patient death or last follow-up
	RFS	The date of surgery to the date of first ICC recurrence, death, or last follow-up visit.
Lei Y et. al	OS	NR
	TTR	NR
Zhang Y et. al	OS	The dates of operation to the dates of death or the dates of last follow-up
	TTR	The interval between the dates of operation and the first recurrence or from the dates of operation to the dates of last follow-up (for the patients without recurrence).

NR: Not Reported

Table 4: Identification and measurement of heterogeneity

Heterogeneity	Any kind of variability among studies in a systematic review.
Statistical heterogeneity	Variability in the intervention effects being evaluated in the different studies.
I^2	This describes the percentage that measures the heterogeneity of the included studies. 0% suggests that chance is responsible for the variability, while 100% suggests that the variability is excessive.
Chi^2	This test assumes the null hypothesis that all studies are homogeneous. If the p-value of the test is low (≤ 0.1), the hypothesis can be rejected and heterogeneity would be present.
Tau^2	Estimates the variance between effect sizes of studies in an MA.