REVIEW

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Prognostic Significance of Up-to-Seven Criteria Versus Milan Criteria for Hepatocellular Carcinoma Patients Undergoing Resection or Locoregional Therapy: A Systematic Review and Meta-Analysis

Ni Putu Sri Indrani Remitha[1], I Komang Wira Ananta Kusuma[1], I Gede Aswin Parisya Sasmana[1], I Gede Putu Supadmanaba[2], Dwijo Anargha Sindhughosa[3], I Ketut Mariadi[4]*

Abstract

Introduction: Every year, the incidence of hepatocellular carcinoma (HCC) rises, making it a persistent global health concern. To help patients with HCC make treatment options for transplant eligibility, a number of selection criteria, including the Milan and Up-to-Seven criteria, have been developed; however, it is unclear how well these predict outcomes. This study aimed to evaluate the prognostic significance of Up-to-Seven versus Milan criteria in HCC patients undergoing resection or locoregional therapy. **Methods:** In accordance with PRISMA criteria, a systematic review and meta-analysis were performed. The Cochrane Library, PubMed, ScienceDirect, Google Scholar, SpringerLink, and Ebsco were searched for relevant literature. Included were studies contrasting prognostic outcomes (disease-free survival [DFS], progression-free survival [PFS], and overall survival [OS]) according to the two criteria. Review Manager 5.4 was used for data analysis. **Results:** Five retrospective cohort studies involving 921 patients were analyzed. The meta-analysis revealed a significant difference in OS (HR = 3.42; 95% CI: 2.23–5.25; $p < 0.00001$) and PFS (HR = 3.39; 95% CI: 1.09–10.54; $p = 0.04$), favoring the Milan criteria. No significant difference was found in DFS (HR = 2.42; 95% CI: 0.95–6.14; $p = 0.06$). **Conclusion:** The Up-to-Seven criteria demonstrated non-inferior prognostic performance to the Milan criteria for DFS, while Milan criteria were associated with significantly better OS and PFS. These findings suggest that the Up-to-Seven criteria may serve as an acceptable alternative in broader patient selection for HCC therapy.

Keywords: Hepatocellular carcinoma- locoregional therapy- Milan criteria- resection- up-to-seven criteria

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Introduction

A major liver cancer that has a major effect on the worldwide burden of illness is hepatocellular carcinoma (HCC) [1]. Over 800,000 fatalities are attributed to HCC each year, making it the fourth most common cause of cancer-related mortality globally. Based on epidemiological trends, it is anticipated that between 2020 and 2040, the incidence of HCC would rise by 55.0%, while the fatality rate will climb by 56.4% The leading cause of morbidity and death worldwide for people with cirrhosis and chronic liver disease is still HCC, which primarily arises as a result of complicated risk factors [2]. Since early discovery allows for a five-year survival rate of over 70%, the prognosis of HCC is heavily influenced by the clinical stage at diagnosis. On the other hand, the prognosis is much worse for advanced-stage disease, with survival rates less than 20% throughout the same time frame [3]. Furthermore, non-alcoholic fatty liver disease (NAFLD) and rising alcohol consumption in many nations are causing the aetiology of HCC to change from viral hepatitis infections to non-viral factors [4].

The patient's overall health, liver function, and disease stage all influence the therapeutic methods for HCC. Liver transplantation and liver resection are the main curative therapy options for early-stage HCC. Several criteria have been devised to identify the best candidates for liver transplantation in order to maximise the allocation

*[1]Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia. [2]Department of Biochemistry, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia. [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, Udayana University, Bali, Indonesia. [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, Udayana University/Ngoerah Hospital, Bali, Indonesia. *For Correspondence: mariadi@unud.ac.id*

of limited donor organs and improve treatment outcomes [5]. Mazzaferro et al. established the Milan Criteria in 1996, and because of their good prognosis roughly 70% five-year survival rate they have become the accepted norm worldwide [6]. Nonetheless, patients with HCC who might still benefit from liver transplantation or other locoregional therapy may be excluded due to the strict restrictions of the Milan Criteria [7].

The Up-to-Seven Criteria is one of the different strategies that have been put forth to increase treatment indications without sacrificing long-term results [8]. Introduced by Mazzaferro et al. in 2009, this criterion determines eligibility for transplantation based on the number of tumour nodules and the size of the largest lesion, with a cumulative total of no more than seven [9]. Numerous studies have examined the Up-to-Seven Criteria's viability in selecting candidates for liver transplantation, and the results show that patients who meet this criterion have survival rates that are on par with those who meet the Milan Criteria [10, 11]. Additionally, individuals who were previously ineligible under the Milan Criteria can now undergo downstaging and become viable candidates for liver resection or transplantation thanks to developments in locoregional methods like radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) [12].

Considering how the Milan and Up-to-Seven Criteria differ in their requirements for selecting candidates, further evaluation of their prognostic significance is necessary. Multiple studies have supported the notion that the Up-to-Seven Criteria may expand transplant eligibility while maintaining favorable survival outcomes. Nong et al.'s retrospective cohort analysis showed that patients with BCLC stage B HCC who satisfied the Up-to-Seven Criteria and had a hepatectomy fared far better overall than those who received TACE, emphasizing the prognostic value of tumor number and supporting surgical resection in select intermediate-stage patients [11]. Similarly, studies evaluating expanded criteria such as the UCSF, Asan, and Kyoto Criteria have shown that patients beyond Milan but within expanded limits can achieve comparable five-year overall survival, suggesting that Milan may be overly restrictive [13]. Moreover, evidence indicates that pre-transplant locoregional therapy such as TACE can effectively downstage tumors to meet Milan Criteria, without compromising post-transplant survival, as shown by Kim et al., further supporting the utility of incorporating broader selection strategies in clinical practice [14]. Therefore, this study aims to conduct a systematic review and meta-analysis to compare clinical outcomes among HCC patients undergoing liver resection or locoregional therapy based on the Milan Criteria versus the Up-to-Seven Criteria.

Materials and Methods

This meta-analysis uses Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15]. Since this study made use of already-published research data, ethical approval was not needed. Our systematic review and meta-analysis have been registered on the PROSPERO database with registration number CRD420251018746.

Literature Selection

Using the following keywords, a literature search was carried out through databases like PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco to find pertinent topics up until March 2024: "up-to-seven criteria" AND "Milan criteria" AND "hepatocellular carcinoma (HCC) AND "resection" AND "locoregional therapy". Studies were selected by I.K.W.A.K and I.G.A.P.S. under the supervision of I.G.P.S. as the investigator.

Inclusion and Exclusion Criteria

The inclusion criteria for this meta-analysis study were (1) the study had to be a type of randomized controlled trial (RCT) such as with or without blinds published in English both domestically and internationally and observational study (prospective and retrospective cohort, case-control, cross-sectional) studies were considered eligible for inclusion; (2) adult patients (over the age of 18) with HCC undergoing resection or locoregional therapy (3) evaluating the comparison between up-to-seven criteria versus Milan criteria; (4) providing sufficient information about hazard ratios (HRs) with 95% confidence intervals (CIs); (5) overall survival (OS), progression-free survival (PFS), disease-free survival (DFS) are examples of outcome indicators. The following were the study's exclusion criteria: (1) literature published repeatedly; (2) conference papers and case reports.

Study Quality Assessment

An adapted version of the Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the studies' methodological quality. The selection of the subject groups, the comparability of the subject groups, and the determination of the outcome were the three main criteria employed by this system to evaluate the quality of the study design. The overall quality score fell between 0 and 9. Research with a score of at least six points was considered excellent quality [16].

Data Extraction

The following data were extracted from the selected studies: prognosis, progression-free survival (PFS), disease-free survival (DFS), estimated HR with HR and 95% CI for overall survival (OS), author name, year of publication, country, sample size, age, and HCC categorisation. The missing data on the published articles were further completed by a personal approach toward contacting the author. One of the components included in the computations in this investigation was the 95% confidence interval (CIs). The HR is determined from the rebuilt data using the Kaplan-Meier curve if the data are displayed as a survival plot graph [17].

Statistical Analysis

RevMan 5.4 software was utilized for statistical analysis in this investigation. In computational data, a confidence interval (95% CI) and an odds ratio (OR) are

defined. To examine the heterogeneity among the studies, this study used the X^2 and I^2 tests. Fixed effect model analysis was performed if P>0.1 or I^2 < 50% indicating that there was no statistical heterogeneity between trials. It indicates statistical heterogeneity between the research instead. More investigation on the heterogeneity's causes was required. A random effects model was employed for analysis after overt heterogeneity was eliminated. Using funnel charts, publication bias analysis was carried out (Figure 3), and subgroup analysis based on the type of included studies was carried out. Inspection threshold α = 0.05.

Results

Literature Selection

The initial search of online databases (PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco) yielded a total of 1247 results. After looking through the titles and abstracts, 841 research were eliminated, and up to 59 papers were eliminated for being duplicates. Following a thorough study and evaluation of the entire content, 401 articles were disqualified because they did not meet the inclusion and exclusion criteria. Up to 38 studies lacked the necessary information. Lastly, this analysis contained five papers. The PRISMA Guideline 2022 is followed throughout the entire literature search procedure, which is condensed into the following flowchart (Figure 1).

Characteristics of Included Studies

The up-to-seven group comprised 523 patients, whereas the Millan group contained 398 patients, for a total of 921 participants across all qualified investigations. The years that were released were 2011 through 2021. All of them are cohort studies, according to the study design. Asia was the region under investigation, with the majority of the two studies coming from China, one each from Japan, Italy, and Turkey. Table 1 summarises the attributes of the included studies. The five cohort studies' NOS scores, which ranged from 7 to 8, showed that all of the included studies data (Table 2).

Overall Survival (OS)

Four studies [8, 18–20] that reported OS were included in the OS analysis of prognostic significance of up-to-seven criteria versus Milan criteria in patients with HCC undergoing resection or locoregional therapy. In patients with HCC having resection or locoregional therapy, the meta-analysis revealed a significant difference in OS in prognostic values of up-to-seven criteria against Milan criteria (HR= 3.42; 95%CI: 2.23-5.25,

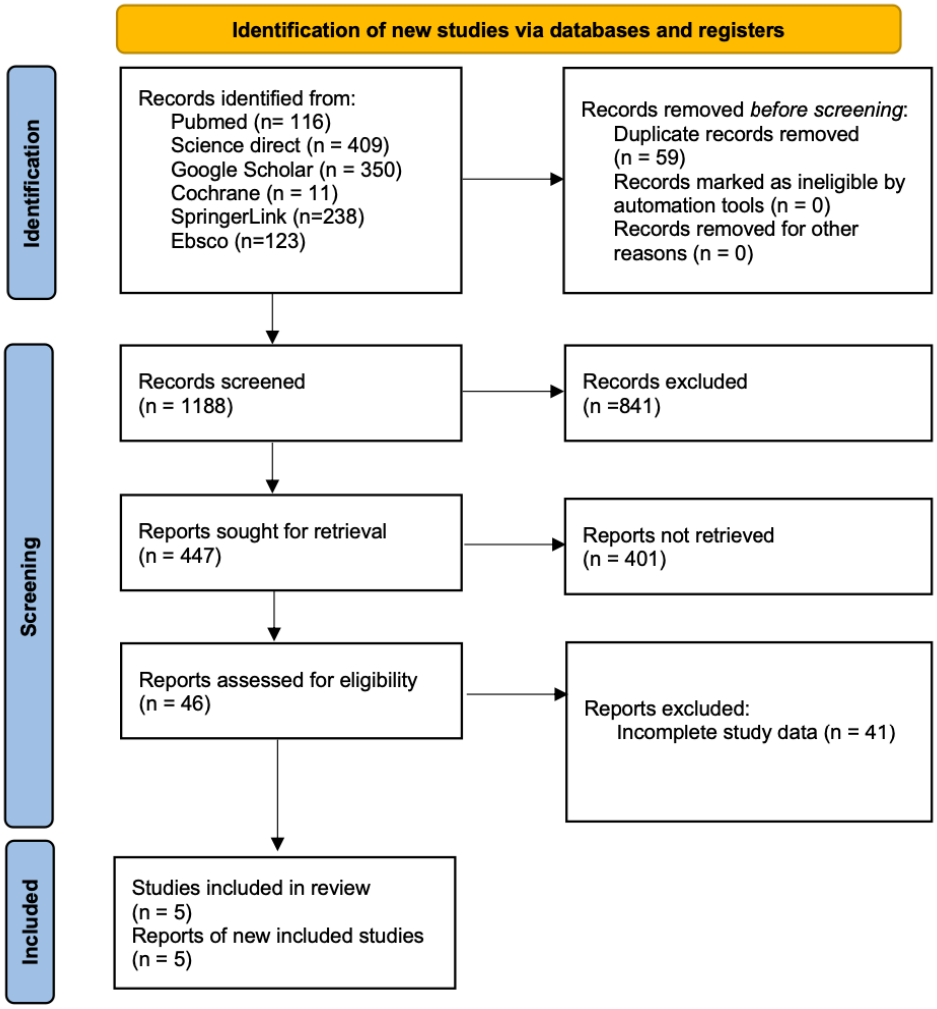

Figure 1. PRISMA Flowchart

Table 2. Modified New Ottawa Castle Scale for Cohort Studies

Author, years	Selection				Comparability		Outcomes		Overall score	Quality of study
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of the study	Comparability of cohorts based on the design or analysis controlled for confounders	Assessment of outcome	Follow-up long enough for outcomes	Adequacy of follow-up of cohorts		
Martino et al, 2021 [18]	1	1	2	1	1	1	1	1	8	Good
Lei et al, 2013 [8]	1	1	1	1	1	1	1	1	7	Good
Pan et al, 2017 [19]	1	1	2	1	1	1	1	1	8	Good
Yasui et al, 2018 [20]	1	1	1	1	1	1	1	1	7	Good
Balci et al, 2011 [21]	1	1	1	1	1	1	1	1	7	Good

Table 1. Characteristic Study

Study, Year	Study Design	Country	Criteria	Number of Samples	Male (N)	Female (N)	Age		Child-Pugh class	
							Range Age	Mean	A	B
Martino et al, 2021 [18]	Cohort	Italy	Up-to-seven Criteria	54	49	5	35-68	59	23	25
			Milan Criteria	47	43	4	45-70	57	15	24
Lei et al, 2013 [8]	Cohort	China	Up-to-seven Criteria	90	81	9	38.0-57.6	46.8	49	23
			Milan Criteria	58	51	9	37.6-59.3	48.4	29	16
Pan et al, 2017 [19]	Cohort	China	Up-to-seven Criteria	282	393	27	18-75	54	402	18
			Milan Criteria	139	N/A	N/A	N/A	N/A	N/A	N/A
Yasui et al, 2018 [20]	Cohort	Japan	Up-to-seven Criteria	88	157	67	N/A	70.6	224	0
			Milan Criteria	136	N/A	N/A	N/A	N/A	N/A	N/A
Balci et al, 2011 [21]	Cohort	Turkey	Up-to-seven Criteria	9	8	1	56.1	N/A	248	22
			Milan Criteria	18	16	2	55.7	N/A	N/A	N/A

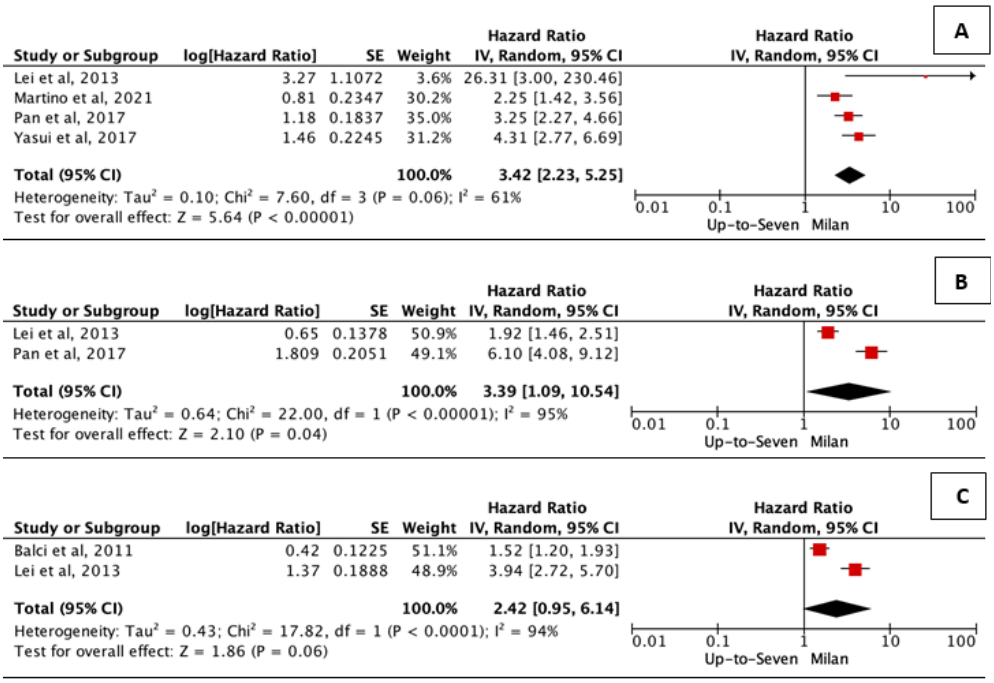

Figure 2. Forest Plot of Hazard Ratio for the Prognostic Value of Up-to-seven criteria versus Milan Criteria in Patients with Hepatocellular Carcinoma (A, OS; B, PFS; C, DFS)

p=<0.00001). Since statistical heterogeneity was found among the included studies, a random-effects model was employed (p = 0.06, I^2 = 61%; Figure 2A).

Progression-Free Survival (PFS)

Two studies [8, 19] that reported PFS were included in the PFS analysis of prognostic significance of up-to-seven criteria versus Milan criteria in patients with HCC undergoing resection or locoregional therapy. For patients with HCC following resection or locoregional treatment, the meta-analysis showed a significant difference in PFS between prognostic values of up-to-seven criteria versus Milan criteria (HR= 3.39; 95%CI: 1.09-1.54; p=0.04). Because statistical heterogeneity was found among the included studies, a random-effects model was employed (p<0.00001, I^2 = 95%; Figure 2B).

Disease-Free Survival (DFS)

Two studies [8, 21] that reported DFS were included in the DFS analysis of prognostic significance of up-to-seven criteria versus Milan criteria in patients with HCC undergoing resection or locoregional therapy. Patients with HCC following resection or locoregional therapy did not significantly vary in DFS in prognostic values of up-to-seven criteria against Milan criteria, according to the meta-analysis (HR: 2.42; 95%CI: 0.95-6.14; p=0.06). A random-effects model was employed since the included studies showed statistical heterogeneity (p<0.0001, I^2 = 94%; Figure 2C).

Discussion

This meta-analysis shows that when evaluating patients with hepatocellular carcinoma (HCC) receiving resection or locoregional therapy, the up-to-seven criteria

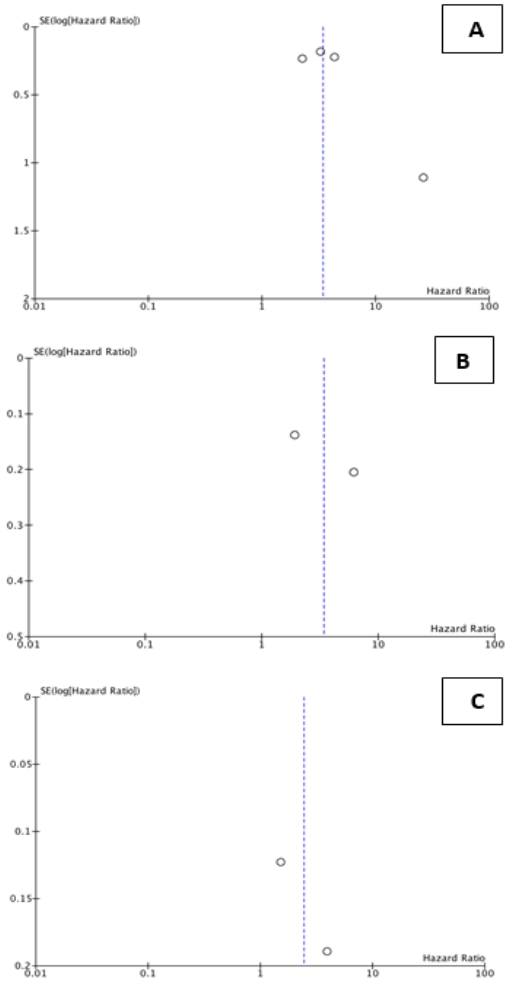

Figure 3. Funnel Plot for Publication Bias Analysis of the Up-to-seven criteria versus Milan Criteria in Patients with Hepatocellular Carcinoma (A, OS; B, PFS; C, DFS)

have a prognostic value that is not worse than the Milan criteria. In particular, whereas Disease-Free Survival (DFS) did not exhibit a significant difference between these two criteria, Overall Survival (OS) and Progression-Free Survival (PFS) did. These results suggest that patients who do not match the Milan criteria but still have the potential for successful therapy may benefit from using the up-to-seven criteria as a more comprehensive option.

In the OS analysis, patients meeting the up-to-seven criteria had a higher mortality risk than those within the Milan criteria (HR = 3.42; 95% CI: 2.23-5.25; $p < 0.00001$). The heterogeneity of this study ($I^2 = 61\%$) suggests variability in population characteristics or methodologies across studies. These results are consistent with a study by Mazzaferro et al. (2009) that established the up-to-seven criterion and showed that patients with this score had a good prognosis even though their tumours were bigger or multifocal [9]. There are no notable distinctions between the Milan Criteria and the Up-to-Seven Criteria, according to some research. Researchers created a software technique to detect tumour characteristics that surpass the Milan Criteria while still producing a five-year overall survival (OS) of at least 70% in a trial comprising 1,556 patients who received liver transplantation for HCC. These traits were dubbed the Up-to-Seven Criteria [22]. No discernible difference was identified in the OS of liver transplant recipients chosen using the Milan Criteria versus the Up-to-Seven Criteria, according to a recent retrospective research [18]. Additionally, Zhang et al.'s latest study from 2022 verified that, when paired with the right adjuvant medicines, patients who met the up-to-seven criterion had OS that was comparable to the Milan criteria [23].

According to this meta-analysis, patients who met the up-to-seven criteria for PFS were more likely to experience a progression of their disease (HR = 3.39; 95% CI: 1.09-1.54; $p = 0.04$). Potential variations in clinical variables, treatment procedures, or techniques among studies are suggested by the significant heterogeneity ($I^2 = 95\%$). Adjuvant therapy, including transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) improved clinical outcomes, even though patients in the up-to-seven group had worse PFS than those meeting the Milan criteria [19]. Another explanation for this discrepancy could be because up to seven patients had a higher incidence of poorly differentiated tumours and microvascular invasion, both of which are linked to a higher risk of progression [19, 24, 25].

In contrast, there was no discernible difference between the two groups in the DFS outcomes (HR = 2.42; 95% CI: 0.95-6.14; $p = 0.06$). The lack of substantial differences in DFS in this analysis may be explained by Hanif et al.'s [26] finding that patients with an up-to-seven score had a greater recurrence rate than those who met the Milan criteria. Variability in DFS outcomes could be caused by a number of factors, including the biological features of the tumour, the existence of microvascular invasion, and the efficacy of adjuvant therapy. Alpha-fetoprotein (AFP) levels and molecular biomarker expression patterns are two examples of extra criteria that require further investigation to determine whether they can improve the precision of risk categorisation in patients with HCC [27–29].

Additionally, evidence-based approaches must be considered in patient selection for curative therapy. While the Milan criteria remain the gold standard for liver transplantation, the up-to-seven criteria offer a broader scope for patients undergoing resection or locoregional therapy [30]. Findings from this meta-analysis suggest that relying solely on tumor morphology may not be optimal in identifying the best therapeutic candidates. A study by Low et al. [31] emphasized that combining morphological factors with biological indicators such as AFP and microvascular invasion could improve prognostic prediction accuracy. From a clinical perspective, these findings reinforce the necessity of incorporating a comprehensive evaluation of additional prognostic factors when applying the up-to-seven criteria. A multidisciplinary approach integrating radiological data, molecular biomarkers, and response to adjuvant therapies is essential to optimizing treatment outcomes in HCC patients.

On the clinical implication aspect, the results show that the Up-to-Seven criteria have comparable and, in some cases, superior prognostic value compared to the Milan criteria for patients with hepatocellular carcinoma (HCC) undergoing resection or locoregional therapy. The implication of these findings is that a more flexible approach to patient selection based on the Up-to-Seven criteria may provide broader access to therapy without compromising survival outcomes. This has the potential to change clinical practice and guidelines for HCC management, especially in the decision-making process for curative or surgical therapy.

The main strength of this meta-analysis is the focus on the Up-to-Seven criteria, which have not been widely studied in comparison to the Milan criteria in the context of curative and locoregional therapy. In addition, the systematic methodology and the use of a random-effects model strengthen the validity of the findings. However, major limitations include the limited number of studies (only 5 studies) and the high heterogeneity in the studies analyses, including OS, PFS, and DFS. Differences in study design, patient characteristics, and type of therapy are sources of heterogeneity that cannot be fully addressed.

In conclusion, the up-to-seven criteria showed non-inferior prognostic outcomes compared to the Milan criteria regarding OS, PFS, and DFS for HCC patients undergoing resection or locoregional therapy. Further research with larger samples and different designs is needed to develop this topic.

Author Contribution Statement

All authors contributed equally to the research process. The idea for the study was conceived by J N.P.S.I.R. and D.A.S.; I.K.W.A.K. and I.G.A.P.S. screened the article based on inclusion and exclusion criteria, then extracted and analyzed the data; the first draft of the manuscript was prepared by N.P.S.I.R., I.G.A.P.S, and I.G.P.S., and edited by D.A.S. and I.K.M.; all authors reviewed the final version..

Acknowledgements

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Ethical Declaration

This meta-analysis is a review article that does not have an ethical declaration file. Our systematic review and meta-analysis have been registered on the PROSPERO database with registration number CRD420251018746.

Data Availability

The datasets used in this study are publicly available in international databases (PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco) and can be accessed using the search terms provided in the Methods section.

Study Registration

This study has been registered in PROSPERO (ID CRD420251018746).

Conflict of Interest

There is no conflict of interest in this systematic review and meta-analysis.

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