의학석사 학위논문

간세포암 환자에서 간이식 시 확장된 기준의 적용가능성 및 우선도에 대한 연구: 체계적 문헌고찰 및 네트워크 메타분석

Acceptability and priority of expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a systematic review and network meta-analysis

울산대학교 대학원

의학과

유동만

Acceptability and priority of expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a systematic review and network meta-analysis

지도교수 심주현

이 논문을 의학석사 학위논문으로 제출함

2021년 12월

울산대학교 대학원

의학과

유동만

유동만의 의학석사학위 논문을 인준함

심사위원 이한주 인

심사위원 송기원 인

심사위원 심주현 인

울산대학교 대학원

2022년 2월

Abstract

Background: The Milan criteria are conventionally used as the upper limit for liver transplantability in patients with hepatocellular carcinoma (HCC). Multiple attempts to expand the selection criteria have been proposed to give more patients a chance of cure. However, there is still no universal adoption of the extended criteria for liver transplantation (LT) as a standard option in treating hepatocellular carcinoma. We aimed to validate and rank prognostic performance of the representative criteria beyond Milan for liver transplantation eligibility of hepatocellular carcinoma recipients based on direct and indirect evidence.

Methods: This fixed effect network meta-analysis was conducted in the context of a systematic review of observational studies comparing post-liver transplantation outcomes between the Milan and each extended criteria in hepatocellular carcinoma patients that were retrieved from PubMed, EMBASE, Cochrane, Web of Science, and CINAHL through October 2020. We included only the criteria on which relevant data were published in two or more articles. We compared the criteria based on overall survival (OS) as the primary outcome, together with disease-free survival (DFS). Criteria estimates were reported as differences of survival rate.

Results: Of the 952 retrieved articles, 20 studies containing 4,631 patients were finally included: they involved 6 different criteria including UCSF and R4 T3, Asan, Kyoto, Hangzhou, and Up-to-7 from US, Korea, Japan, China, and Europe, respectively. The number of studies for each criteria was as follows: 8 UCSF, 3 Asan, 3 Kyoto, 2 Hangzhou, 2 Up-to-7, and 2 R4 T3. Compared with the Milan criteria, the Kyoto and UCSF criteria had significantly better overall survival and worse disease-free survival, respectively (differences of survival rates [95% confidence intervals], 0.12 [0.02, 0.21] and -0.07 [-0.14, -0.001], respectively; Ps<0.05), as did

not the others. The pairwise comparison of overall survival results indicated that the Kyoto criteria were significantly better than others including Milan, except for Asan (0.14 [-0.30, 0.029]; P>0.05). Regarding disease-free survival, only the UCSF criteria were significantly worse than Milan without significant difference for all other pairs. The Kyoto (91%) and Asan criteria (49%) had the highest probability of being best in terms of overall survival and disease-free survival, respectively.

Conclusions: We found that most of the region-specific extended criteria were associated with acceptable post-liver transplantation outcomes in hepatocellular carcinoma recipient, with Kyoto ranked highest for overall survival. Further randomized studies are needed to reach an international consensus on the wide application of liver transplantation for hepatocellular carcinoma above Milan.

Key words: hepatocellular carcinoma; liver transplantation; Milan criteria; expanded criteria

Contents

List of Figures and Tables

Introduction

The Barcelona clinic liver cancer (BCLC) algorithm for managing patients with hepatocellular carcinoma (HCC) recommends liver transplantation (LT) as a standard curative option for non-resectable stage A disease within the Milan criteria (MC) (1). The Milan upper borders (i.e., single tumor ≤5 cm or up to three tumors, each ≤3 cm, and without major vascular invasion) have been worldwide acknowledged for liver transplantability, especially with cadaveric livers, which expect the 5-year overall survival rate of >60% after liver transplantation (2). Given the stringency of such criteria based on only narrow ranges of tumor number and size, expansion outside the conventional selection rule has been purposed and currently employed across transplant centers to provide more patients a chance of being cured (3-8). Indeed, the move toward liver transplantation decision-making for hepatocellular carcinoma patients by the expanded criteria (EC) is being more active in eastern countries, where living donor liver transplantation remains dominant and it does not affect a potential recipient's status on the national wait list (9, 10). The expanded criteria for hepatocellular carcinoma generally consisting of morphological, serological, pathological tumor characteristics, and/or their combinations have demonstrated acceptable thresholds for post-liver transplantation results comparable to the Milan criteria that should be required due to insufficient grafts available to meet the demand, more seriously under the COVID-19 pandemic. Although a number of expanded sets of liver transplantation criteria has been individually compared to the Milan criteria limit and resulted in similar patient- and tumor-free survivals, it is a critical issue to determine which one would be the optimal strategy, considering an equipoise between ethical fairness of organ allocation and clinical possibility of survival chance.

Practical context of no guidelines-based expanded criteria recommendation in deciding liver transplantation eligibility for hepatocellular carcinoma prompted us to compare in a pairwise manner and rank prognostic performance of all the relevantly validated criteria

center- and region-specific through this hierarchical network meta-analysis (NMA) of direct and indirect evidence with the Milan criteria reference.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement (11). This study was registered in International prospective register of systematic reviews (PROSPERO) about registration number CRD42021258253.

Search strategy

The search terms used were "hepatocellular carcinoma", "liver transplantation", "Milan criteria", “extended criteria”, “expanded criteria”, "Asan criteria", "Clinica Universitaria de Navarra criteria", "Hangzhou criteria", "Kyoto criteria", "Kyushu criteria", "Samsung criteria", "Tokyo criteria", "Total tumor volume", "University of California San Francisco criteria", "Barcelona Clinic Liver Cancer criteria" and "up-to-7 criteria". We used the database of Pubmed, EMBASE, Cochrane, Web of science and CINAHL. The last search date was October 13, 2020.

Selection criteria

Inclusion criteria were as follows: (a) studies comparing Milan criteria with expanded criteria; (b) studies demonstrating the outcomes of interest (5 year overall survival rate, 5 year disease-free survival rate). Exclusion criteria were as follows: (a) obviously irrelevant; (b) review article, correspondence, guideline, case report and editorial; (c) not in English; (d) retracted article. We included only the criteria on which relevant data were published in two or more articles

Data extraction

The following data was extracted from each study: publication year, author, number of patients, applied criteria, kind of staging, 5 year overall survival rate, 5 year disease-free survival rate, 5 year recurrence rate.

Outcomes of Interest

The primary outcome was 5 year disease-free survival rate. If 5 year disease-free survival rate was not available, it was replaced with [1 – (5 year recurrence rate)]. The secondary outcome was 5 year overall survival rate.

Risk of bias and Quality of evidence

To rate the risk of bias and the quality of evidence, the Newcastle-Ottawa Scale (NOS) was applied (12).

Statistical Analysis

In order to simultaneously assess the comparative effects among Milan criteria and expanded criteria for liver transplantation, a network meta-analysis was conducted. As for outcome variables, 5 year overall survival and disease-free survival rate was estimated from each study, the network meta-analysis was carried out using weighted least squares regression (13). The fixed effects consistency model was used, as most direct evidence was consistent and the residual variances among treatment groups account for the between-trial homogeneity. Overall consistency and heterogeneity was evaluated using Q statistics and heterogeneity for each pairwise meta-analysis of direct comparisons was evaluated. All the

pairwise comparison was depicted using forest plot and the probability of being the best intervention in each outcome was estimated and ranked using rankogram.

Results

Literature Search and selection

A total of 952 articles were identified from database searching and no additional articles were identified through other sources. 502 articles were remained after removing duplicates. Title and abstract review were performed, and 380 articles were excluded according to our exclusion criteria. Through full-text review for potentially relative articles, 102 articles were excluded because of the lack of information about outcomes of interest. Finally, 20 studies were included in the meta-analysis (**Figure 1**).

Study characteristics

20 studies contained a total of 4087 patients. All studies were observational cohort studies. The number of studies for each criteria was as follows: 8 UCSF, 3 Asan, 3 Kyoto, 2 Hangzhou, 2 Up to 7, 2 R4 T3. 12 studies used pathologic staging, 5 studies used radiologic staging, and 3 studies used both radiologic and pathologic staging respectively. 5 year overall survival rate was not reported in one study, and 5 year disease-free survival rate was not reported in 8 studies. 5 studies reported 5 year recurrence rate (**Table 1**).

Risk of bias

Risk of bias of included studies was assessed based on Newcastle-Ottawa Scale (NOS), and summarized in **Table S1**. One study was rated as a total score of 5, and the others was rated as total score of ≥6 (**Supplementary table 1**).

Network meta-analysis

In the network meta-analysis, compared with the Milan criteria, the Kyoto criteria had significantly better 5 year overall survival rate (differences of survival rates [95% confidence intervals], 0.12 [0.02, 0.21]; Ps<0.05) and the UCSF criteria had significantly worse 5 year disease-free survival rate (differences of survival rates [95% confidence intervals], -0.07 [-0.14, -0.001]; Ps<0.05) (**Figure 2**).

The pairwise comparison of 5 year overall survival rate results indicated that the Kyoto criteria were significantly better than Milan, Hangzhou, UCSF, Up to 7, and R4 T3 (Ps<0.05), except for Asan criteria (Ps>0.05). Regarding 5 year disease-free survival rate, only the UCSF criteria were significantly worse than Milan criteria (Ps=0.045) and all other pairs did not showed significant difference (**Table 2**).

Rankogram

Regarding 5 year overall survival rate, the Kyoto criteria had the highest probability of being best (91%) and the Milan criteria were ranked as the 2nd highest (8%). Regarding 5 year disease-free survival rate, the Asan criteria had the highest probability of being best (49%) and the Milan criteria were ranked as the 2nd highest (16%) (**Figure 3**).

Discussion

The scope of indications for liver transplantation has been expanding ever since the development of living donor-liver transplantation increased the availability of liver grafts. Until now, various criteria from different countries and centers have been proposed to expand the eligibility of patients with hepatocellular carcinoma exceeding the Milan criteria for liver transplantation. In this network meta-analysis, we found that among six validated expanded criteria, only the application of the Kyoto criteria achieved the better post-liver transplantation survival than the Milan criteria. In fact, the Kyoto criteria include serum PIVKA-II ≤400 mAU/mL in addition to tumor components, and this is the most substantial difference from the Milan criteria. Numerous studies have reported the prognostic or predictive role of serum PIVKA-II level in patients receiving any treatment for hepatocellular carcinoma, including liver transplantation. Kim and colleagues showed that although an ability of preoperative tumor size to predict hepatocellular carcinoma recurrence after liver transplantation tended to be superior to PIVKA-II, it was not shown difference significantly (14). Moreover, when compared with serum AFP, preoperative PIVKA-II level has appeared to be a more useful marker for the prediction of HCC recurrence (15, 16).

A previous Japanese research investigating the role of the Kyushu criteria (i.e., maximum tumor diameter <5 cm and PIVKA-II <300 mAU/mL) in 54 Milan-out patients convincingly showed that the addition of des-carboxyprothrombin to the conventional morphological criteria allowed to raise the ability of identifying “low-risk for recurrence” patients, even if they are outside the conventional Milan criteria (17). Our and prior findings suggest that incorporating biochemical markers such as PIVKA-II into the expanded criteria may increase the power to select the patients who have lower risk of recurrence after liver transplantation.

While individual comparative studies reported the similar predictability for post-liver transplantation outcomes of the Asan or UCSF criteria to the Milan criteria, our network meta-analysis identified that patients meeting the former had the highest probability of being best in 5 year disease-free survival rate, and those within the latter had worse 5 year disease-free survival rate than the Milan criteria. Given that the Asan protocol requires the stricter cut-off for tumor size (≤5 cm vs. ≤6.5 cm) in contrast to that for number of nodules (6 vs. 3), it is more likely critical to limit tumor diameters in optimally selecting candidates with hepatocellular carcinoma beyond the traditional criteria. On the other hand, a difference in the donor type (living or deceased for the Asan and UCSF criteria, respectively) of populations used to develop and validate the criteria could also affect the integrated results from this network meta-analysis. More importantly, different methods for estimating tumor stage (pathologic or radiologic for the Asan and UCSF criteria, respectively) between the relevant studies should be considered to interpret the present observations (18).

Overall, most of the expanded criteria evaluated in this study showed comparable outcomes with the Milan criteria in terms of 5 year overall survival rate and 5 year disease-free survival rate. Taken together, however, considering potential risks of living donors and ethical issues in organ allocation, it may be strongly recommended to apply a more narrow range of tumors' maximum size rather than their number and to include biological markers, especially PIVKA-II, into the expanded criteria for liver transplantation eligibility in patients with hepatocellular carcinoma on the basis of our network meta-analysis data.

Our results should be interpreted in the context of their inherent limitations, shared by all network meta-analyses, namely the inclusion of data derived from indirect comparisons for most of the evidence in the network, as well as the fact that the estimates are based on study-level data, not individual patient data. Another consideration is the use of surrogate data, [1 –

(5 year recurrence rate)], in place of missing endpoints regarding 5 year disease-free survival rate for some studies. Lastly, all evaluated studies were observational studies with low level evidence. However, validated studies were included in the network meta-analysis to improve the accuracy and reliability of reported data for each criterion.

In conclusion, our network meta-analysis results, based on 20 studies identifying the prognostic performance of the six expanded criteria, compared with the standard Milan criteria, showed that most of the region-specific expanded criteria were associated with acceptable post-liver transplantation outcomes in hepatocellular carcinoma recipient, with the Kyoto protocol ranked highest for 5 year overall survival rate. Further randomized studies are needed to reach an international consensus on the wide application of liver transplantation for hepatocellular carcinoma above the Milan criteria.

References

1. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-750.

2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236.

3. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001;33(6):1394-403.

4. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10(1):35-43.

5. Lee SG, Hwang S, Moon DB, Ahn CS, Kim KH, Sung KB, et al. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. Liver Transpl. 2008;14(7):935-45.

6. Zheng SS, Xu X, Wu J, Chen J, Wang WL, Zhang M, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experience. Transplantation. 2008;85(12):1726–1732.

7. Guiteau JJ, Cotton RT, Washburn WK, Harper A, O'Mahony CA, Sebastian A, et al. An early regional experience with expansion of Milan Criteria for liver transplant recipients. Am J Transplant. 2010;10(9):2092-8.

8. Takada Y, Ito T, Ueda M, Sakamoto S, Haga H, Maetani Y, et al. Living donor liver transplantation for patients with HCC exceeding the Milan criteria: a proposal of expanded criteria. Dig Dis. 2007;25(4):299-302.

9. 대한간암학회·국립암센터. 2014 간세포암종 진료 가이드라인.

10. Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, et al. Management of Hepatocellular Carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 Update. Liver Cancer. 2021;10(3):181-223.

11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;29;372:n71.

12. Wells GA, Shea B, O'Connell D, et al. The Newcastle Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Ottawa Hospital Research Institute [cited 2021 6

December]. Available from: www.ohri.ca/programs/clinical_epidemiology/oxford.asp

13. Rücker G. Network meta-analysis, electrical networks and graph theory. Res Synth Methods. 2012;3(4):312-24.

14. Kim SH, Moon DB, Kim WJ, Kang WH, Kwon JH, Jwa EK, et al. Preoperative prognostic values of α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-Ⅱ (PIVKA-Ⅱ) in patients with hepatocellular carcinoma for living donor liver transplantation. Hepatobiliary Surg Nutr. 2016;5(6):461-469.

15. Sakon M, Monden M, Gotoh M, Kanai T, Umeshita K, Nakano Y, et al. Relationship between pathologic prognostic factors and abnormal levels of des-gamma-carboxy prothrombin and alpha-fetoprotein in hepatocellular carcinoma. Am J Surg. 1992;163(2):251-6.

16. Nanashima A, Morino S, Yamaguchi H, Tanaka K, Shibasaki S, Tsuji T, et al. Modified CLIP using PIVKA-II for evaluating prognosis after hepatectomy for hepatocellular carcinoma. Eur J Surg Oncol. 2003;29(9):735-42.

17. Lai Q, Iesari S, Levi Sandri GB, Lerut J. Des-gamma-carboxy prothrombin in hepatocellular cancer patients waiting for liver transplant: a systematic review and meta-analysis. Int J Biol Markers. 2017;32(4):e370-e374.

18. Unek T, Karademir S, Arslan NC, Egeli T, Atasoy G, Sagol O, et al. Comparison of Milan and UCSF criteria for liver transplantation to treat hepatocellular carcinoma. World J Gastroenterol 2011;17(37): 4206-4212.

Table 1. Characteristics of the included studies

Year	Author	Criteria	Staging	Donor type	No. of patients		5 year OS		5 year DFS		5 year RR	
					Within MC	Beyond MC, Within EC	Within MC	Beyond MC, Within EC	Within MC	Beyond MC, Within EC	Within MC	Beyond MC, Within EC
2006	Decaens	UCSF	Radiology	N/A	279	44	0.601	0.456	0.604	0.478	N/A	N/A
			Pathology	N/A	184	39	0.704	0.636	0.702	0.627	N/A	N/A
2007	Duffy	UCSF	Radiology	DDLT	173	185	0.79	0.64	0.74	0.65	N/A	N/A
			Pathology	DDLT	126	208	0.86	0.81	0.628	0.55	N/A	N/A
2008	Lee	Asan	Pathology	LDLT	164	22	0.76	0.8	N/A	N/A	0.1577	0.091
2009	Fujiki	Kyoto	Radiology	LDLT	79	28	0.78	0.89	N/A	N/A	0.07	0.04
2010	Guiteau	R4 T3	Radiology	DDLT	363	82	0.729	0.771	0.905	0.869	N/A	N/A
2010	Takada	Kyoto	Radiology	LDLT	74	23	0.75	N/A	N/A	N/A	0.07	0.05
2011	Balci	Asan	Pathology	LDLT	18	9	0.8333	0.68	0.8889	0.79	N/A	N/A
2011	Unek	UCSF	Pathology	DDLT 25 (44.6%) LDLT 31 (55.4%)	34	7	0.877*	0.536*	0.877*	0.536*	N/A	N/A
2012	Piardi	UCSF	Pathology	N/A	106	28	0.77	0.74	N/A	N/A	N/A	N/A
2013	Gugenheim	Up to 7	Pathology	N/A	299	84	0.749	0.676	N/A	N/A	0.094*	0.158*

2013	Kaido	Kyoto	Radiology	LDLT	118	42	0.76	0.88	N/A	N/A	0.05*	0.11*
2014	Chen	Hangzhou	Pathology	LDLT	17	9	0.94	0.727	0.88	0.626	N/A	N/A
2015	Bonadio	Asan	Pathology	DDLT 48 (63.2%) LDLT 28 (36.8%)	39	19	0.74	0.67	0.85	0.8	N/A	N/A
2016	Diaz	Up to 7	Pathology	N/A	74	12	0.581	0.583	0.581	0.5	N/A	N/A
2017	Kositamongkol	UCSF	Pathology	DDLT	40	10	0.675	0.8	0.825	N/A	N/A	N/A
2017	Zakaria	UCSF	Pathology	LDLT	44	5	0.771*	0.3*	N/A	N/A	N/A	N/A
2018	Abdelfattah	UCSF	Pathology	DDLT 38 (43.2%) LDLT 50 (56.8%)	60	16	0.751	0.75	0.902	0.857	N/A	N/A
2018	Commander	R4 T3	Radiology	DDLT	1888	180	0.73	0.68	0.69	0.68	N/A	N/A
2018	Qu	Hangzhou	Pathology	N/A	68	41	0.758	0.741	0.758	0.719	N/A	N/A
2020	Victor	UCSF	Pathology	N/A	138	23	0.81	0.88	0.92	0.886	N/A	N/A
			Radiology	N/A	150	27	0.77	0.816	0.934	0.77	N/A	N/A

OS, overall survival rate; DFS, disease-free survival rate; RR, recurrence rate; N/A, not available; DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; MC, Milan criteria; EC, expanded criteria

Table 2. Pairwise comparison of overall survival and disease-free survival rate*

OS	Milan	Asan	Hangzhou	Kyoto	UCSF	Up to 7	R4 T3
Milan		0.0202	0.0612	**-0.1158****	0.0368	0.0639	0.0199
Asan	-0.0202		0.0410	-0.1360	0.0166	0.0437	-0.0003
Hangzhou	-0.0612	-0.0410		**-0.1770****	-0.0243	0.0028	-0.0413
Kyoto	**0.1158****	0.1360	**0.1770****		**0.1527****	**0.1798****	**0.1357****
UCSF	-0.0368	-0.0166	0.0243	**-0.1527****		0.0271	-0.0170
Up to 7	-0.0639	-0.0437	-0.0028	**-0.1798****	-0.0271		-0.0441
R4 T3	-0.0199	0.0003	0.0413	**-0.1357****	0.0170	0.0441	

DFS	Milan	Asan	Hangzhou	Kyoto	UCSF	Up to 7	R4 T3
Milan		-0.0179	0.0801	0.0013	**0.0704****	0.0652	0.0217
Asan	0.0179		0.0980	0.0192	0.0882	0.0831	0.0395
Hangzhou	-0.0801	-0.0980		-0.0789	-0.0098	-0.0149	-0.0585
Kyoto	-0.0013	-0.0192	0.0789		0.0691	0.0639	0.0204
UCSF	**-0.0704****	-0.0882	0.0098	-0.0691		-0.0051	-0.0487
Up to 7	-0.0652	-0.0831	0.0149	-0.0639	0.0051		-0.0436
R4 T3	-0.0217	-0.0395	0.0585	-0.0204	0.0487	0.0436	

*Difference of survival rate for the pairwise comparisons of the network meta-analysis. Comparison should be read from left to right.

**statistically significant pairs were shown in bold (P<0.05).

OS, overall survival rate; DFS, disease-free survival rate

Figure 1. Flow diagram of search and literature selection.

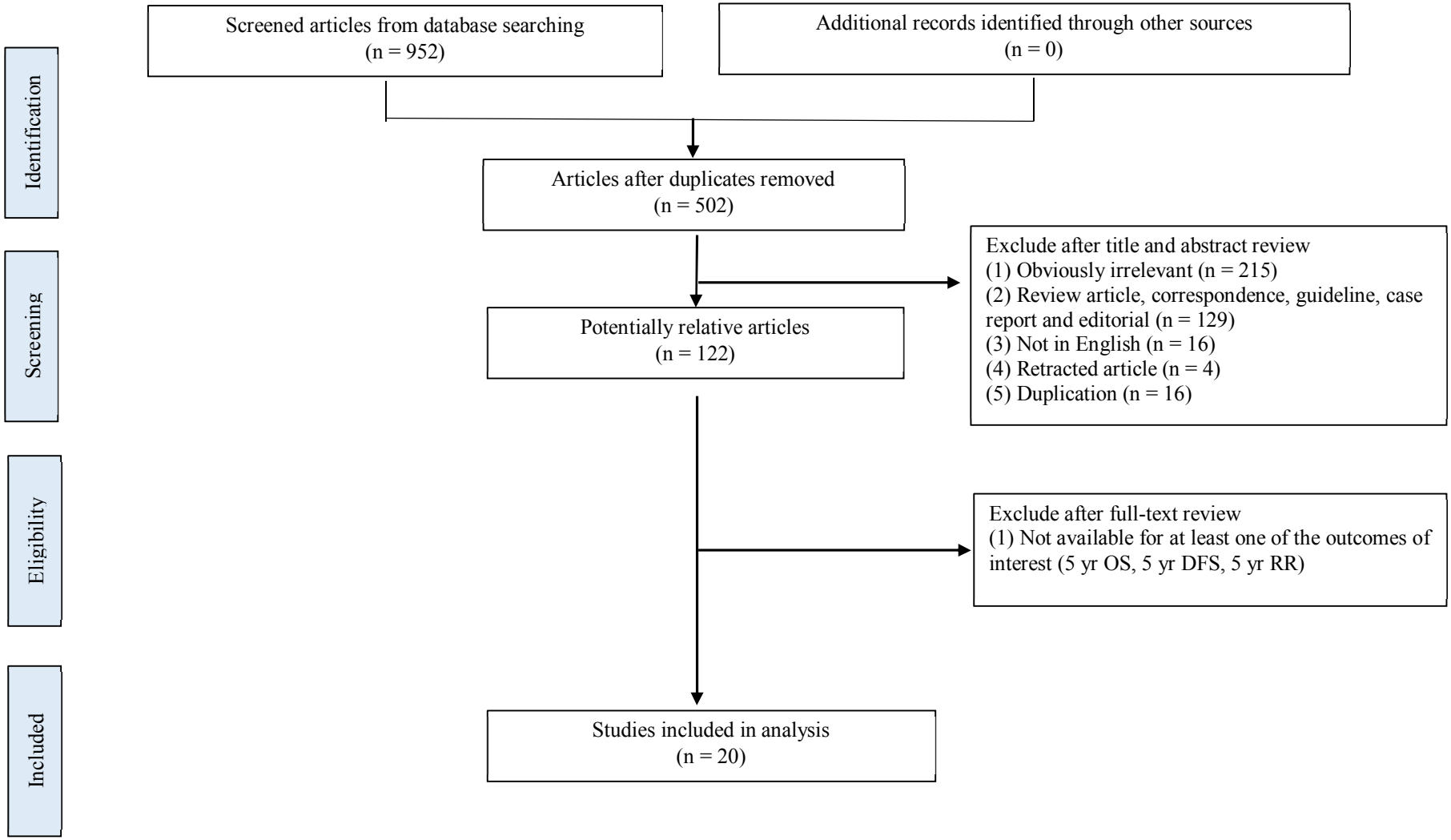
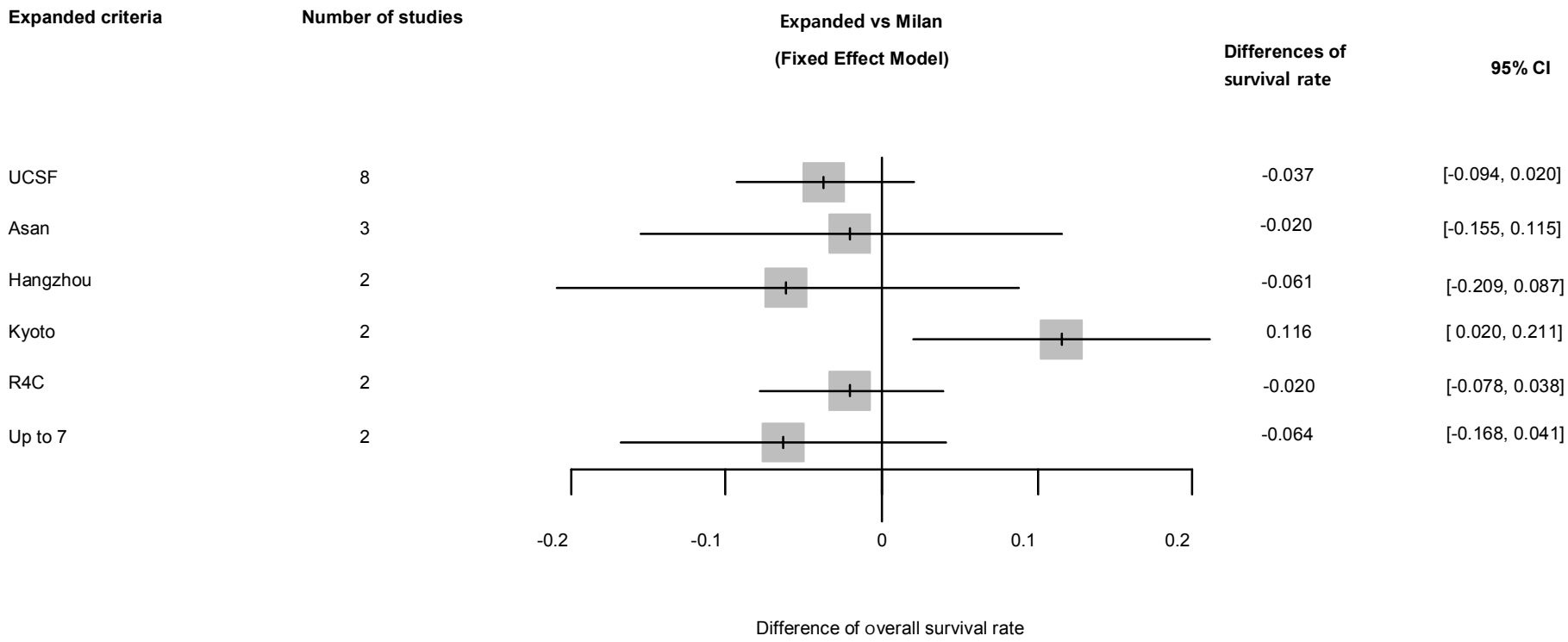
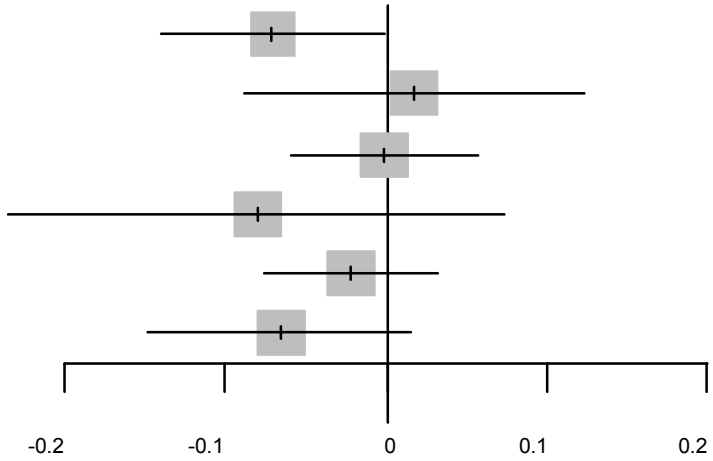


Figure 2. Forest plots of overall survival and disease-free survival rate



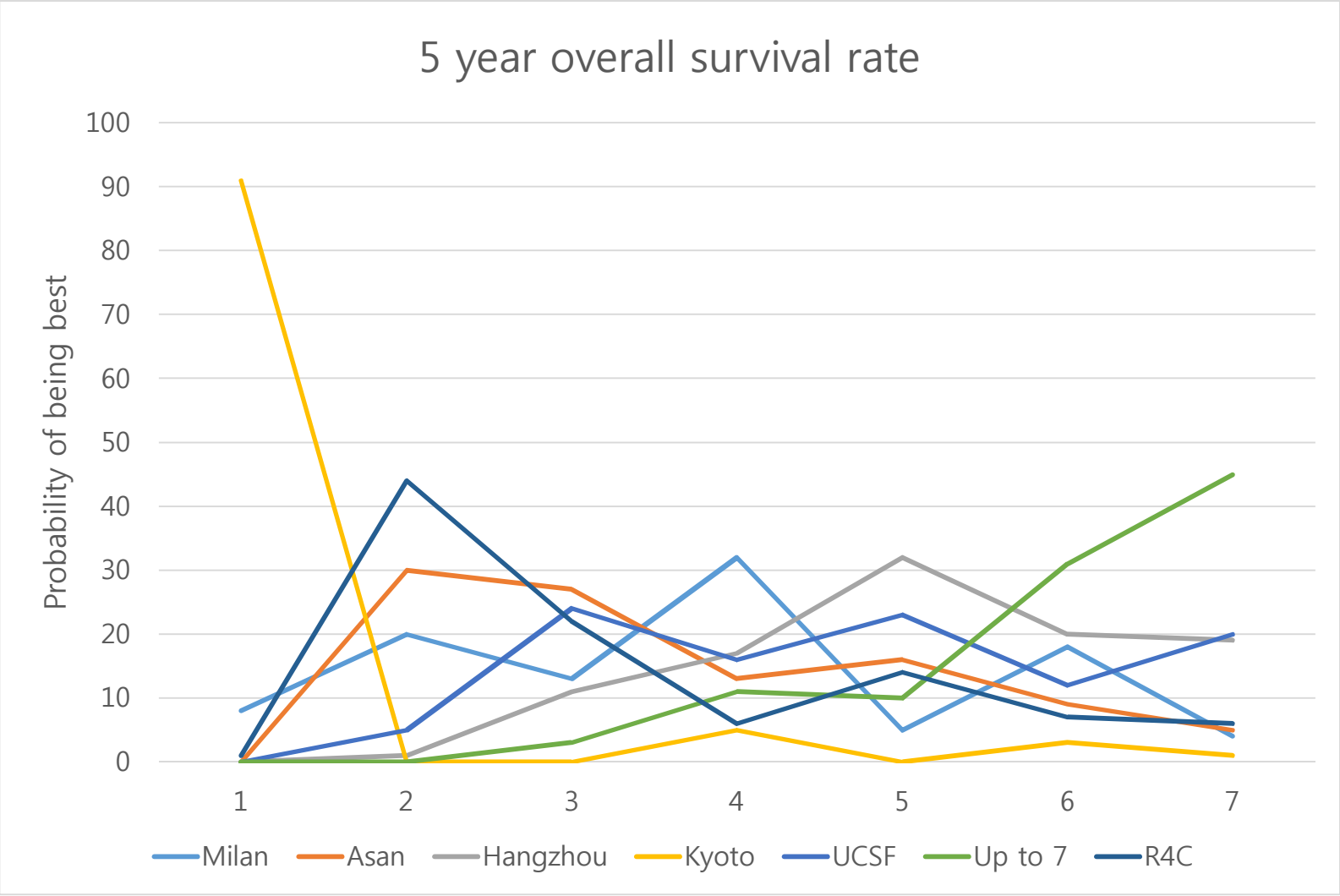
CI, confidence interval

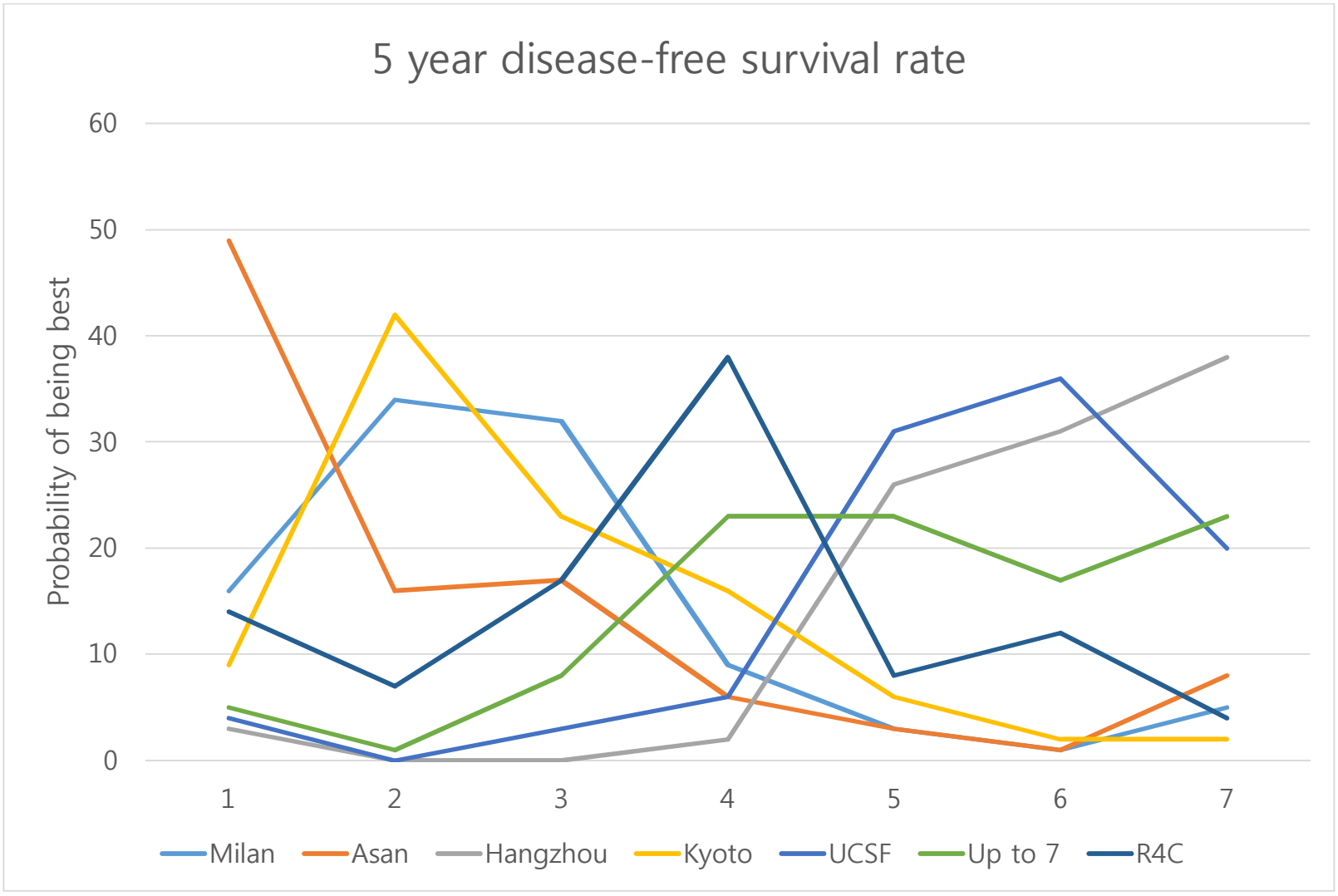
Expanded criteria	Number of studies	Expanded vs Milan (Fixed Effect Model)	95% CI
UCSF	5	-0.070	[-0.139; -0.001]
Asan	3	0.018	[-0.087; 0.123]
Kyoto	3	-0.001	[-0.059; 0.056]
Hangzhou	2	-0.080	[-0.234; 0.074]
R4C	2	-0.022	[-0.075; 0.031]
Up to 7	2	-0.065	[-0.147; 0.016]



CI, confidence interval

Figure 3. Rankogram of overall survival and disease-free survival rate




5 year disease-free survival rate
Probability of being best
60
50
40
30
20
10
0
1
2
3
4
5
6
7
Milan
Asan
Hangzhou
Kyoto
UCSF
Up to 7
R4C

Supplementary Table 1. Assessment of risk of bias of included studies using Newcastle-Ottawa Scale

Author	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 (MELD score)	Comparability of cohorts on the basis of the design or analysis (age)	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohort	Total score
Abdelfattah et al.	★	★	★	★	★	★	★		★	8
Balci et al.	★	★	★	★	★	★	★		★	8
Bonadio et al.	★	★	★	★			★	★	★	7
Chen et al.	★	★	★	★			★		★	6
Commander et al.	★	★	★	★		★	★			6
Decaens et al.	★	★	★	★		★	★		★	7
Diaz et al.	★	★	★	★	★	★	★		★	9
Duffy et al.	★	★	★	★			★	★	★	7
Fujiki et al.	★	★	★	★			★		★	6
Gugenheim et al.	★	★	★	★			★		★	6

Guiteau et al.	★	★	★	★	★	★	★			7
Kaido et al.	★	★	★	★			★		★	6
Kositamongkol et al.	★	★	★	★			★			5
Lee et al.	★	★	★	★			★		★	6
Piardi et al.	★	★	★	★			★	★	★	7
Qu et al.	★	★	★	★		★	★			6
Takada et al.	★	★	★	★			★		★	6
Unek et al.	★	★	★	★	★	★	★			7
Victor et al.	★	★	★	★	★	★	★			7
Zakaria et al.	★	★	★	★			★		★	6

MELD, model for end-stage liver disease

국문요약

제목: 간세포암 환자에서 간이식 시 확장된 기준의 적용가능성 및 우선도에 대한 연구: 체계적 문헌고찰 및 네트워크 메타분석

연구 배경: 밀란 기준은 간세포암 환자에서 간이식이 적합한지 평가하는 기준으로 사용되고 있다. 더 많은 환자에게 간이식의 기회를 제공하기 위해 밀란 기준보다 확장된 기준을 적용하려는 시도들이 여럿 있었으나, 아직까지 널리 받아들여지는 기준은 없는 상태이다. 이 연구에서는 체계적 문헌고찰 및 네트워크 메타분석을 통해 각각의 확장된 기준들이 실제로 적용 가능한 것인지 검증하고 확장된 기준들의 우선도의 순위를 매기고자 하였다.

연구 방법: PubMed, EMBASE, Cochrane, Web of Science, CINAHL에서 2020년 10월까지 문헌검색을 통해 밀란 기준과 확장된 기준의 간이식 후 성적을 비교한 문헌들을 찾고 각각의 확장된 기준 당 최소 2개 이상의 문헌이 존재하는 기준들을 분석에 포함하였다. 분석에 포함된 문헌들에서 밀란 기준과 확장된 기준의 5년 전체생존율(overall survival rate)과 5년 무질병생존율(disease-free survival rate)을 추출하였고 각각의 생존율의 차이로 우선도를 평가하였다.

결과: 952개의 검색된 문헌 중 20개의 문헌이 분석에 포함되었다. 분석에 포함된 확장된 기준은 총 6개 였다(UCSF, R4 T3, Asan, Kyoto, Hangzhou, up-to-7). 밀란 기준과 비교하였을 때 Kyoto 기준이 통계적으로 유의하게 5년 전체생존율이 높았고(생존율의 차이 [95% 신뢰구간], 0.12 [0.02, 0.21]), UCSF 기준이 5년 무질병생존율이 낮았다(생존율의 차이[95% 신뢰구간], -0.07 [-0.14, -0.001]). 5년 전체생존율 쌍별비교(pairwise

comparison)에서 Kyoto 기준은 Asan 기준을 제외한 다른 기준들보다 통계적으로 유의하게 생존율이 높았고, 5년 무질병생존율 쌍별비교에서 UCSF 기준이 유일하게 밀란 기준보다 생존율이 낮았다. Probability of being best는 5년 전체생존율에서는 Kyoto 기준이 91%로 가장 높았고 5년 무질병생존율에서는 Asan 기준이 49%로 가장 높았다.

결론: 대부분의 확장된 기준들이 밀란 기준과 비교하여 간이식 수술 후 5년 생존율 및 5년 무질병생존율이 수용 가능한 범위에 있음을 확인하였고 그 중에서도 Kyoto 기준이 가장 좋은 것으로 나타났다. 간세포암 환자에서 간이식 시 밀란 기준보다 확장된 기준을 적용하는 것에 대한 국제적인 합의에 도달하기 위해서는 추후 무작위 배정 연구가 필요할 것으로 생각된다.

중심단어: 간세포암; 간이식; 밀란 기준; 확장된 기준