Prognostic role of selection criteria for liver transplantation in patients with hepatocellular carcinoma: a network meta-analysis

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Abstract

Background: Patients with hepatocellular carcinoma (HCC) are selected for transplantation if they have a low tumour burden and low risk of recurrence. The morphometric Milan criteria have been the cornerstone for patient selection, but dynamic morphological and biological tumour characteristics surfaced as an encouraging tool to refine the selection of patients with HCC and to support the expansion of the Milan criteria. The outcomes of the most prevalent models that select patients with HCC for liver transplantation were analysed in this study, which aimed to identify the selection model that offered the best recurrence-free and overall survival after transplantation.

Methods: Studies that compared Milan, University of California San Francisco (UCSF), up-to-seven (UPTS), alpha-fetoprotein (AFP), and MetroTicket 2.0 (MT2) models were included. One-year, 3-year, and 5-year recurrence-free and overall survival rates of patients selected for transplantation using different models were analysed.

Results: A total of 60 850 adult patients with HCC selected for liver transplantation using Milan, UCSF, UPTS, AFP, or MT2 criteria were included. Patients selected for transplantation using the MT2 model had the highest 1-, 3-, and 5-year recurrence-free survival. In addition, patients selected for transplantation using MT2 criteria had the best 1- and 3-year overall survival, whereas patients selected for transplantation using the Milan criteria had the best 5-year overall survival rates.

Conclusion: The MT2 model offered the best post-transplant outcomes in patients with HCC, highlighting the importance of considering tumour morphology and biology when selecting patients with HCC for liver transplantation.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related death worldwide. Continuing developments in surgical and medical therapy have improved the outcome of patients with operable and advanced HCC, but liver transplantation (LT) is the only treatment that improves survival rates in patients with HCC with end-stage liver disease[1–4]. However, HCC is only diagnosed early enough for this curative therapy in 30–40 per cent of patients[5]. Moreover, tumour recurrence occurs in up to 15 per cent of patients and therapeutic options for recurring tumours are limited[1].

HCC prevalence is similar in Europe and the USA, and the European Liver Transplant Registry and United Network for Organ Sharing (UNOS) have reported comparable liver transplant rates (17.6 per cent and 17.4 per cent, respectively)[6,7]. Because the demand for donor organs exceeds the supply in most countries,

there are long waiting lists for patients with HCC and liver cirrhosis, and 7–55 per cent of them drop out of the waiting lists because their disease progresses and they exceed the criteria for transplantation[8]. To avoid this, major extended donor criteria (maEDC; biopsy-proven macrovesicular steatosis >40 per cent, donor age >65 years, and cold ischaemia time >14 hours) donor organs were proposed as acceptable alternative for patients with HCC with lower laboratory model of end-stage liver disease (labMELD) scores who generally are in a better condition[9,10].

Because HCC recurrence rates are high after LT, patients with HCC are selected for transplantation if they have a low tumour burden and low risk of recurrence[11]. The selection criteria have fuelled a fierce debate in the past two decades and the morphometric Milan criteria have been the cornerstone for patient selection in most European countries[12]. However, growing evidence supports the expansion of these criteria[5]. To avoid patients

missing out on a lifesaving transplant because of strict selection criteria, dynamic morphological and biological tumour characteristics surfaced as an encouraging tool to refine the selection of patients with HCC for LT[13]. Many transplant centres worldwide have performed LT in patients with HCC with higher tumour burdens than permitted by the Milan criteria and have moderately expanded these criteria[14–19]. However, expanding the criteria has increased recurrence rates—the so-called Metroticket paradigm, which states that the further the ride (i.e. the higher the tumour load before transplantation), the higher the ticket price (i.e. the higher the chance of HCC recurrence)[17]. Today, the most prevalent selection models are the Milan criteria, the University of California San Francisco (UCSF), up-to-seven (UPTS), French alpha-fetoprotein (AFP), and MetroTicket 2.0 (MT2)[14,17–19]. However, not all of these models have been directly compared yet.

It is necessary to identify which selection model maximizes the benefit of LT in patients with HCC. To test the hypothesis of whether a single model could offer the best clinical outcome after LT, the recurrence-free and overall survival of patients with HCC selected for transplantation using these different models were compared directly and indirectly across trials.

Methods

This network meta-analysis was conducted according to a predefined protocol (*Supplementary material*, protocol for a network meta-analysis) and adheres to the PRISMA guidelines and network meta-analysis extension statement[20].

Literature search

The MEDLINE, Web of Science, and CENTRAL (Cochrane Central Register of Controlled Trials) databases were searched systematically and without any restrictions on date of publication. Studies that evaluated recurrence-free and overall survival of patients with HCC selected for primary liver transplantation according to the Milan, UCSF, UPTS, AFP, and MT2 selection criteria, and that compared outcomes of these selection criteria until 31 December 2020 were identified. Citations of relevant articles were also screened for additional eligible studies. The search terms used

for the Milan, UCSF, UPTS, AFP, and MT2 criteria were ('criteria' OR 'Milan' OR 'UCSF' OR 'California' OR 'UPTS' OR 'UT7' OR 'up-to-seven' OR 'up to seven' OR 'French-AFP' OR 'AFP' OR 'metro' OR 'metroticket' OR 'ticket') AND ('liver' OR 'hepatic') AND ('transplant' OR 'transplantation') AND ('HCC' OR 'hepatocellular' OR 'cancer' OR 'carcinoma').

Terminology and definitions

The definitions of the selection criteria and models are shown in *Table 1*. Recurrence-free survival was defined as the time from liver transplantation to either first recurrence (locoregional or distant metastasis) or patient's death, whichever came first. Overall patient survival was defined as the time between the initial (primary) liver transplantation and death; otherwise, patients were censored at time of last known contact.

Eligibility criteria, study selection, and data extraction

The population, intervention, comparator, outcome, timing and setting (PICOTS) strategy was used to formulate the study question and to select studies with the following inclusion criteria:

- Population: adult patients (≥18 years of age) with HCC undergoing primary LT.
- Intervention: LT.
- Comparator: Milan, UCSF, UPTS, AFP, and MT2 criteria.
- Outcome: recurrence-free survival and overall patient survival.
- Timing: recurrence-free survival and overall patient survival at 1, 3, and 5 years after transplantation.
- Setting: any study design (case–control and cohort studies) except study protocols, narrative or systematic reviews, common overviews, letters, case reports, experimental (animal model) studies, and conference abstracts. Recurrence-free survival and overall survival were considered valid parameters for assessing the clinical outcome of subgroups created by different patient selection models[21–23].

Studies not meeting these inclusion criteria and studies that did not report the outcomes of interest were excluded. Articles were

Table 1 Definitions of the allocation criteria and models

Criteria	Year	Calculation	RFS	OS
Milan[12]	1996	Single lesion ≤5 cm or up to three separate lesions, none larger than 3 cm, without gross vascular invasion or regional nodal or distant metastases	ND	75% (4 year)
UCSF[19]	2001	Solitary tumour ≤6.5 cm or ≤3 nodules with the largest lesion ≤4.5 cm and a total diameter ≤8 cm	80.9% (5 year)	ND
UPTS[17]	2009	Sum of the tumour number and size of the largest tumour ≤7 without microvascular invasion	ND	71.2% (5 year)
French AFP[14]	2012	Largest tumour diameter (<3 cm = 0 points; 3–6 cm = 1 point; >6 = 4 points) + Number of lesions (1–3 = 0 points and >4 = 2 points) + AFP level (<100 ng/ml = 0 points; 100–1000 ng/ml = 2 points; >1000 ng/ml = 3 points) (Sum of points ≤2)	ND	67.8% (5 year)
MT2[18]	2018	Number of lesions + largest lesion size (cm) <7 and AFP <200 ng/ml or Number of lesions + largest lesion size (cm) <5 and AFP <400 ng/ml or Number of lesions + largest lesion size (cm) <4 and AFP <1000 ng/ml	ND	78% (5 year)

RFS, recurrence-free survival; OS, overall survival; ND, not defined; UCSF, University of California San Francisco; UPTS, up-to-seven; AFP, alpha-fetoprotein; MT2, MetroTicket 2.

carefully reviewed to exclude overlapping reports and duplicate publications. Studies that assessed the same patient cohort more than once without providing additional information were excluded and only the study with the largest patient cohort was included. Studies in languages other than English and German were also excluded, as were studies describing paediatric patient collectives, patient cohorts with simultaneous cholangiocarcinoma and HCC, living donor LT collectives, and salvage, domino, and combined transplantation collectives. This study aimed to evaluate recurrence-free survival and overall survival of subgroups created by different patient selection models based on scenarios that best reflect clinical practice. Therefore, studies that analysed post-transplant outcomes of the different HCC patient selection models based on histopathology results of the explanted liver were excluded. All included studies were retrospective and analysed patients who had already been transplanted. Therefore, a binary approach ('in' or 'out') was used to determine if patients had fulfilled the specific selection criteria or not.

Two reviewers screened article titles and abstracts according to the inclusion and exclusion criteria, and the resulting full-text articles were further assessed for eligibility based on the inclusion criteria by the same reviewers (A.R. and S.A.H.A.S.). Study data were extracted using a standardized data sheet (E.A.). The first or the senior author resolved any discrepancies (V.J.L. or A.M.). If a study did not report the number of events for a specific outcome, these numbers were extracted from the estimated number of patients using Kaplan–Meier curves, as previously reported[24].

Geometry of the network

Network geometry was evaluated for the outcomes of interest. Nodes represent the different criteria (study arms), and the size of the nodes is proportional to the sample size in each arm. The connecting edges show direct comparisons between criteria, and the thickness of the connecting edges reflects the number of studies that compare outcomes directly. The geometry plot assessed the presence of common nodes. Absence of a common node prevented the analysis in a network setting. However, when a common node connected at least three criteria, the analysis was carried out as part of the network. The reference arm was the Milan criteria.

Quality assessment

Study quality and risk of bias were evaluated using the ROBINS-I (Risk Of Bias In Non-randomized Studies—of Interventions) tool for non-randomized studies[25]. Two independent authors evaluated risk of bias in seven domains, using predefined signalling questions for each domain: confounding; selection of participants; classification of interventions; deviations from intended interventions; missing data; measurements of outcomes; and selection of the reported result. The risk of bias was rated as low, moderate, serious, or critical. No information was documented when there were insufficient data to make a valid risk judgement (*Table S1*). The quality of the results was assessed using an adapted version of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system for prognostic studies[26,27]. The GRADE rating system has five categories for downgrading (limitations in study design (risk of bias), inconsistency, indirectness, imprecision, and publication bias) and two categories for upgrading (moderate or large size effect and exposure–gradient response)[27]. The level of evidence was downgraded

when the downgrading criteria were met, and was upgraded when the upgrade criteria were met. The quality of the evidence was rated as high, moderate, low, or very low (*Table S2*)[28]. A treatment–design interaction model separated effects within and between different designs, and was visualized by net heat plots, which depicted the inconsistencies between the direct evidence and indirect evidence using the inconsistency model. Warm colours indicated higher heterogeneity (*Fig. S1*)[29].

Statistical analysis

R (R Foundation for Statistical Computing, Vienna, Austria, 2019; https://www.r-project.org) and the R packages 'gemtc', 'meta', 'netmeta', and 'pairwise' were used for statistical analysis. A Mantel–Haenszel random-effects model was used to compare the intervention measures[30,31]. Dissemination bias was evaluated by funnel plots for each direct pairwise comparison and the Harbord test was conducted to investigate small study effects. Dichotomous data were presented as odd ratios (ORs) with 95 per cent confidence intervals (c.i.). In cases of direct comparisons between two arms, node splitting in a Bayesian method was adopted to evaluate the difference and inconsistency between the direct and indirect comparison as previously reported[32]. STATA 16.0 (StataCorp, College Station, TX, USA) was used to assess the statistical heterogeneity between included studies using the I^2 index, and to produce network geometry diagrams and study contribution plots.

Results

Search results and study characteristics

The systematic literature search yielded 6764 potentially eligible articles. After excluding duplicates and screening titles and abstracts, the full texts of 573 articles were further assessed for eligibility. Of these, 515 articles were excluded because they did not meet the inclusion criteria. This left 58 studies to be included in the qualitative synthesis and network meta-analysis (*Fig. 1*). A total of 60 850 adult patients with HCC selected for liver transplantation using the Milan, UCSF, UPTS, AFP, or MT2 criteria were included in the analysis; 76.8 per cent were male. The age of the patients ranged from 46 to 61 years. Twenty-eight (48.3 per cent), 16 (27.6 per cent), nine (15.5 per cent), and five (8.6 per cent) studies were performed in Europe, North America, Asia, and South America, respectively. Study characteristics are shown in *Tables 2* and *3*. There were eight three-arm studies and one four-arm study that evaluated and compared survival of subgroups created by two or three different selection models with the Milan criteria[59,68,73,78,82,83,86–88]. Fifty-eight studies that compared the Milan criteria with other criteria were included in the study. Of these, 41 studies compared the Milan and UCSF criteria[33–45,47–51,53,55–60,63,64,67,68,70–73,76–79,83,85,86,90], 16 studies compared the Milan and UPTS criteria[46,52,54,59,61,62,65,66,68,73,74,78,83,84,86,87], seven studies compared the Milan and AFP criteria[69,75,80–82,87,88], four studies compared the Milan and MT2 criteria[82,87–89], one study compared the UPTS and MT2 criteria[87], one study compared the UPTS and AFP criteria[87], three studies compared the MT2 and AFP criteria[82,87,88], and six studies compared the UCSF and UPTS criteria[59,68,73,78,83,86].

Risk-of-bias assessment

The quality assessment of the 58 included studies using the ROBINS-I tool is shown in *Table S3*. The risk of bias was low in the 'confounding' domain in 13 studies (22 per cent) and moderate in
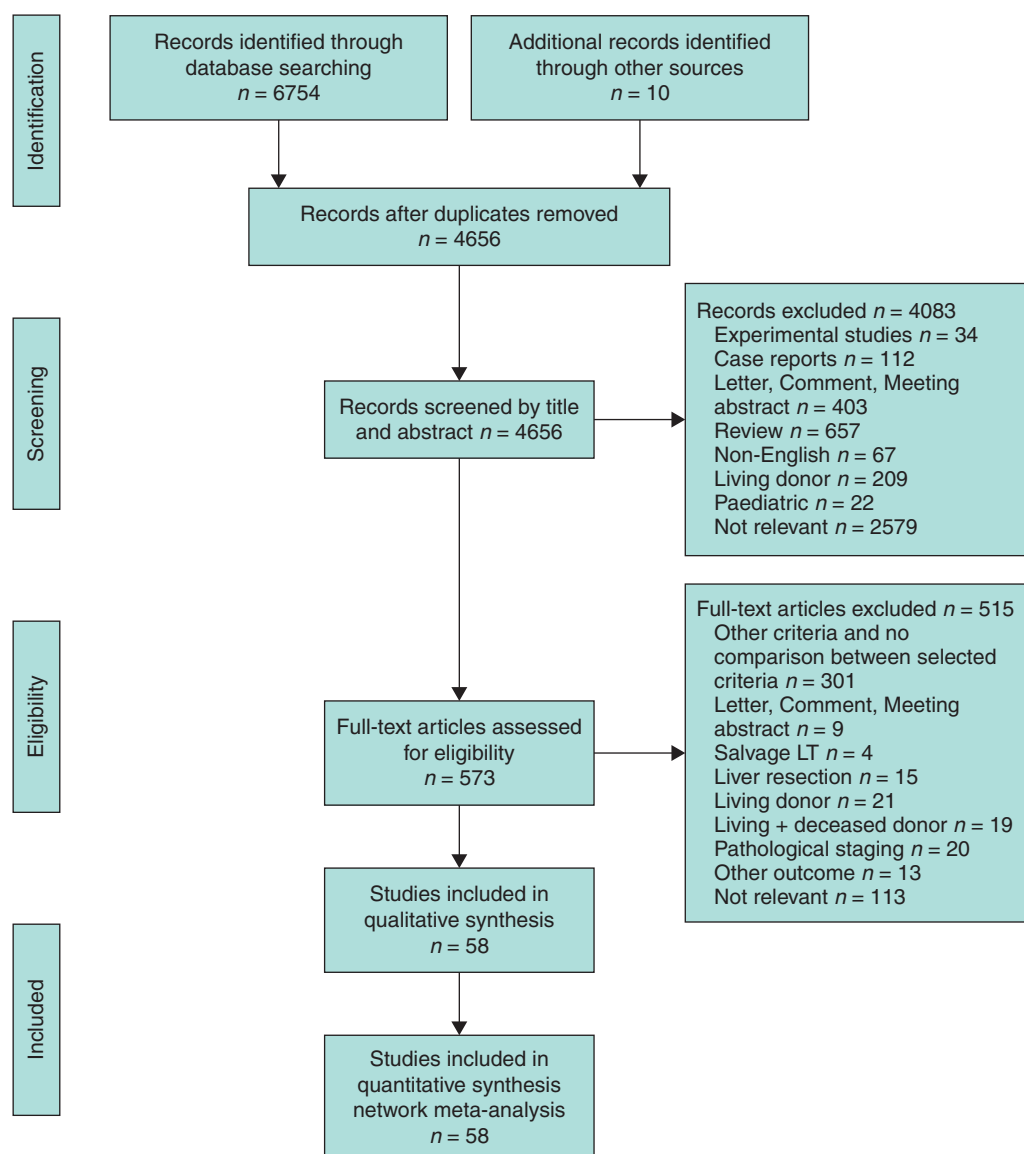
Fig. 1 PRISMA flow chart of enrolled studies
LT, liver transplantation.

28 studies (48 per cent), whereas 17 studies had a serious risk of bias in this domain (29 per cent)[33,35,42,47,50,53–55,58,60,63,64,67,70,72,84,86]. In 40 (69 per cent) studies the risk of bias was low in the 'selection of participants' domain, whereas 16 studies (27.6 per cent) scored moderate risk of bias, and two studies (3.4 per cent) scored serious risk of bias[41,86]. In the 'deviations from intended interventions' domain the risk of bias was low in 46 studies (79 per cent), moderate in 11 studies (19 per cent), and serious in one study (2 per cent)[58]. The risk of bias due to 'missing data' was low in 20 studies (34 per cent), moderate in 37 studies (64 per cent), and serious in one study (2 per cent)[50]. In the 'selection of the reported result' domain, almost all records had moderate risk of bias (54 studies (93.1 per cent)) and two studies had serious risk of bias[50,58]. Almost all records scored a low risk of bias in the 'classification of interventions' and 'measurements of outcomes' domains (52 and 56 studies, respectively). Overall, only one study (1.7 per cent) had a low risk of bias, 39 studies (67.2 per cent) had a moderate risk, and 18 studies (31 per cent) had a serious risk of bias[33,35,41,42,47,50,53–55,58,60,63,64,67,70,72,84,86].

Quality of evidence and data heterogeneity

The GRADE assessment for each outcome is shown in *Table S4* and GRADE assessment of evidence quality is shown in *Table S5*. Data heterogeneity was very low for all outcomes (I^2 = 24 per cent, 27.4 per cent, and 0 per cent for 1-, 3-, and 5-year recurrence-free survival, respectively, and I^2 = 0 per cent, 5.9 per cent, and 0 per cent for 1-, 3-, and 5-year overall survival, respectively). According to the node-splitting analysis and inconsistency-detecting heat maps, there were no statistically significant inconsistencies between direct and indirect evidence for all outcomes (*Figs S1* and *S2*). However, the level of evidence was very low in all comparisons and the quality of evidence, and overall quality of the studies was very low (*Tables S4* and *S5*).

Network structures, geometries, and outcomes

The network geometry of all included studies that compared the clinical outcome of subgroups created by different selection criteria and evaluated recurrence-free survival and overall patient

Table 2 Demographic characteristics of included studies

First author (year)	Data collection period	Country	All patients	Number of patients	Recipient age (year/range) (s.d.)	Sex (male/ female)
Fernández (2003)[33]	May 1998–July 2001	Spain	53	Milan: 33 UCSF: 36	ND	ND
Leung (2004)[34]	September 1992–March 2003	USA	144	Milan: 74 UCSF: 81	53.2 (mean)	129/15
Decaens (2006)[35]	1985–1998	France	468	Milan: 274 UCSF: 316	52.7 (9.2)	384/84
Duffy (2007)[36]	1984–2006	USA	467	Milan: 173 UCSF: 185	56.6 (3.9)	281/186
Millonig (2007)[37]	September 1994–December 2004	Austria	116	Milan: 68 UCSF: 101	58 (7)	100/16
Toso (2008)[38]	December 1996–January 2007	Canada	288	Milan: 157 UCSF: 193	52.75	249/39
Chen (2009)[39]	July 1985–August 2003	Australia	186	Milan: 112 UCSF: 126	52.8 (mean)	155/31
Halazun (2009)[40]	January 2001–January 2007	USA	150	Milan: 95 UCSF: 104	57.1 (7.9)	119/31
Lai (2009)[41]	January 1998–December 2007	Italy	85	Milan: 59 UCSF: 66	54.38 (mean)	69/16
Li (2009)[42]	January 2000–October 2006	China	148	Milan: 24 UCSF: 33	47.75 (14.7)	133/15
Muscari (2009)[43]	1990–2005	France	110	Milan: 73 UCSF: 75	57 (median)	93/17
Toso (2009)[44]	March 2002–January 2008	Canada	6478	Milan: 6268 UCSF: 6427	56 (8)	5001/1477
Xiao (2009)[45]	2001–2006	China	224	Milan: 68 UCSF: 100	ND	205/19
Cescon (2010)[46]	January 1997–September 2009	Italy	283	Milan: 224 UPTS: 267	53.75 (10.08)	241/42
Macaron (2010)[47]	2002–2008	USA	107	Milan: 78 UCSF: 91	56.2 (2.7)	93/14
Wang (2010)[48]	2001–2007	China	255	Milan: 75 UCSF: 110	48 (9)	231/24
Bhangui (2011)[49]	March 2000–November 2009	France	120	Milan: 86 UCSF: 94	56 (8)	100/20
Hanouneh (2011)[50]	2002–2008	USA	92	Milan: 68 UCSF: 79	56.27 (2.52)	81/11
Koniaris (2011)[51]	2001–2009	USA	307	Milan: 237 UCSF: 248	58 (8.54)	230/77
Raj (2011)[52]	January 1998–November 2009	New Zealand	95	Milan: 58 UPTS: 67	53.25 (3.18)	73/22
Unek (2011)[53]	1998–2009	Turkey	56	Milan: 44 UCSF: 49	ND	50/6
de Ataide (2012)[54]	January 1997–December 2010	Brazil	84	Milan: 58 UPTS: 68	ND	67/17
Patel (2012)[55]	2002–2007	USA	1972	Milan: 1913 UCSF: 1972	56 (8)	1571/418
Seehofer (2012)[56]	January 1989–December 2008	Germany	177	Milan: 117 UCSF: 141	ND	151/26
Bittermann (2014)[57]	January 2005–March 2011	USA	2184	Milan: 915 UCSF: 1495	57.5 (2.88)	1518/666
Foltys (2014)[58]	September 1998–March 2012	Germany	57	Milan: 31 UCSF: 36	58.15 (8.42)	47/10
Grąt (2014)[59]	December 1994–June 2012	Poland	121	Milan: 67 UCSF: 83 UPTS: 90	49.25 (13.55)	92/29
Kashkoush (2014)[60]	October 1990–February 2010	Canada	115	Milan: 54 UCSF: 77	55.1 (8.5)	100/15
Zhang (2014)[61]	July 2002–December 2006	China	203	Milan: 114 UPTS: 203	52.2 (9.1)	184/19
Machado (2015)[62]	December 1997–July 2008	Brazil	109	Milan: 88 UPTS: 96	55.7 (7.7)	79/30
Marques (2015)[63]	September 1992–February 2014	Portugal	146	Milan: 100 UCSF: 117	55 (13)	127/19
Fu (2016)[64]	January 2008–May 2013	China	130	Milan: 46 UCSF: 69	46 (17)	121/9
Guerrini (2016)[65]	October 1997–December 2011	Italy	131	Milan: 92 UPTS: 106	55 (7)	112/19
León Díaz (2016)[66]	January 2002–December 2010	Spain	91	Milan: 74 UPTS: 86	55.9 (mean)	69/22
O'Connor (2016)[67]	January 1995–September 2009	Ireland	57	Milan: 41	58.82 (2.9)	44/13

Table 2 (continued)

First author (year)	Data collection period	Country	All patients	Number of patients	Recipient age (year/range) (s.d.)	Sex (male/ female)
Piñero (2016)[68]	May 2005–December 2011	Argentina	87	UCSF: 49 Milan: 70	59 (8)	ND
Piñero (2016)[69]	June 2005–December 2011	Argentina	327	UCSF: 76 UPTS: 77 Milan: 269	57 (8)	267/60
Xu (2016)[70]	2006–2012	China	142	AFP: 257 Milan: 72	ND	137/5
Xu (2016)[71]	1990–December 2012	China	6012	UCSF: 108 Milan: 2626	31.9 (3–154.4)	ND
Chapman (2017)[72]	January 2002–December 2014	USA	302	UCSF: 3049 Milan: 237	58.3 (mean)	239/63
Grąt (2017)[73]	December 1989–April 2015	Poland	240	UCSF: 257 Milan: 143	ND	ND
Kornberg (2017)[74]	1996–2012	Germany	116	UCSF: 171 UPTS: 181 Milan: 66	58.7 (6.7)	68/48
Notarpaolo (2017)[75]	2002–2010	Italy	574	UPTS: 85 Milan: 431	56.9 (7.6)	497/77
Daoud (2018)[76]	February 2002–December 2013	Egypt, USA	11 928	AFP: 512 Milan: 11 555	57.4 (7.4)	9194/2734
Piñero (2018)[77]	June 2005–December 2011	Argentina	527	UCSF: 11 846 Milan: 354	57 (9)	431/96
Pinto-Marques (2018)[78]	September 1992–February 2014	Portugal	231	UCSF: 394 Milan: 187	56 (median)	205/26
Sternby Eilard (2018)[79]	1996–2014	Sweden	336	UCSF: 205 UPTS: 208 Milan: 205	58 (20–74)	267/68
Al-Ameri (2019)[80]	January 2015–January 2019	China	589	UCSF: 256 Milan: 365	52.2 (8.7)	521/68
Al-Ameri (2019)[81]	January 2015–February 2019	China	486	AFP: 398 Milan: 259	51.6 (8.6)	439/47
Firl (2020)[82]	2002–2014	USA	4089	AFP: 301 Milan: 2289 AFP: 2413	57.75 (3.16)	2822/1267
Herden (2019)[83]	January 2007–December 2013	Germany	1168	MT2: 2561 Milan: 864 UCSF: 946	57.9 (8.4)	906/262
Mirón Fernández (2019)[84]	2006–January 2015	Spain	105	UPTS: 1004 Milan: 85	56.24 (7.97)	80/25
Vutien (2019)[85]	2002–2014	USA	16 558	UPTS: 100 Milan: 16 063	58 (53–63)	12 822/3736
Assalino (2020)[86]	September 2004–July 2018	Switzerland	30	UCSF: 16 435 Milan: 23 UCSF: 27	57 (6.92)	25/5
Degroote (2020)[87]	1999–2016	Belgium	526	UPTS: 28 Milan: 436 AFP: 479	58.7 (8.1)	407/119
Grąt (2020)[88]	March 2001–March 2017	Poland	282	UPTS : 482 MT2: 468 Milan: 170 AFP: 204	56.75 (2.58)	209/73
Meischl (2021)[89]	1997–2014	Austria	166	MT2: 201 Milan: 139	57.7 (8.7)	145/21
Victor (2020)[90]	2008–2017	USA	220	MT2: 139 Milan: 138 UCSF: 161	61 (56–66)	159/61

ND, not defined; UCSF, University of California San Francisco; UPTS, Up-To-Seven; AFP, alpha-fetoprotein; MT2, MetroTicket 2.

survival rates following LT in patients with HCC is shown in *Fig. 2.* Milan criteria were the cornerstone for patient selection and served as a benchmark for comparison in the included studies.

One-year recurrence-free survival

Twenty-nine studies reported 1-year recurrence-free survival after LT in patients with HCC. Four triangular loops (Milan *versus* AFP *versus* MT2 and Milan *versus* UCSF *versus* UPTS) were reported in each of four studies[73,82,83,88]. One study reported a quadrangular loop (AFP *versus* Milan *versus* MT2 *versus* UPTS)[87]. Patients selected for transplantation using the MT2 model had the highest 1-year recurrence-free survival rates and were followed by patients selected for transplantation using the UCSF criteria with the second best 1-year recurrence-free survival

Table 3 Characteristics of included studies that analysed recurrence-free survival and overall survival after liver transplantation (LT) in patients with hepatocellular carcinoma patients who were selected according to the Milan, University of California San Francisco (UCSF), up-to-seven (UPTS), alpha-fetoprotein (AFP), and MetroTicket 2.0 (MT2) criteria

First author (year)	Number of patients	HBV/ non-HBV	HCV/ non-HCV	Cirrhosis/no cirrhosis	Pre-LT neoadjuvant therapies	TACE/no TACE	RFA/no RFA	Outcome	Follow-up (month/ range) (s.d.)
Fernández (2003)[33]	Milan: 33 UCSF: 36	6/47	23/30	53/0	ND	ND	ND	OS	ND
Leung (2004)[34]	Milan: 74 UCSF: 81	16/128	87/57	144/0	33/111	ND	ND	OS	ND
Decaens (2006)[35]	Milan: 274 UCSF: 316	ND	ND	425/43	ND	ND	ND	RFS	68 (mean)
Duffy (2007)[36]	Milan: 173 UCSF: 185	79/388	257/210	ND	ND	ND	ND	RFS, OS	79.2 (10.8)
Millonig (2007)[37]	Milan: 68 UCSF: 101	17/99	53/63	ND	ND	ND	ND	RFS	37.2 (31.2)
Toso (2008)[38]	Milan: 157 UCSF: 193	52/236	164/124	288/0	ND	50/238	46/242	OS	25 (range 1–112)
Chen (2009)[39]	Milan: 112 UCSF: 126	61/125	52/134	ND	56/121	29/157	1/185	OS	110.8 (62.4)
Halazun (2009)[40]	Milan: 95 UCSF: 104	23/127	95/55	150/0	116/34	103/47	17/133	DFS	37.2 (18)
Lai (2009)[41]	Milan: 59 UCSF: 66	15/70	48/37	76/9	24/61	ND	ND	RFS	23.9 (19.8)
Li (2009)[42]	Milan: 24 UCSF: 33	139/9	2/146	135/13	47/101	ND	ND	RFS, OS	24.5 (19.2)
Muscari (2009)[43]	Milan: 73 UCSF: 75	ND	ND	110/0	ND	40/70	5/105	OS	45.75 (32.5)
Toso (2009)[44]	Milan: 6268 UCSF: 6427	392/6086	3221/3257	ND	ND	ND	ND	OS	13.4 (range 0–67.9)
Xiao (2009)[45]	Milan: 68 UCSF: 100	224/0	ND	224/0	ND	36/188	ND	RFS, OS	60 (mean)
Cescon (2010)[46]	Milan: 224 UPTS: 267	70/213	152/131	267/16	222/61	158/125	63/220	RFS, DFS	59.2 (43.6)
Macaron (2010)[47]	Milan: 78 UCSF: 91	10/97	67/40	107/0	38/69	ND	ND	RFS, OS	21.57 (5.97)
Wang (2010)[48]	Milan: 75 UCSF: 110	247/8	ND	ND	ND	40/215	5/250	RFS, OS	22.77 (14.16)
Bhangui (2011)[49]	Milan: 86 UCSF: 94	ND	ND	120/0	ND	42/78	3/117	RFS, OS	50 (31)
Hanouneh (2011)[50]	Milan: 68 UCSF: 79	8/84	60/32	ND	ND	ND	ND	RFS	20.1 (5.77)
Koniaris (2011)[51]	Milan: 237 UCSF: 248	17/290	221/86	ND	ND	ND	ND	RFS, OS	ND
Raj (2011)[52]	Milan: 58 UPTS: 67	48/47	34/61	ND	ND	ND	ND	OS	67.6 (median)
Unek (2011)[53]	Milan: 44 UCSF: 49	ND	ND	56/0	ND	ND	ND	OS, DFS	39.5 (range 1–124)
de Ataide (2012)[54]	Milan: 58 UPTS: 68	ND	ND	ND	ND	ND	ND	OS	ND
Patel (2012)[55]	Milan: 1913 UCSF: 1972	662/1111	1130/639	1972/0	ND	ND	ND	OS	ND
Seehofer (2012)[56]	Milan: 117 UCSF: 141	25/152	63/114	ND	ND	71/106	ND	RFS	ND
Bittermann (2014)[57]	Milan: 915 UCSF: 1495	194/1990	1034/1150	ND	ND	ND	ND	OS	ND
Foltys (2014)[58]	Milan: 31 UCSF: 36	11/46	17/40	57/0	ND	ND	ND	OS	66.6 (48)
Grąt (2014)[59]	Milan: 67 UCSF: 83 UPTS: 90	45/76	77/44	ND	ND	ND	ND	OS	30 (median)
Kashkoush (2014)[60]	Milan: 54 UCSF: 77	ND	59/56	ND	71/44	ND	ND	RFS	60 (50.7)
Zhang (2014)[61]	Milan: 114 UPTS: 203	203/0	ND	203/0	ND	203/0	ND	RFS, OS	57.4 (31.5)
Machado (2015)[62]	Milan: 88 UPTS: 96	12/97	92/17	ND	ND	ND	ND	OS	ND
Marques (2015)[63]	Milan: 100 UCSF: 117	26/120	64/82	ND	82/64	77/69	2/144	OS	32.5 (median)
Fu (2016)[64]	Milan: 46 UCSF: 69	119/11	ND	130/0	ND	ND	ND	OS, DFS	50.65 (33.49)
Guerrini (2016)[65]	Milan: 92 UPTS: 106	43/88	72/59	131/0	ND	46/85	80/51	RFS	44.2 (34.9)
León Díaz (2016)[66]	Milan: 74 UPTS: 86	14/77	35/56	ND	ND	ND	ND	RFS, OS	ND
O'Connor (2016)[67]	Milan: 41 UCSF: 49	2/55	ND	53/4	ND	ND	ND	RFS, OS	41.9 (15.29)
Piñero (2016)[68]	Milan: 70 UCSF: 76 UPTS: 77	15/72	53/34	82/5	ND	29/58	6/81	RFS	42 (26.4)
Piñero (2016)[69]	Milan: 269 AFP: 257	94/233	89/238	321/6	ND	85/243	19/308	RFS, OS	46.5 (10.39)
Xu (2016)[70]	Milan: 72 UCSF: 108	ND	ND	ND	ND	42/100	15/127	DFS	60 (mean)
Xu (2016)[71]	Milan: 2626 UCSF: 3049	5483/529	ND	5185/827	ND	1813/4199	270/5742	RFS, OS	31.9 (range 3–154.4)
Chapman (2017)[72]	Milan: 237 UCSF: 257	ND	203/99	280/22	210/92	171/131	11/291	RFS, OS, DFS	51.4 (median)
Grąt (2017)[73]	Milan: 143 UCSF: 171 UPTS: 181	ND	ND	ND	ND	ND	ND	RFS, OS	34 (median)
Kornberg (2017)[74]	Milan: 66 UPTS: 85	12/104	22/96	ND	ND	76/40	ND	RFS, OS	84.25 (51.68)
Notarpaolo (2017)[75]	Milan: 431 AFP: 512	138/436	387/187	574/0	ND	ND	ND	RFS, OS	43.45 (15.94)
Daoud (2018)[76]	Milan : 11 555 UCSF: 11 846	1029/10 038	7246/3616	ND	ND	ND	ND	OS	ND
Piñero (2018)[77]	Milan: 354 UCSF: 394	131/396	177/350	520/7	193/242	ND	ND	RFS	38.87 (14.57)
Pinto-Marques (2018)[78]	Milan: 187 UCSF: 205 UPTS: 208	32/199	103/128	ND	117/114	113/118	1/230	OS, DFS	78.5 (56)
Sternby Eilard (2018)[79]	Milan: 205 UCSF: 256	ND	ND	321/14	ND	63/273	ND	OS	63.6 (mean)
Al-Ameri (2019)[80]	Milan: 365 AFP: 398	554/35	ND	589/0	ND	235/353	111/478	RFS, OS	9 (mean)
Al-Ameri (2019)[81]	Milan: 259 AFP: 301	462/24	ND	411/75	ND	195/291	85/401	RFS	12 (mean)
Firl (2020)[82]	Milan: 2289 AFP: 2413 MT2: 2561	693/3396	2243/1846	ND	ND	ND	ND	RFS, OS	50.76 (mean)
Herden (2019)[83]	Milan: 864 UCSF: 946 UPTS: 1004	ND	ND	1110/58	ND	876/292	210/958	RFS	ND
Mirón Fernández (2019)[84]	Milan: 85 UPTS: 100	17/88	41/64	ND	ND	ND	ND	OS, DFS	min. 60
Vutien (2019)[85]	Milan: 16 063 UCSF: 16 435	1051/15 507	10 114/6444	ND	ND	ND	ND	RFS	30 (range 12–61.2)
Assalino (2020)[86]	Milan: 23 UCSF: 27 UPTS: 28	7/23	ND	ND	ND	15/15	ND	RFS	54 (mean)
Degroote (2020)[87]	Milan: 436 AFP: 479 UPTS: 482 MT2: 468	50/476	167/359	526/0	ND	ND	ND	RFS, OS	56.1 (43.7)
Grąt (2020)[88]	Milan: 170 AFP: 204 MT2: 201	122/160	196/86	ND	137/145	ND	ND	RFS	50.9 (median)
Meischl (2021)[89]	Milan: 139 MT2: 139	18/148	78/88	ND	121/45	37/129	16/150	RFS, OS	111 (median)
Victor (2020)[90]	Milan: 138 UCSF: 161	11/209	153/67	ND	ND	182/38	63/157	RFS, OS	60 (mean)

HBV, hepatitis B virus; HCV, hepatitis C virus; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; ND, not defined; OS, overall survival; RFS, recurrence-free survival; DFS, disease-free survival.

rates. The corresponding ORs for the MT2 and UCSF criteria, compared to the Milan criteria, were 1.18 (95 per cent c.i. 0.87 to 1.60) and 1.03 (95 per cent c.i. 0.85 to 1.25), respectively. MT2 was associated with slightly higher 1-year recurrence-free survival rates than the other selection criteria in the network estimate. Although insignificant, this difference was most prominent when MT2 was compared to the AFP model (Fig. 3a).

Three-year recurrence-free survival

Thirty studies reported 3-year recurrence-free survival after LT in patients with HCC and compared two or more criteria. Four studies had triangular loops (AFP *versus* Milan *versus* MT2 and Milan *versus* UCSF *versus* UPTS, both in two studies)[73,82,83,88]. A quadrangular loop was observed in one study (AFP *versus* Milan *versus* MT2 *versus* UPTS)[87]. Patients selected for transplantation using the MT2 model had the highest 3-year recurrence-free survival of all patient selection models and were the only patients who had higher recurrence-free survival rates than the Milan criteria. The corresponding OR for the MT2 criteria, compared to the Milan criteria, was 1.02 (95 per cent c.i. 0.83 to 1.25). The difference between 3-year recurrence-free survival rates was most prominent between patients selected for transplantation using the MT2 and patients selected using the AFP model (Fig. 3b).

Five-year recurrence-free survival

Five-year recurrence-free survival was reported in 32 studies. Six studies reported triangular loops (AFP *versus* Milan *versus* MT2 in two studies and Milan *versus* UCSF *versus* UPTS in four studies)[68,73,82,83,86,88]. A quadrangular loop was observed in one study (AFP *versus* Milan *versus* MT2 *versus* UPTS)[87]. Patients selected for transplantation using the MT2 model had the highest 5-year recurrence-free survival rates, even higher than the survival rates of patients selected for transplantation using the benchmark Milan criteria (OR 1.10, 95 per cent c.i. 0.96 to 1.27). The difference between 5-year recurrence-free survival rates was most prominent between patients selected for transplantation using the MT2 and patients selected using the AFP model (Fig. 3c).

One-year overall survival

Thirty-five studies reported 1-year overall survival following LT in patients with HCC. Three studies had triangular loops (AFP *versus* Milan *versus* MT2 in one study and Milan *versus* UCSF *versus* UPTS in two studies)[59,73,82]. A quadrangular loop was observed in one study (AFP *versus* Milan *versus* MT2 *versus* UPTS)[87]. The pairwise comparison of the 1-year overall survival rates between patients selected for transplantation using the MT2, UCSF, and Milan criteria revealed identical ORs, indicating no relevant survival differences between patients selected for LT using these models. However, patients selected for transplantation using the MT2 model had higher 1-year overall survival rates than the AFP and UPTS criteria (Fig. 3d).

Three-year overall survival

Thirty-five studies reported 3-year overall survival in patients with HCC. Three studies reported triangular loops (AFP *versus* Milan *versus* MT2 in one study and Milan *versus* UCSF *versus* UPTS in two studies)[59,73,82]. A quadrangular loop was observed in one study (AFP *versus* Milan *versus* MT2 *versus* UPTS)[87]. Patients selected for transplantation using the MT2 model had the highest 3-year overall survival rates and were followed by patients selected for transplantation using the UPTS criteria with the second best 3-year overall survival rates with corresponding ORs, compared to the Milan criteria, of 1.07 (95 per cent c.i. 0.94 to 1.22) and 1.02 (95 per

cent c.i. 0.85 to 1.24), respectively. The pairwise comparison showed the highest OR when the MT2 and Milan criteria were compared, but the difference was not significant (OR 1.07, 95 per cent c.i. 0.94 to 1.22). The survival rate difference was most prominent when patients selected for transplantation using the MT2 were compared with the AFP model (Fig. 3e).

Five-year overall survival

Five-year overall survival was evaluated in 40 studies. Four studies had triangular loops (AFP *versus* Milan *versus* MT2 in one study and Milan *versus* UCSF *versus* UPTS in three studies)[59,73,78,82]. Only one study had a quadrangular loop (AFP *versus* Milan *versus* MT2 *versus* UPTS)[87]. Patients selected for transplantation using the benchmark Milan criteria were associated with the best 5-year overall survival rates (Fig. 3f).

Dissemination bias and small study effects

The funnel plots for the outcomes were symmetric and revealed no dissemination bias and the Harbord test did not reveal evidence for small study effects (Fig. S3).

Discussion

Compound criteria that consider tumour morphology, tumour biology, response to neoadjuvant bridging treatments, and waiting time are likely to replace conventional transplant selection criteria[1]. This study showed that patients with HCC selected for transplantation using the MT2 model had the best recurrence-free and overall survival rates.

The Milan criteria are still the cornerstone for selecting patients with HCC for LT in the Eurotransplant and UNOS regions. Selecting HCC patients for transplantation based on these criteria yields post-transplant survival rates similar to the survival rates of transplant patients with cirrhosis and no HCC[12]. However, the Milan criteria do not consider the biological properties and aggressiveness of a tumour. On the one hand, basing patient selection purely on morphometric criteria may be too strict and unjust to specific patients who would otherwise benefit from a lifesaving liver transplant. On the other hand, these same criteria may be too permissive for high-risk individuals with lower tumour burden[88]. The Milan criteria were first challenged when histopathological analyses of explanted livers showed that one-quarter of patients who were judged to be within the Milan criteria before transplantation had actually exceeded these criteria[87]. High (≥70 per cent) 5-year survival rates have been achieved in patients who were selected for transplantation based on alternative extended patient selection criteria[5,14,17–19]. This has led to changes in selection policies.

Fernández *et al.* compared the Milan criteria with the UCSF criteria in 2003 for the first time[33]. Patients with HCC selected for LT using the UCSF criteria had better survival than patients selected using the Milan criteria. Patients meeting the UCSF criteria have shown 1- and 5-year survival rates of 90 per cent and 75 per cent, respectively[19,91]. Mehta *et al.* reported 87.3 per cent 5-year recurrence-free survival and 79.7 per cent 5-year survival in patients with HCC who initially met the UCSF criteria and were then down-staged to the Milan criteria[92]. Similar results from European cohorts have highlighted the importance of bridging therapies[86]. Since 2017, UNOS awards standardized MELD exception points to transplant candidates who are within the UCSF criteria, who have been successfully down-staged to the Milan criteria, and who have stable AFP levels <500 ng/ml until transplantation[5]. However, studies comparing the Milan and UCSF criteria have
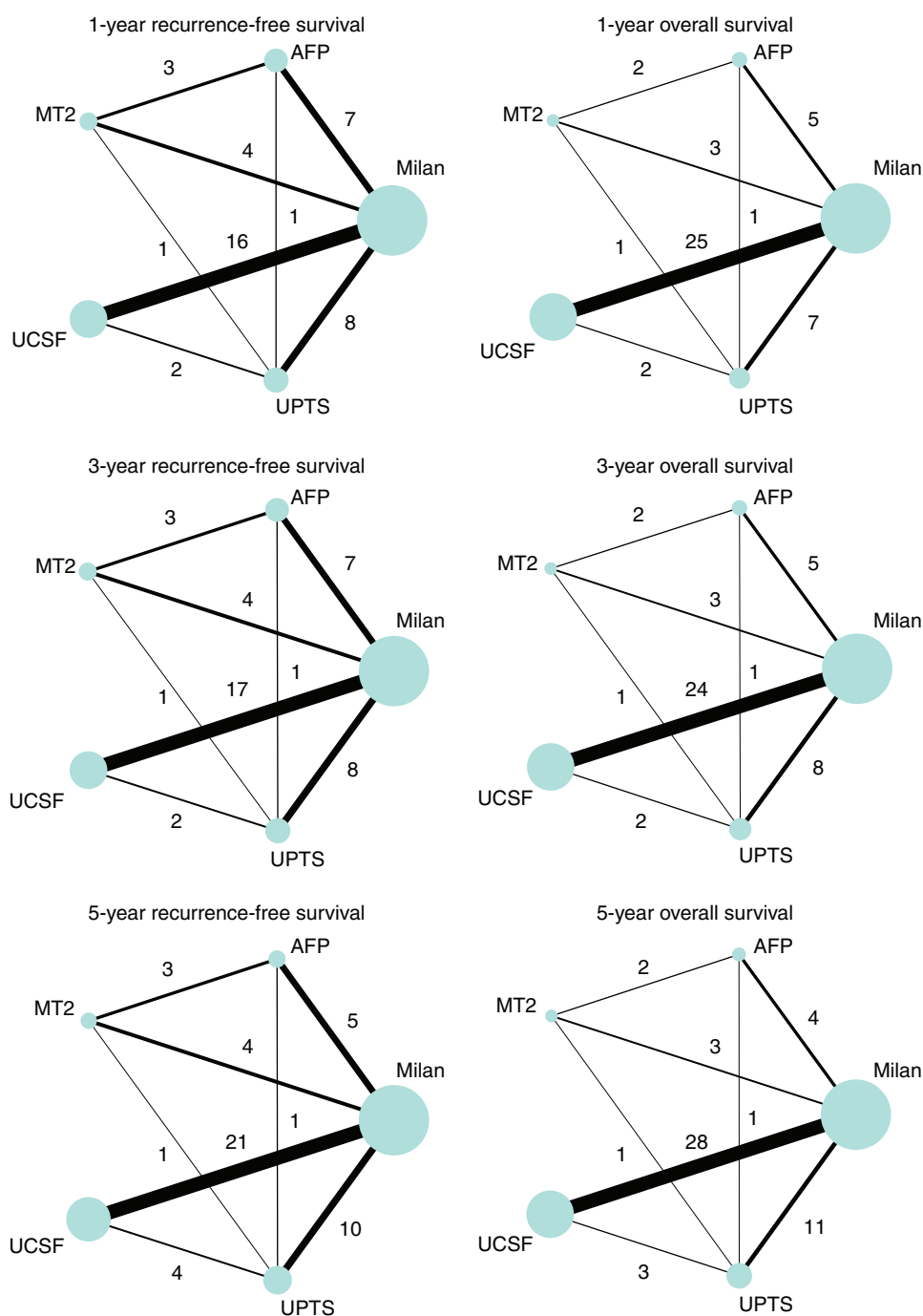
Fig. 2 Network of included studies comparing different selection models for recurrence-free and overall survival after liver transplantation in patients with hepatocellular carcinoma

The size of each node is proportional to the sample size of each selection model. The number adjacent to the lines connecting agents indicates the number of pairwise comparisons. AFP, alpha-fetoprotein; MT2, MetroTicket 2.0; UCSF, University of California San Francisco; UPTS, up-to-seven.

shown conflicting results between centres, which may reflect variations in pretransplant imaging that may under- or overestimate tumour size or number of lesions[93]. This is not surprising considering the small morphometric differences between the two criteria. Therefore, the Milan criteria offer a safer margin for patient selection by reducing the influence of underestimated tumour staging during pretransplant imaging[53]. This may explain why the UCSF criteria were associated with worse survival than the Milan criteria in the present study, which included only studies that evaluated the outcomes of selection criteria based on preoperative imaging.

The UCSF criteria were associated with better 1-year and 3-year recurrence-free survival, and 1-year overall survival than the UPTS criteria. Data heterogeneity was insignificant, but the low number of studies comparing UCSF and UPTS criteria may explain this variability. Moreover, all included studies compared the UCSF criteria with Milan and UPTS criteria, and any deductions about superiority in the triangular loop MT2, AFP, and UCSF can only be made indirectly and should be interpreted with caution.

Patients with HCC who met the UPTS criteria had a 9.1 per cent 5-year recurrence rate and a 71.2 per cent 5-year overall
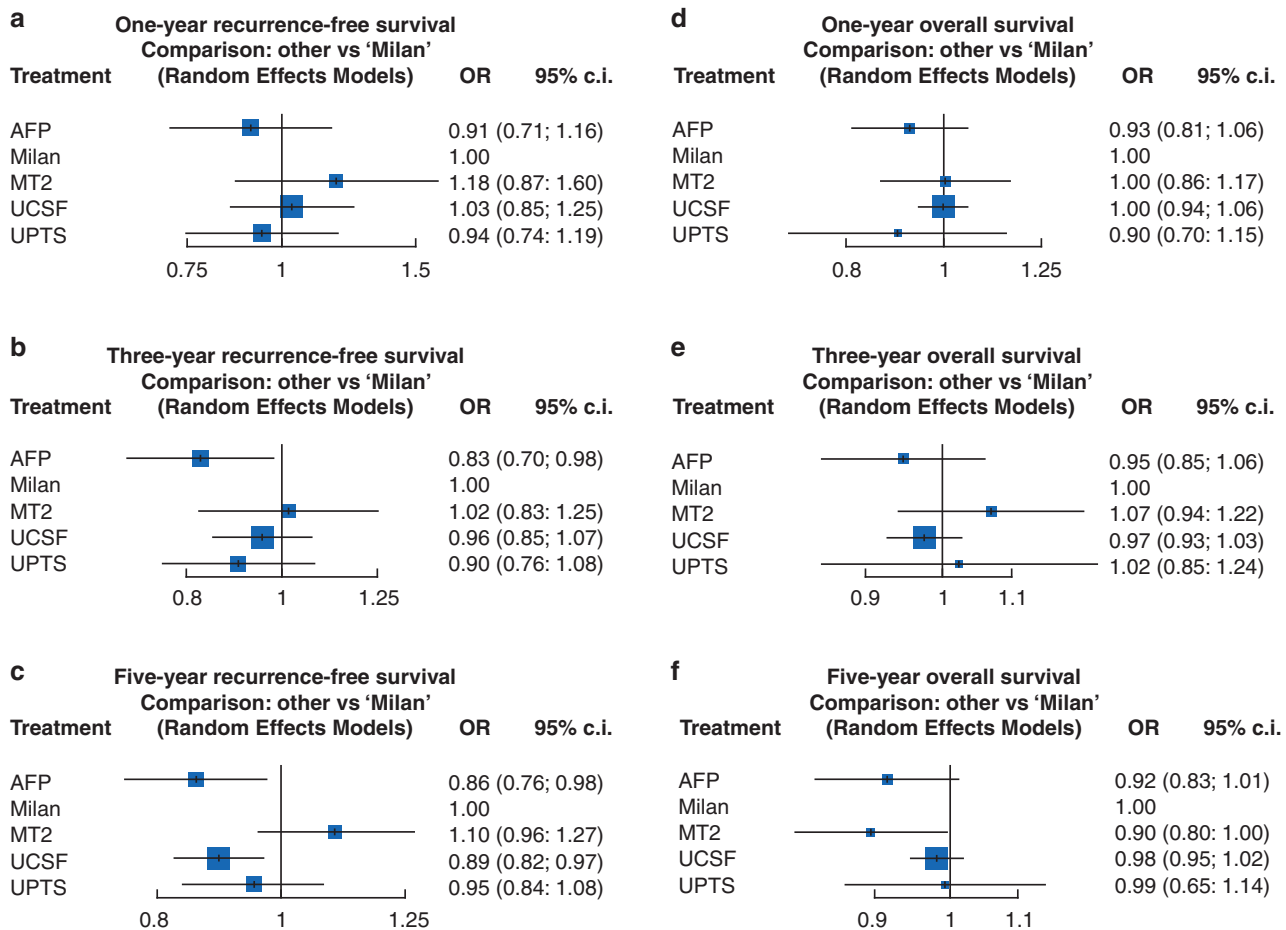
Fig. 3 Forest plots of recurrence-free and overall survival of different selection criteria for patients with hepatocellular carcinoma who underwent liver transplantation

a One-year recurrence-free survival. **b** Three-year recurrence-free survival. **c** Five-year recurrence-free survival. **d** One-year overall survival. **e** Three-year overall survival. **f** Five-year overall survival. Odds ratio (OR) >1 favoured the criteria in means of outcomes. AFP, alpha-fetoprotein; c.i., confidence interval; MT2, MetroTicket 2.0; UCSF, University of California San Francisco; UPTS, Up-to-Seven.

survival rate, which are similar to rates reported in patients with HCC meeting the Milan criteria[17]. Patients not meeting the Milan criteria but meeting the extended criteria were transplanted sooner than other patients on the waiting lists. The 5-year overall survival rates exceeded 60 per cent in these patients, supporting the ethics of this decision[87]. In the present study, the UPTS criteria were associated with better results at later time points and had better 5-year overall patient survival rates than the MT2 and UCSF criteria. The UPTS model was compared directly with the other selection models, but not all studies reported on 1-, 3-, and 5-year recurrence-free and overall patient survival. Moreover, survival differences were marginal and may be attributed to the low number of patients and the lack of power in individual studies.

AFP is a surrogate for tumour aggressiveness and is a prognostic factor for poor overall and disease-free survival because of its association with progressive microvascular invasion and poorly differentiated HCC with intrahepatic metastases[5]. Enhanced AFP dynamics increased tumour aggressiveness, satellite lesions, and extrahepatic growth even in small single-lesion tumours. An increase in AFP levels by >15 ng/ml per month after bridging therapy was predictive of HCC recurrence and decreased 5-year overall survival (77 per cent *versus* 54 per cent, $P < 0.0001$) and 5-year recurrence-free survival (74 per cent *versus* 47 per cent, $P = 0.01$)[94,95]. Duvoux *et al.* suggested combining AFP levels with

tumour morphology characteristics to predict recurrence rates and post-transplant survival in patients with HCC[14]. They demonstrated the superiority of their AFP score in predicting HCC recurrence, compared to the Milan criteria, and identified the number of lesions, tumour size, and AFP levels as three strong predictors of tumour recurrence. According to the AFP model, acceptable survival rates close to 70 per cent can be achieved in patients who exceed the Milan criteria but meet the AFP criteria[14]. AFP scores that exceeded the proposed cut-off value (AFP score >2 *versus* AFP score ≤2) were associated with an increased 5-year risk of recurrence (50.6 per cent *versus* 8.8 per cent ($P < 0.001$), respectively) and decreased 5-year survival (47.5 per cent vs. 67.8 per cent ($P < 0.002$), respectively). In patients with HCC who exceeded the Milan criteria, the risk of recurrence was ~14 per cent among patients who met the AFP criteria (AFP ≤2) and ~59 per cent in patients who did not meet them (AFP >2)[14,75]. Other studies confirmed the ability of the AFP score to discriminate between low- and high-risk patients with HCC regarding 5-year survival[69,75]. However, in a recent study, patients with HCC selected for transplantation based on the AFP model had equal or worse overall survival and higher risk of recurrence than those patients selected with the Milan, UPTS, and MT2 criteria[87]. In another study, the AFP model identified patients with HCC who fulfilled the Milan criteria and who had a low or high risk of tumour recurrence, but it was not able to do the same for

patients who exceeded the Milan criteria[80]. In the study by Grąt *et al.*, patients who did not meet the Milan criteria but did meet the AFP criteria had a 74.1 per cent 5-year recurrence-free survival rate, which was inferior to the recurrence-free survival of patients who met the Milan criteria ($P = 0.045$). In contrast, patients who were within the Milan and AFP criteria had higher 5-year recurrence-free survival rates than patients within the AFP criteria but beyond the Milan criteria (89.2 per cent *versus* 74.1 per cent, $P = 0.014$)[88]. The authors suggested more individualized use of the AFP model because its c-statistics were no longer superior to those of the Milan criteria when the AFP cut-off value of 2 points was applied[88]. These results contrast those of Piñero *et al.*[69]. The risk of 5-year recurrence in the two studies was 24.8 per cent *versus* 15 per cent for the entire cohort and was 25.9 per cent *versus* 5.3 per cent for patients beyond the Milan criteria and within the AFP criteria[69,88]. Grąt *et al.* included more patients with four or more tumour lesions in their study than Piñero *et al.* did (17.9 per cent *versus* 4 per cent), so selection bias may explain these differences[69,88].

The MT2 model combines tumour morphology (UPTS criteria) and tumour biology (AFP values)[18]. This model states that AFP levels should not exceed 1000 ng/ml and suggests three clinical scenarios (up to seven, up to five, or up to four) that predicted a 70 per cent chance of 5-year survival, which was higher if all the MT2 criteria were met. With a c-statistic of 0.78 (95 per cent c.i. 0.763 to 0.798), the MT2 model is a good tool for predicting the cumulative incidence of HCC-specific death[18]. In line with this, the results of the retrospective multicentric Be-LIAC study showed similar recurrence and overall survival rates in patients within the MT2 and Milan criteria[87]. Moreover, Meischl *et al.* showed excellent overall and 5-year survival rates of patients who met the MT2 criteria and significantly higher recurrence rates in patients who did not meet them[89]. Although statistically insignificant, inferior 5-year recurrence-free survival rates were reported in patients who were beyond the Milan criteria but within the MT2 criteria compared with patients with HCC who were selected for transplantation based on the Milan criteria only (75.3 per cent *versus* 87.1 per cent; $P = 0.067$). In contrast, patients within the MT2 and Milan criteria had better 5-year survival rates than those who exceeded the Milan criteria (89.5 per cent *versus* 75.3 per cent; $P = 0.021$)[88]. Grąt *et al.* encouraged replacing the Milan criteria with the MT2 and AFP criteria, despite higher HCC recurrence, higher microvascular invasion, and poorer tumour differentiation in patients who were beyond the Milan criteria but within the AFP and MT2 criteria, because the absolute risk of recurrence was lower (<30 per cent) and the 5-year recurrence-free survival rates stayed above >70 per cent in these patients, compared to alternative palliative and best supportive care treatments[88]. Importantly, the AFP and the MT2 patient selection models partially replace high-risk patients who are within the Milan criteria with moderate-risk patients who exceed these criteria. This is in contrast to other proposals that aim to widen access to LT for low-risk patients beyond the Milan criteria to keep recurrence low[88]. Based on low-certainty evidence, the present study showed that the MT2 model is associated with better post-transplant outcomes than other selection models at most investigated time points. MT2 was followed by UPTS in the network estimate, possibly because the UPTS criteria optimally estimated the tumour volume cut-off associated with acceptable outcomes but did not consider tumour biology and aggressiveness. The finding that the MT2 model had best clinical outcome supports the importance of combining a biomarker with tumour morphological features when selecting patients with HCC for LT. However,

whether other parameters (e.g. MELD score) need to be considered when selecting patients with HCC for LT needs to be further evaluated[82]. The AFP model ranked fourth or fifth. This may be because a low number of studies directly compared the AFP model to other models or because these studies were affected by selection bias and low evidence quality. These results need to be interpreted with caution because studies comparing the MT2 and AFP criteria showed heterogeneous results, even for patients who fulfilled the respective criteria[5,88]. In addition to the low number of studies, this may also explain why the patients selected for transplantation using the MT2 model had lower 5-year overall survival rates.

Major extended donor criteria (maEDC) organs are a good alternative for patients with HCC who are in a better condition and have lower labMELD scores[9,96]. The studies included in the present analysis did not provide donor data, which means that an analysis of whether maEDC grafts or grafts with a higher donor risk index are suitable for patients who exceed the Milan criteria but meet the extended selection criteria was not possible[97,98]. This may be interesting, because while recurrence-free survival depends mostly on the recipient characteristics, overall survival may be also affected by donor and organ factors that are not considered by the selection models. Current patient selection models only analyse criteria that are available at the time of transplantation and disregard the dynamics of the waiting lists, which does not adhere to the intention-to-treat principle[13]. The European Association for the Study of the Liver recommends using the Milan criteria to select patients with HCC for LT, and argues that uniform consensus is hindered by limitations associated with the retrospective character of the analyses[1,5]. Moreover, increasing the proportion of patients who do not meet the Milan criteria but are accepted for liver transplant may affect long-term outcomes, but this is yet to be analysed.

The results of the present study should be interpreted with caution because only a few studies have compared the more recent patient selection models directly, and the quality of evidence was low. Also, the number of patients at the highest limits of the extended criteria was low and the model performances may have been overestimated. The identification of the upper limit of tumour burden for down-staging beyond which successful transplantation becomes an unrealistic goal is still a matter of debate[13]. This is important when evaluating selection models because co-mingling bridging therapies may also have led to bias. Moreover, selection criteria based on imaging done at the time of going on the waiting list may underestimate the current tumour load or overestimate the performance of the model by disregarding the therapeutic effects of down-staging. To address this issue may be difficult because down-staging treatment protocols are not uniform worldwide, but assessing imaging results at the time of transplantation may resolve this bias. Also, response to bridging treatments has been suggested as a reliable marker of tumour biology, with a possible influence on patient prioritization and selection[99]. Including information provided by the modified Response Evaluation Criteria In Solid Tumors (mRECIST) criteria in the patient selection models could be used to better judge the suitability of candidates for LT after bridging therapies and improve postoperative outcomes[100].

A deeper understanding of HCC biology is needed to improve outcomes after transplantation. The present study evaluated existing selection models and found that patients selected for transplantation using the MT2 model had best outcomes confirming that not only tumour morphology, but also tumour biology should be considered when selecting patients with HCC for

transplantation. The results of this study fuel the debate whether to expand the Milan criteria or not, but because of heterogeneity across studies further prospective, well-designed trials that also consider donor and organ factors are urgently needed to determine which selection model best predicts transplant outcomes.

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Supplementary material

Supplementary material is available at *BJS Open* online.

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