A Meta-Analysis of Survival Rates of Untreated Patients in Randomized Clinical Trials of Hepatocellular Carcinoma

Giuseppe Cabibbo,[1,4] Marco Enea,[2] Massimo Attanasio,[2] Jordi Bruix,[3] Antonio Craxì,[1] and Calogero Cammà[1,5]

Knowing the spontaneous outcome of hepatocellular carcinoma (HCC) is important for designing randomized controlled trials (RCTs) of new therapeutic approaches; however, survival of patients in the absence of treatment is highly variable, and prognostic factors influencing outcomes are incompletely defined. The aims of this meta-analysis were to estimate the 1-year and 2-year survival rates of untreated HCC patients enrolled in RCTs of palliative treatments, and to identify prognostic factors. RCTs evaluating therapies for HCC with placebo or no-treatment arms were identified on MEDLINE through April 2009. Data were combined in a random effect model. Primary outcomes were 1-year and 2-year survival. Thirty studies met the inclusion criteria. The pooled estimates of the survival rates were 17.5% at 1 year (95% confidence interval [95%CI], 11%-27%; range, 0%-75%) and 7.3% at 2 years (95%CI, 3.9%-13%; range, 0%-50%). Heterogeneity among studies was highly significant ($P < 0.0001$) both for 1-year and 2-year survival, and persisted when RCTs were stratified according to all patient and study features. Through meta-regression, impaired performance status, Child-Pugh B-C class, and presence of portal vein thrombosis were all independently associated with shorter survival. Ascites was strongly linked to a worse outcome in intermediate/advanced Barcelona Clinic Liver Cancer stages. *Conclusion:* This meta-analysis confirms the heterogeneity of behavior of untreated HCC and provides a sound basis for stratifying patients with HCC according to expected survival in future trials of new anti-cancer agents. (HEPATOLOGY 2010;51:000-000.)

The extensive application of surveillance programs for early detection of small (<5 cm) hepatocellular carcinoma (HCC) has increased the number of tumors detected within the Milan criteria[1] at Barcelona Clinic Liver Cancer (BCLC) stages 0 or A (very early or early),[2] and potentially responsive to curative treatments, such as liver transplantation and percutaneous or surgical ablation.[3,4] Nonetheless, most patients with HCC (approximately 70%) are diagnosed at BCLC B (intermediate) and C (advanced) stages (approximately 50%) or BCLC D (end stage, approximately 20%).[4]

A previous systematic review[5] showed that the survival rates of untreated patients or of those who received placebo in randomized controlled trials (RCTs) of unresectable HCC vary among the studies, ranging from 10% to 72% at 1 year and from 8% to 50% at 2 years.

In the setting of unresectable HCC, an accurate estimate of survival among untreated patients is essential for (1) evaluating the natural history and assessing the validity of biological or radiological surrogate markers, (2) controlling for confounding factors in observational studies, (3) calculating the sample size and stratifying subjects in RCTs, and (4) assessing treatment effect size to formulate therapeutic strategies. Knowledge of the factors influencing the outcome of untreated patients also may be important for interpreting the results of RCTs of different treatments.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RCT, randomized controlled trial.

From the [1]Cattedra di Gastroenterologia, DIBIMIS, University of Palermo, Italy; the [2]Dipartimento di Scienze Statistiche e Matematiche "S. Vianelli," University of Palermo, Italy; [3]Barcelona Clinic Liver Cancer Group, Liver Unit, Hospital Clinic, IDIBAPS, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), University of Barcelona, Barcelona, Spain; the [4]Dipartimento di Biopatologia e Metodologie Biomediche, University of Palermo, Italy; and [5]IBIM, Consiglio Nazionale delle Ricerche (CNR), Palermo, Italy.

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Address reprint requests to: Professor Calogero Cammà, Cattedra di Gastroenterologia, Dipartimento Biomedico di Medicina Interna e Specialistica, University of Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy. E-mail: carlo.camma@unipa.it; fax: (39) 091 65 62 156.

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Current guidelines for the management of HCC recommend mortality risk estimates as a decision-making support.[3] Although different palliative treatments (chemoembolization and recently, sorafenib) have been proposed for patients with HCC, prognosis remains poor. In BCLC B or C, the survival of treated patients is assumed to be 10% to 40% at 3 years.[6] In end-stage HCC (BCLC D), the prognosis is very poor, with a median survival of only 3 months.[4] Interpretation of the results of the RCTs of palliative treatments is problematic, with conflicting data, and there is no consensus for all HCC stages on the best algorithm of treatment, although chemoembolization and sorafenib are currently considered the standard of care for BCLC B and BCLC C stages, respectively.[6]

To resolve uncertainty by increasing the statistical power, we chose to do a meta-analysis of the placebo or inactive treatment arms of RCTs of palliative treatments for HCC, with the aims of (1) estimating the 1-year and 2-year rates of survival among patients receiving no treatment, or placebo; (2) analyzing the variability in survival rates by looking at the heterogeneity among the RCTs as a means of interpreting this variability; and finally, (3) identifying factors associated with a longer survival.

Patients and Methods

Selection of Trials. This analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[7] The primary sources of the reviewed studies, exclusively in English, were MEDLINE, CANCERLIT, the Cochrane Controlled Trials Register, and the Cochrane Library, with the following medical subject headings (MeSH): *hepatocellular carcinoma*; *liver cancer*, *primary liver carcinoma*; *placebo*, *double-blind*; *therapy*; *treatment*; *chemoembolization*; *systemic therapy*; *randomized* or *randomised trial,* and *clinical trial*. The search included literature published through April 2009 with no lower date limit on the search results. The computer search was supplemented with manual searches for reference lists of all retrieved review articles, primary studies, and abstracts from meetings to identify other studies not found in the computer search. When the results of a single study were reported in more than one publication, only the most recent and complete data were included in the meta-analysis.

Studies were included in the analysis if (1) they were RCTs comparing any therapy with placebo, no treatment, or supportive care; (2) they included HCC patients with or without metastatic disease; (3) 1-year or 2-year survival was assessed as an outcome measure of the effect of the treatment; and (4) they had been published or accepted for publication as full-length articles.

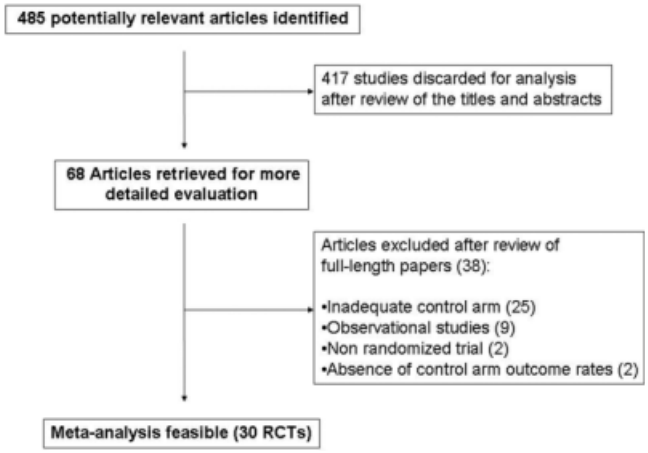

Fig. 1. Study flowchart.

Among the 485 studies reviewed (Fig. 1), 30 RCTs[8-37] met the inclusion criteria. Studies were excluded if they did not have an adequate control arm; if they were nonrandomized or if they enrolled randomized and nonrandomized patients; and if they were published only in abstract form. The rationale for excluding studies published as abstracts only was that the methodological quality could not be assessed.

Review of the Trials. The RCTs were reviewed using a list of predefined, pertinent questions that concerned the characteristics of patients, treatments, outcomes, and study validity. Each trial was evaluated and classified by three independent investigators (C.C., A.C., and G.C.). Discrepancies among reviewers were infrequent (overall interobserver variation of $<10\%$) and were resolved by discussion.

The methodological quality of the studies was assessed by five principal criteria (Supporting Table 1), using those established by Jadad et al.[38] and Bañares et al.,[39] as suggested by the Panel of Experts in HCC-Design Clinical Trials.[4] The quality of trials was evaluated according to each separate component. The maximum possible score was 10 points.

Statistical Analyses. Pooled estimates of 1-year and 2-year survival rates were calculated using random-effects logistic regression analysis after applying sample weights according to the sample size. Heterogeneity among studies was assessed with the Pearson chi-squared test. Three different methods were used to explore and explain the diversity among studies: (1) stratum analysis of variables suspected of having caused inconsistency, (2) meta-regression, and (3) subgroup analysis. Therefore, stratum-specific rates of the 1-year and 2-year survival rates for different patient-level and study-level covariates were cal-

culated. We used 16 stratifying variables: publication year, study validity, study location, mean age, percentage of males, percentage of alcohol-related liver disease, percentage of hepatitis B virus (HBV)–related liver disease, percentage of hepatitis C virus (HCV)–related liver disease, percentage of performance status 0 subjects, mean serum albumin, mean total bilirubin, prothrombin activity, percentage of solitary tumors, percentage of portal thrombosis, percentage of Child-Pugh A patients, and percentage of Okuda stage I patients.

Only univariate logistic regression analyses were used to examine the association between features of the study and the 1-year survival rates. We did not consider multivariate analysis because of the wide heterogeneity and lack of complete data for identification of possible variables that could explain heterogeneity. A chi-squared for interaction was used to examine whether the 1-year survival varied significantly between subgroups.

Begg's funnel plots were generated, and Egger's regression asymmetry test was used to examine potential publication bias related to the 1-year survival rates. For all analyses, $P < 0.05$ was considered statistically significant. All analyses were completed with SAS version 8.1 (SAS Institute, Cary, NC) software.

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Results

Description of the Studies. After review of the titles and abstracts, 30 RCTs[8-37] fulfilled the inclusion criteria and were selected for review. Twenty studies[9,12-21,23,25,26,28,31,33-35,37] were North American and European, and 10[8,10,11,22,24,27,29,30,32,36] were Asian-Pacific. Of the 30 RCTs, 14[8-21] were published before 2000, and the other 16[22-37] since 2000. The distribution of the main characteristics of patients in the control arm of the 30 RCTs[8-37] considered in the current analysis is reported in Table 1. Characteristics of arms (treatment and control) of RCTs included in the meta-analysis are detailed in Supporting Table 2. In 15 RCTs, there was an inactive placebo arm,[12,15-17,19,24,25,29,30,32-37] whereas in the others, untreated patients received no treatment or supportive care only.[8-11,13,14,18,20-23,26-28,31]

A total of 4335 patients were included in these 30 studies, 1927 of whom were in the control group. The size of the control groups in each study ranged from 11[12] to 303[35] patients. The percentage of men ranged from 65[26] to 100.[11] Mean patient age was 62.3, ranging from 49[11] to 69.[34,37] The proportion of patients with cirrhosis ranged from 63[34] to 100%.[12,19,20,23]

Data on the cause of liver disease were missing in many trials. HCV status was not reported in 11 trials,[8-12,17,22,24,27,30,37] and anti-HCV, when reported, was positive in 4[36] to 94%[13] of the patients. HBV status was not reported in six trials,[9,11,12,22,30,37] and hepatitis B surface antigen, when reported, was positive in 0[13,23] to 94.4%.[10] The proportion of patients with alcohol-related liver disease was not reported in 13 RCTs,[8,10-12,18,22,24,26,27,30,32,34,36] and ranged from 2.5[25] to 78%[31] in studies reporting alcohol consumption.

Among the studies providing data on the distribution of the ECOG Performance Status (ECOG PS),[13,16,17,20,27,28,30,31,32,35-37] the frequency of an ECOG PS = 0 went from 0[32] to 77%.[28] Information on the presence of ascites was missing from most trials[8,11,12,14,15,17-19,21,22,24,25,27,29,30,33-37] and ranged from 8%[26] to 63%[16] in the studies reporting it. Mean albumin levels were comparable in the RCTs, ranging from 3 g/dL[26] to 4 g/dL.[35] Mean bilirubin levels differed greatly among RCTs, ranging from 0.7 mg/dL[35] to 6.6 mg/dL.[18]

Only 13 RCTs[14,16,18-21,23,25,27-29,33,34] provided information about the tumor pattern at diagnosis (solitary versus multinodular/diffuse). Solitary tumor rates varied greatly, ranging from 0[34] to 57%.[18] The proportion of patients with portal vein thrombosis was reported in 20 studies[9,13,14,16,19-23,25-29,31,33-37] and differed greatly among the trials, ranging from 0[9,20,28,34] to 65%.[22]

Methodological quality scores ranged from 4[12,32] to 10[33,35,36] on a scale of 2 to 10 (Supporting Table 3). With regard to the quality of the studies, all trials except one[30] reported an adequate efficacy of randomization, and only five studies[12,13,19,24,32] did not report an adequate follow-up. Adequate blinding was used in eight RCTs.[15-17,19,30,33,35,36] Twenty-three trials (77%) showed a high-quality score (≥6 points).[8-11,14-21,23,26-30,33-37]

Survival Rates. The pooled estimate of the 1-year survival rate was 17.5% (95% confidence interval [CI], 11%-27%; range, 0-75%). There was a statistically significant heterogeneity among studies, $P < 0.0001$ (Fig. 2).

Logistic regression analysis was used to identify potential sources of heterogeneity among the studies. Using the univariate logistic regression, of the 16 variables assessed only nine were associated with an increase in the 1-year survival rate: North American and European studies ($P = 0.001$), female sex ($P = 0.043$), low percentage of hepatitis B surface antigen–positive patients ($P = 0.001$), high percentage of ECOG PS = 0 patients ($P = 0.001$), high albumin level ($P = 0.038$), high prothrombin activity ($P = 0.001$), low percentage of portal vein thrombosis ($P = 0.001$), high percentage of Child-Pugh class A patients ($P = 0.042$), and high percentage of Okuda stage I patients ($P = 0.001$) (Table 2).

Table 1. Characteristics of Untreated, or Treated with Placebo, Patients in RCTs of Hepatocellular Carcinoma

Author	Year	Sample*	Centers	Regions†	Mean Age	Male Sex (%)	Etiology (%) Alcohol/HCV/HBV	Prothrombin Activity (%)	Albumin	Bilirubin	Ascites (%)	C-P Class A/B/C (%)	PT (%)	AFP	ECOG PS 0/1/2 (%)	Solitary %	Okuda Stage I/II/III (%)	Survival (%) 1 Year	Survival (%) 2 Year
Lai et al.[8]	1988	46	1	2	57	82	NA/NA/67.3	NA	NA	1.8	NA	NA	NA	800	NA	NA	NA	3.5	0
Pelletier et al.[9]	1990	21	1	1	66	86	85.7/NA/NA	76	3.3	2.3	57	NA	0	1983	NA	NA	24/52/24	24	NA
Lai et al.[10]	1993	36	1	2	60	81	NA/NA/94,4	NA	NA	1.1	19	NA	NA	NA	NA	NA	NA	3.3	0
Madden et al.[11]	1993	25	1	2	49	100	NA/NA/NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	0
Elba et al.[12]	1994	11	1	1	64	73	NA/NA/NA	NA	NA	NA	NA	82/18/0	NA	NA	NA	NA	27/73/0	47	10
Martinez Cerezo et al.[13]	1994	16	1	1	65	81	50/94/0	NA	3.5	2.4	44	44/38/18	12	NA	37.5/56.2/6.3	NA	NA	9,1	NA
GRETCH[14]	1995	46	24	1	65	96	73/10/7	75	3.8	1.4	NA	NA	13	92	NA	30	NA	43.5	26
Manesis et al.[15]	1995	29	1	1	62	79	22/20/58	52	NA	NA	NA	NA	NA	NA	NA	NA	24.1/59/17.2	0	NA
Castells et al.[16]	1995	62	1	1	65	69	8.1/74/6	76	3.6	1.8	63	NA	39	NA	46.8/43.5/9.7	24	45/55/0	43	29
Grimaldi et al.[17]	1998	59	multi	1	NA	78	39/NA/35	NA	NA	NA	NA	NA	NA	NA	26/58/17	NA	NA	36.6	11.6
Kouroumalis et al.[18]	1998	30	NA	1	68	83	NA/53/27	NA	3.2	6.6	NA	6/38/56	NA	NA	NA	57	10/33/57	13	NA
Riestra et al.[19]	1998	37	4	1	65	78	27/29.7/8.1	77	NA	2	NA	NA	22	NA	NA	35	43/43/14	37.8	NA
Bruix et al.[20]	1998	40	1	1	64	75	2.5/77/2.5	79	3.5	1.5	18	NA	0	NA	67.5/27.5/5	27,5	67.5/32.5/0	75	50
CLIP Group[21]	1998	240	30	1	67	76	2.5/78.1/11.4	73	3.5	1.9	NA	44/36/15	15,8	NA	NA	47,5	42.1/37.5/5.8	57	37
Chung et al.[22]	2000	26	1	2	53	NA	NA/NA/NA	NA	NA	NA	NA	46/42/12	65	NA	NA	NA	NA	0	0
Llovet et al.[23]	2000	28	multi	1	63	78	18/78/0	84	3.5	1.4	61	NA	39	NA	NA	36	28.6/71.4/0	36	12
Liu et al.[24]	2000	58	1	2	60	95	NA/NA/81	NA	NA	1.8	NA	48/36/16	NA	1,377	NA	NA	10.3/67.2/22.4	0,0	0
Villa et al.[25]	2001	24	1	1	60	92	0/62.5/37.5	77	3.1	1.7	NA	42/29/29	17	NA	NA	54,2	NA	29	15
Ishikawa et al.[26]	2001	20	1	1	61	65	NA/85/15	56	3	2.3	8	20/65/15	40	NA	NA	NA	20/60/20	5.5	0
Lo et al.[27]	2002	39	1	2	63	87	NA/NA/74	NA	3.7	0.8	NA	NA	31	NA	35.9/48.7/15.4	38	46.2/53.8/0	32	11
Llovet et al.[28]	2002	35	3	1	66	66	3/91/3	77	3.5	1.5	31	60/40/0	0	NA	77/11.5/11.5	23	62.8/37.2/0	63	27
Yuen et al.[29]	2002	35	1	2	62	94	2.8/5.7/66	NA	3.2	1.4	NA	34/63/3	60	721	NA	54	8.6/74.3/17.1	0	0
Chow et al.[30]	2002	130	10	2	60	82	NA/NA/NA	NA	NA	NA	NA	40/48/12	NA	NA	19/45/36	NA	11/69/20	12	5
Barbare et al.[31]	2005	210	78	1	67	90	78/11/6	NA	NA	NA	35	50/44/4	37,4	NA	14.8/53.3/31.9	NA	35/57/8	19.9	6
Sarin et al.[32]	2006	19	NA	2	52	79	NA/15.8/78.9	NA	3.5	2.2	53	32/68/0	NA	NA	0/NA/NA	NA	0/100/0	15.8	5.3
Becker et al.[33]	2007	59	7	1	67	85	52/16/10	NA	NA	NA	NA	53/37/10	44	NA	NA	21	32/58/10	25	15.6
Dimitroulopoulos et al.[34]	2007	30	1	1	69	73	NA/57/10	NA	NA	NA	NA	27/63/0	0	3208	NA	0	NA	3	0
Llovet et al.[35]	2008	303	121	1	66	87	26/27/55	NA	4	0.7	NA	98/2/0	41	99	54/39/7	NA	NA	33	NA
Cheng et al.[36]	2009	76	23	2	52	66	NA/4/78	NA	NA	NA	NA	97/3/0	34	NA	27.6/67.1/5.3	NA	NA	17.5	NA
Barbare et al.[37]	2009	137	79	1	69	69	74/NA/NA	NA	NA	NA	NA	67/23/0	23	NA	PS0-1% 80	NA	NA	30	14

*Control arm sample.

†For regions, 1 corresponds to North American and European studies; 2 to Asia-Pacific studies.

HCV, hepatitis C virus; HBV, hepatitis B virus; C-P, Child-Pugh; PT, portal vein thrombosis; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group—performance status.

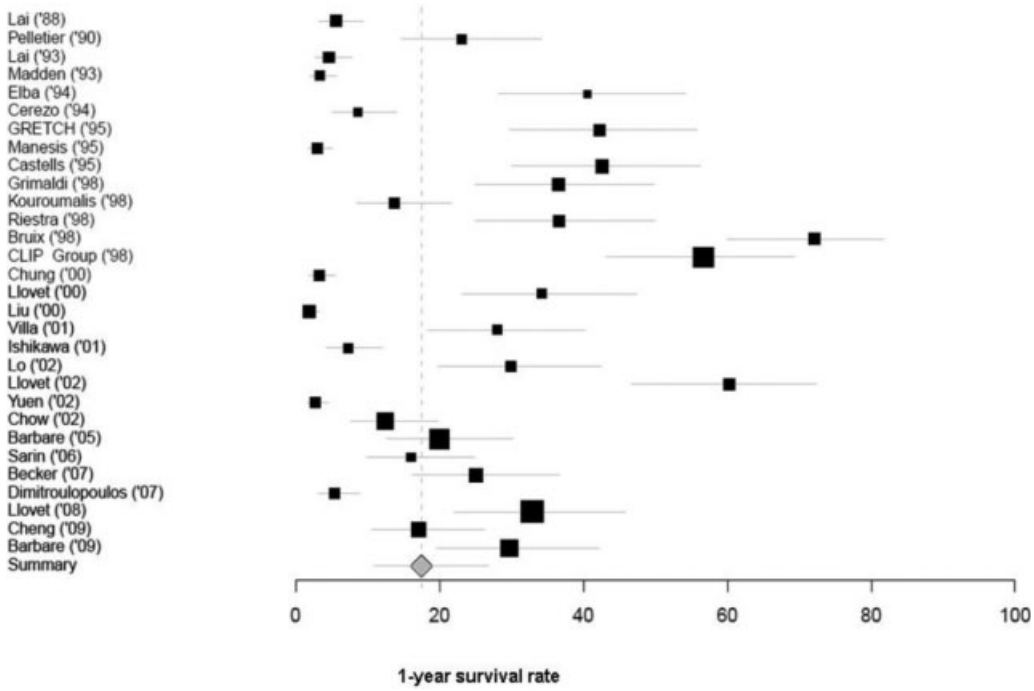

Fig. 2. Forest plot of 1-year survival rates of the placebo or untreated arms of 30 RCTs using random-effects model. Studies are arranged by publication year.

To assess any differences causing heterogeneity within each stratum of relevant study features, we calculated the pooled estimates of the 1-year survival rate within each stratum and evaluated heterogeneity among strata. However, heterogeneity was equally evident in all strata (Supporting Table 4).

The pooled estimate of the 2-year survival rate was 7.3% (95%CI, 3.9%-13%; range, 0-50%). Again, there was a statistically significant heterogeneity among studies ($P < 0.0001$) (Fig. 3).

Subgroup Analyses. Subgroup analyses were performed to evaluate whether the 1-year survival was differ-

Table 2. Predictors of 1-Year Survival Among All Studies

	Outcome (1-Year Survival)				
Study Characteristics	**No. of studies**	**No. of patients**	***β***	**SE**	***P***
Publication year	30	1927	0.03	0.05	0.487
Study validity	30	1927	0.21	0.17	0.228
Study location* (2 versus 1)	30	1927	−2.01	0.52	0.001
Male sex, %	29	1901	−0.06	0.03	0.043
Cause of liver disease					
Alcohol, %	17	1381	−0.01	0.01	0.413
HCV, %	19	1339	0.01	0.01	0.131
HBV, %	24	1577	−0.02	0.01	0.001
ECOG PS 0,† %	12	1126	0.03	0.01	0.001
Albumin, g/dL	15	958	2.34	1.13	0.038
Bilirubin, mg/dL	19	1135	−0.19	0.31	0.533
Prothrombin activity, %	11	582	0.13	0.03	0.001
Presence of ascites, %	10	487	−0.01	0.02	0.569
Tumor stage					
Solitary, %	13	705	−0.01	0.02	0.699
Multinodular/massive, %	13	705	0.01	0.02	0.699
Portal vein thrombosis, %	20	1484	−0.03	0.01	0.001
Child-Pugh class A, %	18	1459	0.02	0.01	0.042
Okuda stage I, %	18	1103	0.06	0.01	0.001

*For study location, 1 corresponds to North American and European studies; 2 to Asia-Pacific studies.

†Eastern Cooperative Oncology Group—performance status.

HCV, hepatitis C virus; HBV, hepatitis B virus; SE, standard error.

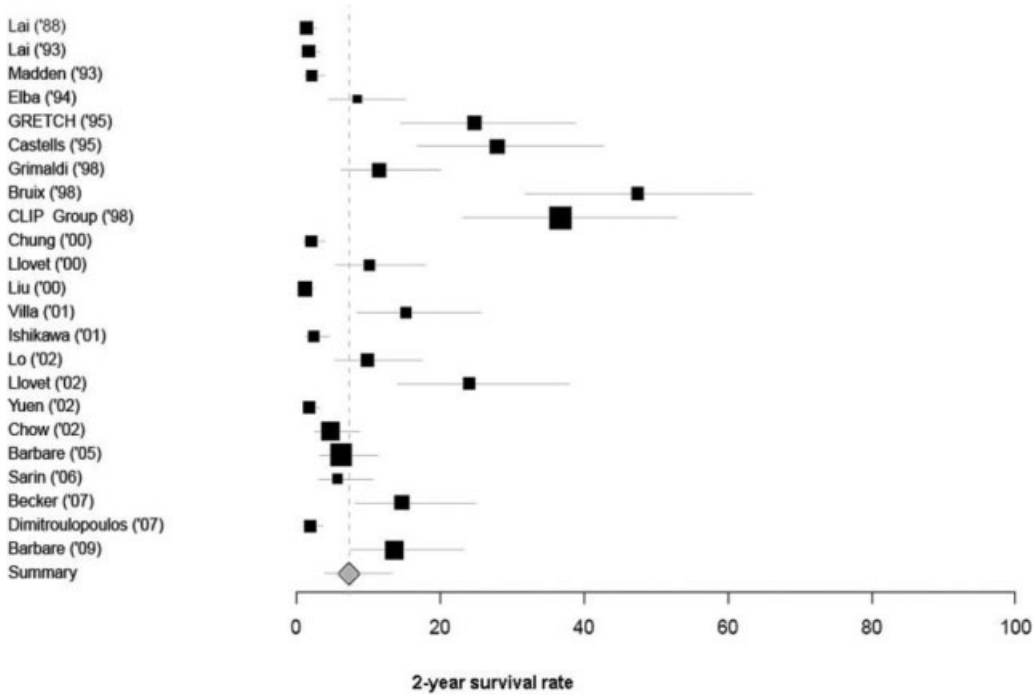

Fig. 3. Forest plot of 2-year survival rates, using random-effects model, in the placebo or untreated arms of 23 RCTs. Studies are arranged by publication year.

ent according to the various BCLC stages. Because BCLC classification was specifically reported only by a minority of studies,[23,28,32,34,35,36] we extrapolated from RCTs that provided information on Child-Pugh class or Okuda stage [9,12,13,15,18-30] so that patients belonging to Child-Pugh class C or to Okuda stage III could be considered BCLC D stage. Thus, according to the BCLC classification, we separated RCTs including only intermediate (B) and advanced (C) BCLC patients (named B+C stage studies) from those that also included patients in the end-stage D (named D stage studies).

The pooled estimate of BCLC B+C stage 1-year survival rate was 34% (95%CI, 22-48; range, 3%-75%). There was a statistically significant heterogeneity among studies, $P < 0.0001$ (Fig. 4A).

The pooled estimate of BCLC B stage 1-year survival rate was 49.6% (95%CI, 32-75; range, 3%-75%). There was a statistically significant heterogeneity among studies, $P < 0.0001$ (Supporting Fig. 1A).

The pooled estimate of BCLC C stage 1-year survival rate was 25% (95%CI, 14-40; range, 3%-63%). There was a statistically significant heterogeneity among studies, $P < 0.0001$ (Supporting Fig. 1B).

The pooled estimate of BCLC D stage 1-year survival rate was 11% (95%CI, 4.7-22; range, 0-57%), and there was a statistically significant heterogeneity among studies, $P < 0.0001$ (Fig. 4B).

We in turn excluded each study to ensure that no single study would be solely responsible for the heterogeneity of any result (so-called robust analysis). In all the robust analyses, heterogeneity among studies was significant. Moreover, in all the sensitivity analyses excluding the 2 RCTs with the highest and the lowest survival rates, heterogeneity was significant.

Regression analysis for the B+C stage studies showed that six variables were associated with an increased 1-year survival rate: studies published before 2000 ($P = 0.001$), low prevalence of alcohol-related disease ($P = 0.016$), high prevalence of HCV-related disease ($P = 0.021$), high percentage of ECOG PS = 0 patients ($P = 0.001$), low percentage of patients with ascites ($P = 0.001$), and high percentage of Okuda stage I patients ($P = 0.001$) (Table 3).

Regression analysis for the D stage studies showed that three variables were associated with an increased 1-year survival rate: North American and European studies ($P = 0.006$), low percentage of HBV-related disease ($P = 0.004$), and low percentage of portal vein thrombosis ($P = 0.01$)

To examine any potential differences in study features, we next calculated pooled estimates of the 1-year survival rate within each stratum and evaluated heterogeneity among strata. However, heterogeneity was equally evident in all strata (Supporting Table 5).

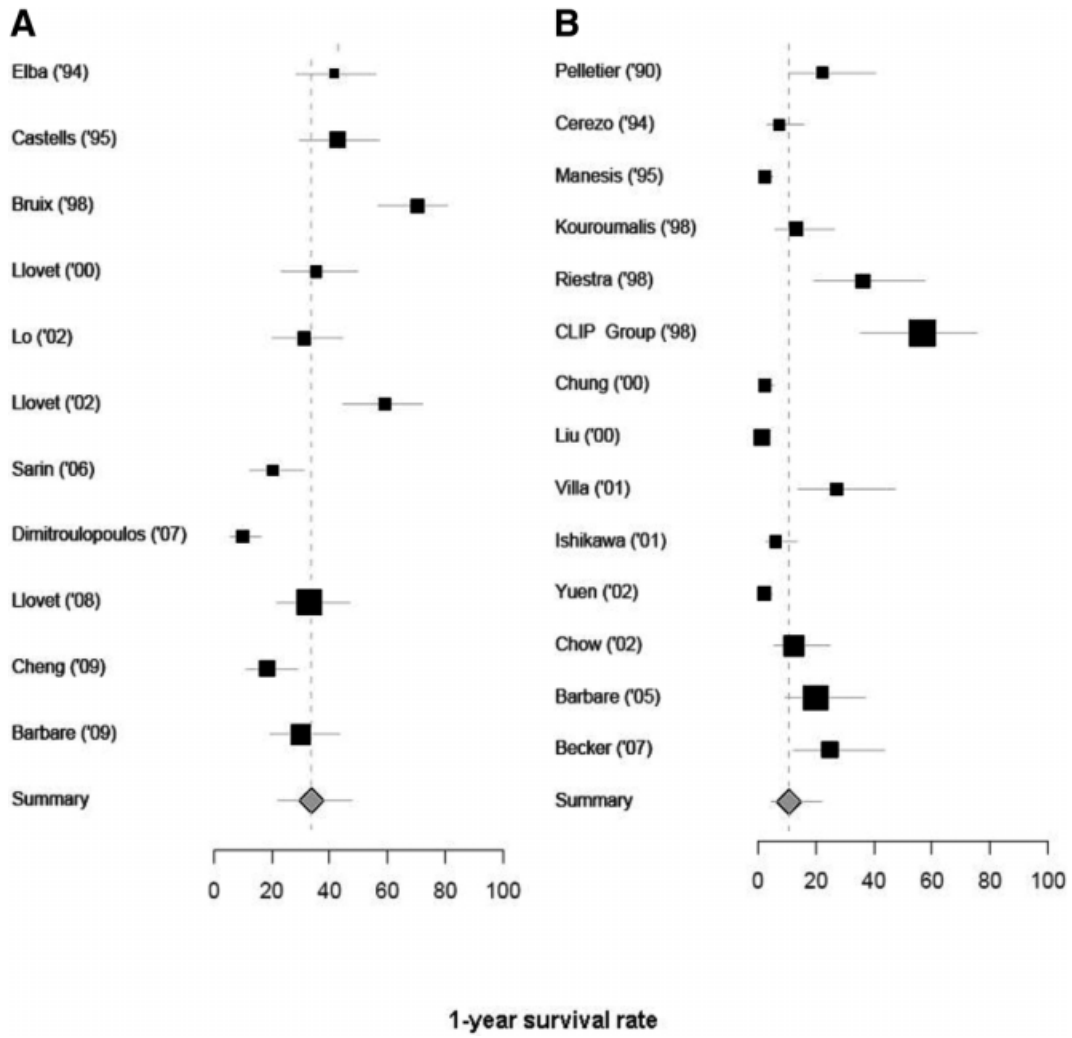

Fig. 4. Forest plot of 1-year survival rates, using random-effects model, of B+C stage studies (A), and Forest plot of 1-year survival rates, using random-effects model, of D stage studies (B) in the placebo or untreated arms. Studies are arranged by publication year.

Publication Bias. The funnel and the Egger publication bias plots for 1-year survival rates are shown in Supporting Fig. 2. The plots and the Egger test for publication bias showed that the risk of having missed or overlooked trials was significant: the *P* value was 0.0003 with the Egger test.

The funnel and the Egger publication bias plots for 2-year survival rates are shown in Supporting Fig. 3. The plots and the Egger test for publication bias showed that the risk of having missed or overlooked trials was significant: the *P* value was 0.003 with the Egger test.

Discussion

The survival rate in the placebo or untreated arm of RCTs of HCC patients may be a reliable measure of the spontaneous course of disease and a basic measure for both calculating sample size and providing a better prognostic stratification in RCTs evaluating new drugs or new multimodal approaches in the palliative setting. Until recently, new agents for patients with advanced HCC (BCLC stage C) were usually compared with either placebo or best supportive care. Recently, sorafenib was shown to significantly improve overall survival in two double-blind phase 3 RCTs,[35,36] although other anti-angiogenic agents are currently being compared alone or in combination. Most investigators and clinicians are now accepting sorafenib as the standard of care, and an expert panel has recommended it as a standard of care control arm for future RCTs of first-line systemic agents,[4,6] if the new agents are detected to have a powerful signal in phase 1 or 2 investigations.[40] As a result, it will be unfeasible to design future trials with an untreated control arm. The 1-year overall survival rate of 34% obtained in this meta-analysis in intermediate/advanced untreated controls can be considered a useful reference value for determining the sample size of future studies and for obtaining indirect

Table 3. Predictors of 1-Year Survival Among B+C Stage Studies

	Outcome (1-Year Survival)				
Study Characteristics	**No. of studies**	**No. of patients**	**β**	**SE**	***P***
Publication year	11	780	−0.08	0.02	0.001
Study validity	11	780	0.03	0.83	0.686
Study location* (2 versus 1)	11	780	−2.92	0.60	0.124
Male sex, %	11	780	−0.01	0.04	0.787
Cause of liver disease					
Alcohol, %	6	605	−0.01	0.01	0.016
HCV, %	8	593	0.02	0.01	0.021
HBV, %	9	632	−0.01	0.01	0.097
ECOG PS 0,† %	8	711	0.03	0.01	0.001
Albumin, g/dL	7	526	−1.43	1.45	0.316
Bilirubin, mg/dL	7	526	0.03	0.61	0.960
Prothrombin activity, %	4	165	−0.07	0.10	0.473
Presence of ascites, %	5	184	−0.03	0.01	0.001
Tumor stage					
Solitary, %	6	234	0.06	0.03	0.102
Multinodular/massive, %	6	234	−0.06	0.03	0.102
Portal vein thrombosis, %	9	750	−0.01	0.01	0.536
Child-Pugh class A, %	7	611	0.01	0.01	0.224
Okuda stage I, %	7	234	0.03	0.01	0.001

*Study location 1 corresponds to North American and European studies; 2 to Asian-Pacific studies.
†Eastern Cooperative Oncology Group—performance status.
HCV, hepatitis C virus; HBV, hepatitis B virus; SE, standard error.

comparisons among different trials estimating drug efficacy. The 1-year survival observed in the control arm of the SHARP RCT[35] was comparable (35%) to that estimated in this meta-analysis, but much higher than that observed in the Asian Pacific sorafenib study (17.5%).[36] While underlining the external validity of the results of this meta-analysis, this difference prompts a specific warning against generalizing results to all patient settings. Indirect comparison among trials assessing different drugs is to be discouraged because the different estimates of drug efficacy could be entirely related to the different baseline risks of the populations studied.

This meta-analysis of aggregated data from the placebo or untreated arms of 30 RCTs of palliative treatment in HCC clearly demonstrates that the heterogeneity of 1-year and 2-year survival is a common feature of these studies. There were significant differences between the studies, with observed survival rates ranging from 0%-75% at 1 year and from 0%-50% at 2 years. In our analysis, the pooled survival rate estimated by the random effects model was 17.5% at 1 year and 6.9% at 2 years. Although the number of included patients in the available studies was large, suggesting robustness of the estimated survival rates, the confidence intervals of the estimates at 1 year (95%CI, 11%-27%) and 2 years (95%CI, 3.5%-13%) remain wide. This inconsistency among RCTs of palliative treatments for HCC is not surprising if one considers all potential biases in the selection of patients with different demographic and clinical characteristics, different timing of referral and diagnostic criteria, true differences in case mix, cause, severity of the underlying cirrhosis, and tumor burden in terms of number and size of HCC nodules and of presence of macrovascular invasion or extrahepatic spread. An attempt to explain the wide variability in the natural course of eligible to palliative treatment of HCC was made by stratifying studies according to variables that described the patients studied and the study design features. However, a significant heterogeneity in survival among RCTs remained even after stratifying patients and study features, and heterogeneity in the survival rates persisted even in the stratum of high-quality studies, implying that this was not explained by study validity alone. Therefore, the evaluation of the methodological quality did not seem to influence the variability of the assessed outcome, because of the mean high quality of the studies (75% of these RCTs were high-quality studies). Heterogeneity of these rates among RCTs may reflect both inclusion of patients with different stages of disease and variability in the molecular characteristics and biological behavior of the tumor, which are not included in any of the currently available staging systems.

In our analysis, when studies were separated according to the BCLC stage, the 1-year survival was much higher in RCTs including only BCLC B or C patients (34%) than in those also including BCLC D patients (11%). This provides further evidence that the BCLC staging system has a good discriminative capacity for prognosticating

survival not only in patients with early HCC[41] but also in those with intermediate/advanced HCC. However, data on direct BCLC stage were lacking in several trials, and caution must be exercised when interpreting results from subgroup exploratory analyses. We found by meta-regression analysis that ECOG performance status and portal vein thrombosis are robust predictors of death in untreated patients as reported by Tandon and Garcia-Tsao[42] in a recent systematic review of 72 studies on prognostic indicators in HCC. These two individual parameters, both included in the BCLC classification, may explain in large part why this staging system provides accurate information on prognosis in the setting of HCC.

A remarkable difference in survival was found between occidental (North American and European) and oriental (Asia-Pacific) studies. The high prevalence of HBV-related liver disease found in Asia-Pacific countries may account for the different survival observed between oriental and occidental studies in which a high prevalence of HCV-related liver disease was observed. However, the potential role of HBV as a prognostic factor disappears when Asian-Pacific location of the studies and HBV-related disease were both included in a multivariate model.

The survival differences between occidental and Asian studies may be explained by differences in the distribution of other risk and prognostic factors. In fact, the worse survival observed in the Asia-Pacific study[36] could be explained by the higher prevalence of patients in advanced stage than in the SHARP study.[35]

Subgroup analysis of RCTs including only patients in BCLC intermediate (B) or advanced (C) stages provides further evidence that clinically detected ascites is strongly linked to poor survival. The prognostic value of ascites determines the importance of subclassifying the intermediate stage in relation to the therapeutic option. We believe that the benefits of transarterial chemoembolization (TACE) may outweigh the risks for BCLC B patients with Child-Pugh class A or B cirrhosis without ascites, whereas the risks may outweigh the benefits for BCLC B patients with Child-Pugh class A or B cirrhosis with ascites. Recently, in the subgroup analysis of the SHARP RCT,[43] based on BCLC stages, a trend for overall survival benefit was found in patients with BCLC B stage disease treated with sorafenib. However, the small sample size may have affected the study's ability to achieve statistical significance. Further large studies of BCLC B intermediate stage that stratify Child-Pugh class B patients according to ascites are needed to avoid overtreatment by TACE and to confirm the benefit of sorafenib in patients with BCLC B stage.

We found a significant difference in the pooled survival rates among the strata. In particular, studies published before 2000 showed a 1-year survival rate higher than studies published after 2000, perhaps indicating the inclusion of a high number of patients in advanced stages in recent years.

The meta-analysis was performed using summary data, and more detailed comparisons of survival could be made with a meta-analysis of individual patient data. However, it may not always be possible to obtain individual patient data from all the studies, raising the issue that the studies for which data are available may represent a biased subset of the available studies. As with all meta-analyses, the methodology of the current study results in a potential limitation of the generalizability of its results to new populations and settings, because these were obtained in small RCTs performed in highly specialized centers. Furthermore, our study is limited by the patient-level covariates reported in each of the studies, which are not consistent across trials, representing a further source of heterogeneity.

Lack of data on other potential confounders, such as microscopic vascular invasion, histological grading, and gene profiling, also could affect the accuracy of the results.

Finally, we should be especially concerned about publication bias in settings in which many small studies are being conducted. The risk of having missed or overlooked trials in the setting of studies assessing mortality in patients with HCC was substantial. Therefore, it is likely that small studies with a low rate of mortality or small drug (or new treatment) effect remain preferentially unpublished. However, the single large placebo-controlled trial,[44] still unpublished as a full paper, reported 1-year and 2-year survival rates similar to that given in this meta-analysis.

In untreated HCC patients, the available evidence is sufficient to conclude that (1) the 1-year and 2-year survival is extremely variable, and no single patient or study characteristic can explain this heterogeneity; (2) bad performance status, Child-Pugh B-C classes, and presence of portal vein thrombosis are associated with a worse prognosis; and (3) the presence of ascites is associated with poor survival in intermediate/advanced BCLC stages.

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