Outcomes of surgical resection and transarterial chemoembolization in elderly patients with hepatocellular carcinoma: A meta-analysis‡

Ang RCK
Ahorro JS
Bustamante CA
Panlilio MTT

[1]*Division of Internal Medicine*
National Kidney and
Transplant Institute
East Avenue, Quezon City
1100 Philippines

Correspondence:
Dr. Roy Christopher K. Ang
roy3krypton@gmail.com

Abstract

Significance: There is controversy on management options for early to intermediate hepatocellular carcinoma (HCC) in elderly patients due to concerns about safety and efficacy. This meta-analysis aimed to evaluate the overall survival (OS) and treatment complications of surgical resection (SR) and transarterial chemoembolization (TACE) in elderly compared to non-elderly HCC patients. **Methodology:** A systematic search in MEDLINE, Cochrane Library, Scopus, and ScienceDirect from inception up to October 2021 was made to identify comparative studies with outcomes of SR and TACE in elderly and non-elderly patients with HCC. **Results:** Thirty-nine studies were included. The elderly group had more comorbidities than the non-elderly group. Among those who underwent SR, there were more postoperative complications in the elderly (OR 1.16; 95%CI 1.03, 1.39, p = 0.02). In terms of OS, there were similar outcomes in the first year (OR 0.93; 95%CI 0.71, 1.21, p = 0.59), third year (OR 0.96; 95%CI 0.85, 1.07, p = 0.44), and fifth year (OR 0.82; 95%CI 0.68,1.00, p = 0.05). Among patients who underwent TACE, there was a similar prevalence of post-procedure complications (OR 0.95; 95%CI 0.71, 1.26, p = 0.72). Survival outcomes were also similar between the elderly and non-elderly group in the first year (OR 1.21; 95%CI 0.78, 1.88, p = 0.39), third year (OR 1.21; 95%CI 0.79, 1.85, p = 0.37), and fifth year (OR 0.70; 95%CI 0.40, 1.23, p = 0.22). **Conclusion:** Long-term outcomes of SR and TACE are similar between elderly and non-elderly patients with HCC. Hence, age alone should not disqualify HCC patients from receiving curative resection, or even locoregional therapies such as TACE.

Keywords: hepatocellular carcinoma, elderly, transarterial chemoembolization, surgical resection

‡ This paper was presented at the following conferences: (a) Oral presentation at the Philippine Liver Meeting 2022, January 27 to 28, 2022, won first place, meta-analysis category; (b) Oral Presentation at the Joint Annual Convention of the Tripartite Philippine Society of Gastroenterology, Philippine Society of Gastroenterology, Philippine Society of Digestive Endoscopy and Hepatology Society of the Philippines, March 11 to 12, 18 to 19, 2022, won second place, meta-analysis category; (c) E-poster presentation at the 31st Conference of Asian Pacific Association for the Study of the Liver, Coex, Seoul, South Korea, March 30 to April 3, 2022, Travel Grant Awardee; (d) Free paper presentation at the 6th Korea Digestive Disease Week, Grand Hyatt Incheon, South Korea, December 1 to 3, 2022.

Hepatocellular carcinoma (HCC) accounts for 75% of liver cancers, which is the seventh most common cancer in the world. The highest incidence rates of hepatocellular carcinoma are in Asia and Africa.[1] In the Philippines, it ranks as the fourth most common cancer per 100,000 persons in 2005 and is the second most common cause of cancer death among all cancer types.[2]

The risk of developing HCC is age dependent.[3] Its peak incidence in most countries is $\geq$75 years[4], while in the Philippines, the reported mean age of diagnosis is at 60 years old.[2] It is expected that the number of elderly with HCC will increase due to increasing number of non-hepatitis causes of HCC and the effect of antivirals in delaying development of HCC in patients with chronic hepatitis.[3]

In the 2018 guidelines on the management of HCC, the American Association for the Study of Liver Diseases (AASLD) divided therapeutic options into curative and non-curative interventions. Curative therapies include surgical resection (SR), orthotopic liver transplantation, and ablative techniques such as thermal ablation. On the other hand, non-curative therapies include transarterial chemoembolization (TACE), transarterial radio embolization (TARE), stereotactic body radiation therapy (SBRT) and systemic chemotherapy, all of which attempt to prolong survival by slowing tumor progression.[5]

Age-specific treatment guidelines in HCC are lacking and current literature suggests varying outcomes. Because aging is associated with increasing comorbidities, decreased liver mass, and hepatic blood flow, treatment allocation for the elderly remains controversial.[6] The cut-off age for the elderly is conventionally defined as 65 years or even older[7], with most comparative studies using the age cut-off of 70 years. It has been shown that elderly patients with HCC are more likely to choose percutaneous procedures than surgical resection and TACE.[8]

Most recent studies report comparable outcomes between elderly and non-elderly patients, as supported by the meta-analysis of Hung et al. in 2015.[9] However, conflicting data still exist, raising concerns about prognosis and tolerability of the elderly to more aggressive treatment modalities. Most studies report similar survival rates for both elderly and non-elderly patients. This is in contrast with other studies, including that of Hirokawa et al.,[10,] Liu et al.,[11] and Santambrogio et al.,[12] which showed worse outcomes in the elderly after surgical resection. On the other hand, outcomes were comparable for post-TACE patients. One particular study by Yau et al. however showed better outcomes in the elderly.[13]

Conflicting evidence despite the large number of studies in the background of an aging population[14] warrants periodic assessment of therapeutic outcomes. This meta-analysis therefore aimed to compare the outcomes of elderly and non-elderly patients with hepatocellular carcinoma who underwent surgical resection and transarterial chemoembolization. It aimed to determine if there was no significant difference in overall survival, disease-free survival, postoperative complications, and postoperative mortality between elderly and non-elderly HCC patients who underwent SR. Furthermore, it aimed to determine if there was no significant difference in the OS and post-procedure complications between elderly and non-elderly HCC patients who underwent TACE.

Materials and Methods

Database Search

A systematic search for surgical resection and TACE with comparative outcomes in elderly vs. non-elderly with hepatocellular carcinoma was done in MEDLINE, Cochrane Library, Scopus, and ScienceDirect from inception up to October 2021 (**Table 1**). Reference lists from previous meta-analysis and systematic reviews were also examined.

Search terms included the following: hepatocellular carcinoma, elderly or aged, surgical resection, transarterial chemoembolization or TACE, and survival.

Table 1. Database sources

Source	Search Terms
Medline	(((Hepatocellular OR Liver) AND (cancer OR carcinoma)) OR hepatoma) AND ("aged"[MeSH Terms] OR elder* OR old) AND (young OR non-elderly OR "non elderly") AND ("surgical outcomes" OR resection OR "locoregional therapy" OR TACE OR "transarterial chemoembolization") AND (survival OR progression)). Filters applied to human studies and English language studies.
Cochrane Library	(Hepatocellular Carcinoma) OR (Liver AND neoplasm OR tumor) AND (Aged OR Old age OR elder) AND (resection) OR
Scopus	(Hepatocellular OR Liver) AND (Cancer OR Carcinoma) AND (elder OR old) AND (resection OR hepatectomy OR TACE OR transarterial chemoembolization) AND (survival OR progression) OR
Science-Direct	(((Hepatocellular OR Liver) AND (cancer OR carcinoma)) AND (elder OR old) AND (resection OR TACE OR "transarterial chemoembolization")

Inclusion Criteria

Initially identified were all published studies that were observational, either prospective or retrospective, comparing the outcomes of surgical resection and/or transarterial chemoembolization in elderly and non-elderly hepatocellular carcinoma patients.

Exclusion Criteria

Studies that had multiple age cut-offs, those that included non-HCC liver tumors, and ten patients or less were excluded in the meta-analysis.

Definitions

"Elderly" was defined as more than 65 years of age. Other demographic and clinical characteristics were reviewed. Studies with cirrhosis diagnosed on the basis of clinical, radiographic, or surgical biopsy, were identified. The presence of Hepatitis B virus (HBV) and Hepatitis C (HCV) virus infection, as determined by HBsAg positivity and Anti-HCV antibody or HCV RNA positivity, respectively, were also identified. The prevalence of comorbidities, classified as cardiovascular (CV), pulmonary/respiratory, renal comorbidities, or diabetes mellitus, was identified. The Charlson comorbidity index, if reported, was also included in the meta-analysis. Treatment complications and postoperative mortality were those that occurred within the same hospitalization or 30 days from surgical resection or transarterial chemoembolization. For studies that defined postoperative complications based on the Clavien-Dindo classification[15], Class III and above complications were considered. Overall survival and disease-free survival in the first, third, and fifth years were included in the outcomes.

Data Extraction and Analysis

Three investigators (Ang, Ahorro, and Bustamante) independently screened studies that met the inclusion criteria and none of the exclusion criteria. Data was extracted independently by three independent investigators, and encoded in a prepared table that included study characteristics, demographic and clinical characteristics, and outcomes. Data reported as percentage were calculated as frequency. For studies that performed propensity score matching analysis, post-propensity data was extracted. Issues encountered were resolved by agreement of at least two investigators.

Statistical Analysis

Chi-square test was used to compare clinical and demographic characteristics of elderly and non-elderly patients, with a p value of less than 0.05 considered statistically significant. The meta-analysis was performed using Revman 5.4.1. Outcomes were treated as binary.

Odds ratios and 95% confidence intervals were computed using available post-propensity data for each of the outcomes. Heterogeneity was assessed by the Cochrane Q test, with significant heterogeneity if value exceeded 30%. Both fixed and random effect models, using Mantel-Haenszel, were calculated. Random effect model was used for significant heterogeneity, while fixed effect model was used if no significant heterogeneity was identified. A p-value of less than 0.05 was considered statistically significant. Publication bias was analyzed using funnel plot.

Results

Included Studies

A total of 2,904 references were identified and thirty-nine studies were included in the meta-analysis **(Figure 1)**. Thirty-six studies were included in the SR group, while six studies were included in the TACE group. Three studies included both SR and TACE groups. **Table 2** shows the characteristics of the studies included in the meta-analysis. The largest study included in the meta-analysis was that of Xing, et al.[46], which compared 259 elderly patients with 1,875 non-elderly patients who underwent curative-intent hepatectomy for hepatocellular carcinoma.

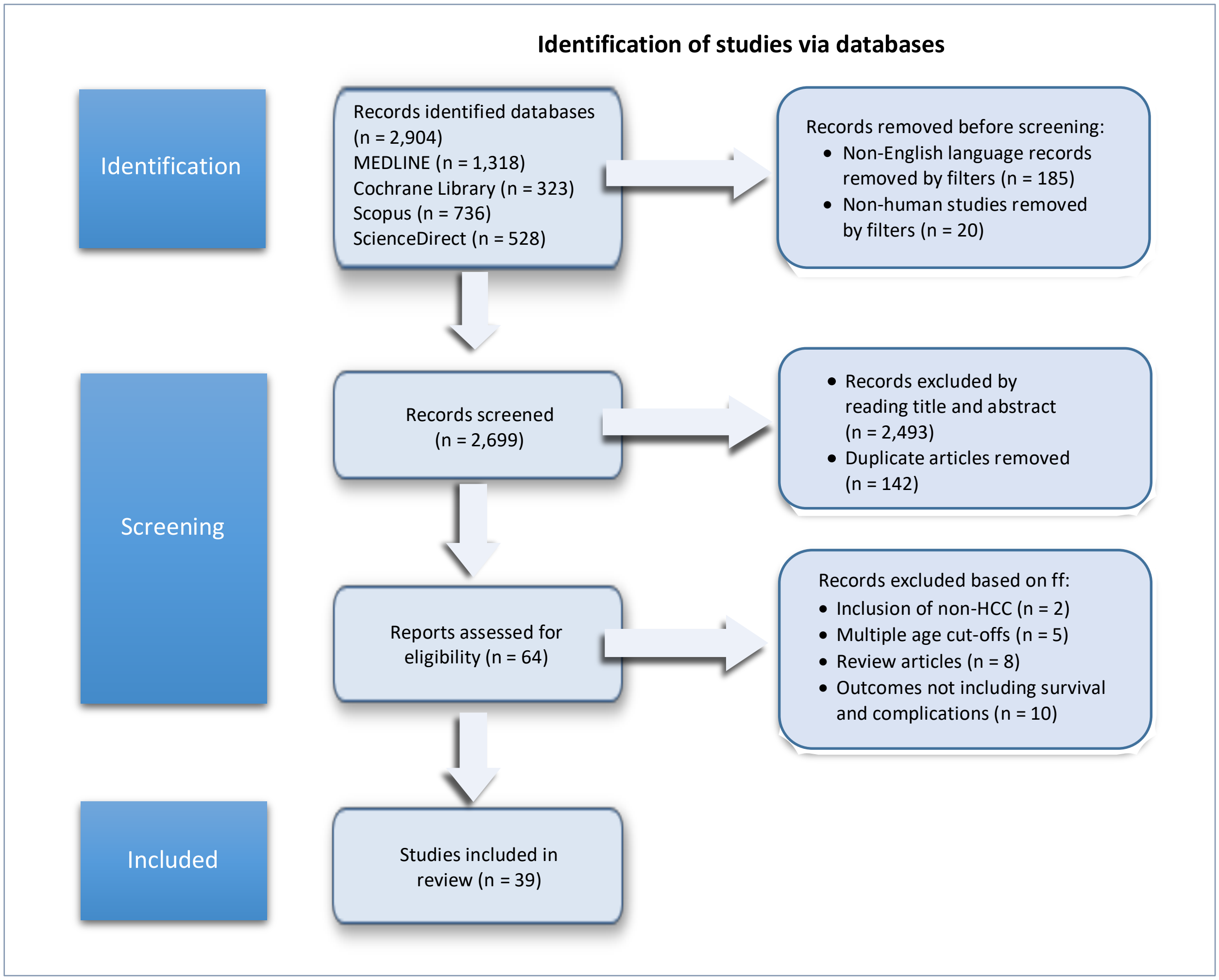

Figure 1. Selection process of meta-analyses. HCC, hepatocellular carcinoma

Table 2. Characteristics of included studies

Study	Country/Region	Enrollment Period	Design	Age cut-off	Treatment (SR/TACE)
Poon 1999[16]	Hong Kong	1989-1997	Prospective	70	SR/TACE
Wu 1999[17]	Taiwan	1991-1997	Retrospective	80	SR
Yau 2009(13)	Hong Kong	1989-2006	Prospective	70	SR/TACE
Hanazaki 2001[18]	USA	1983-1997	Retrospective	70	SR
Ferrero 2005[19]	Italy	1985-2003	Retrospective	70	SR
Zhou 2006[20]	China	1995-2002	Retrospective	65	SR
Kondo 2008[21]	Japan	1990-2007	Retrospective	70	SR
Huang 2009[22]	China	1983-2006	Retrospective	70	SR
Kaibori 2009[23]	Japan	1992-2007	Retrospective	70	SR
Oishi 2009[24]	Japan	1990-2006	Prospective	75	SR
Portolani 2011[25]	Italy	1992-2009	Retrospective	70	SR
Mirici-Cappa 2010[8]	Italy	1987-2004	Retrospective	70	SR/TACE
Lee 2012[26]	Korea	2000-2010	Retrospective	70	SR
Yamada 2012[27]	Japan	1992-2009	Retrospective	80	SR
Faber 2013[28]	Germany	2000-2010	Prospective	70	SR
Hirokawa 2013[10]	Japan	2000-2011	Retrospective	70	SR
Ide 2013[29]	Japan	2000-2010	Retrospective	75	SR
Nishikawa 2013[30]	Japan	2003-2012	Prospective	75	TACE
Taniai 2013[31]	Japan	1990-2010	Retrospective	75	SR
Ueno 2013[32]	Japan	2001-2010	Retrospective	75	SR
Liu 2014[11]	Taiwan	2002-2013	Prospective	75	SR/TACE
Mori 2014[33]	Japan	2000-2012	Retrospective	70	SR
Nozawa 2014[34]	Japan	2000-2010	Retrospective	70	SR
Wang 2014[35]	China	2007-2012	Retrospective	70	SR
Wang H 2014[36]	China	2009-2013	Retrospective	65	SR
Kim 2015[37]	Korea	2006-2010	Retrospective	70	SR
Kishida 2015[38]	Japan	2005-2010	Retrospective	75	SR
Motoyama 2015[39]	Japan	1990-2013	Retrospective	75	SR
Sato 2015[40]	Japan	2000-2010	Retrospective	75	SR
Santambrogio 2017[12]	Italy	1998-2015	Prospective	75	SR
Famularo 2018[41]	Italy	2005-2015	Prospective	75	SR
Hsu 2018[42]	Taiwan	2003-2014	Prospective	70	SR
Okamura 2018[43]	Japan	2002-2014	Retrospective	75	SR
Yu 2018[44]	China	1998-2013	Retrospective	70	SR
Wu 2019[45]	Taiwan	1992-2016	Retrospective	85	SR
Xing 2019[46]	China	2003-2016	Retrospective	70	SR
Chen 2020[47]	China	2006-2016	Retrospective	65	SR
Mosconi 2020[48]	Italy	2011-2016	Retrospective	70	TACE
Shin 2020[49]	Korea	2012-2018	Retrospective	70	SR

Surgical Resection

A total of 16,100 patients who underwent surgical resection for hepatocellular carcinoma were included. **Tables 3** and **4** show the clinical and demographic characteristics of all patients. There were differences in the sex distribution, hepatitis B status, and hepatitis C status. More elderly patients had hepatitis C, while more non-elderly patients had hepatitis B. Similar to the largest study included, this study also showed a greater number of comorbidities and cirrhosis in the elderly. But the studies included did not specify how cirrhosis was diagnosed. Comorbidities identified were cardiovascular (CV), pulmonary, renal, or diabetes mellitus. Only the study of Famularo, et al.[41] included information about the Charlson comorbidity index. **Table 5** shows the outcomes of surgical resection in the included studies.

Table 3. Demographic characteristics, Child Pugh status, and prevalence of viral hepatitis in patients who underwent surgical resection

Study	Elderly n	Non-Elderly n	Male $p < 0.001$		Child Pugh A $p = 0.713$		Hepatitis B $p < 0.001$		Hepatitis C $p < 0.001$	
			Elderly	Non-Elderly	Elderly	Non-Elderly	Elderly	Non-Elderly	Elderly	Non-Elderly
Poon 1999[16]	31	299	21	255	30	285	16	257	N/A	N/A
Wu 1999[17]	21	239	19	190	16	194	6	140	N/A	N/A
Hanazaki 2001[18]	103	283	71	222	76	226	19	67	57	115
Ferrero 2005[19]	64	177	47	145	54	138	7	38	39	69
Zhou 2006[20]	54	125	48	107	46	119	32	106	N/A	N/A
Kondo 2008[21]	109	219	79	159	99	197	11	79	57	89
Huang 2009[22]	67	268	68	222	63	257	44	238	5	3
Kaibori 2009[23]	155	333	119	269	139	302	15	67	111	231
Oishi 2009[24]	64	502	48	381	59	427	1	119	45	330
Portolani 2011[25]	175	276	126	227	163	253	30	85	79	88
Mirici-Cappa 2010[8]	43	142	32	116	40	123	3	21	24	66
Lee 2012[26]	61	90	48	75	N/A	N/A	35	83	11	2
Yamada 2012[27]	11	267	6	205	9	245	4	73	6	154
Faber 2013[28]	63	78	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hirokawa 2013[10]	100	120	69	99	88	98	N/A	N/A	68	60
Ide 2013[29]	64	192	43	157	57	168	8	42	44	125
Taniai 2013[31]	63	353	39	271	56	265	N/A	N/A	N/A	N/A
Ueno 2013[32]	66	186	43	151	60	169	33	186	37	98
Liu 2014[11]	129	730	107	571	119	694	493	730	46	164
Mori 2014[33]	64	131	41	106	50	93	N/A	N/A	53	94
Nozawa 2014[34]	172	239	125	197	N/A	N/A	67	239	121	115
Wang 2014[35]	56	152	40	120	48	122	150	152	2	2
Wang H 2014[36]	207	1336	166	1128	N/A	N/A	1127	1336	N/A	N/A
Kim 2015[37]	60	219	46	168	N/A	N/A	140	219	11	17
Kishida 2015[38]	22	82	20	66	2	81	25	82	12	35
Motoyama 2015[39]	113	499	80	381	107	469	115	499	75	280
Sato 2015[40]	34	195	25	155	25	162	49	195	20	99
Santambrogio 2017[12]	53	115	30	89	53	115	20	115	38	80
Famularo 2018[41]	92	92	41	23	85	88	17	92	49	45
Hsu 2018[42]	79	178	62	146	73	159	125	178	16	31
Okamura 2018[43]	111	310	90	252	109	300	76	310	46	141
Yu 2018[44]	23	58	21	46	21	48	37	58	-	-
Wu 2019[45]	31	1858	25	1421	27	1612	873	1858	13	590
Xing 2019[46]	259	1875	223	1644	249	1696	1682	1875	8	71
Chen 2020[47]	92	738	73	654	84	659	672	738	2	5
Shin 2020[49]	49	184	41	143	N/A	N/A	N/A	N/A	N/A	N/A

N/A: no data reported

Table 4. Prevalence of cirrhosis and comorbidities in patients who underwent surgical resection

			Cirrhosis $p < 0.001$		CV Comorbidity $p < 0.001$		Renal Comorbidity $p < 0.001$		Diabetes Mellitus $p < 0.001$		Respiratory Comorbidity $p < 0.001$	
Study	**Elderly**	**Non-Elderly**	**Elderly** n	**Non-Elderly**	**Elderly**	**Non-Elderly**	**Elderly**	**Non-Elderly**	**Elderly**	**Non-Elderly**	**Elderly**	**Non-Elderly**
Poon 1999[16]	31	299	8	146	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wu 1999[17]	21	239	17	186	6	13	0	3	3	13	3	2
Hanazaki 2001[18]	103	283	47	155	25	31	N/A	N/A	32	24	20	21
Ferrero 2005[19]	64	177	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Zhou 2006[20]	54	125	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kondo 2008[21]	109	219	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Huang 2009[22]	67	268	52	217	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kaibori 2009[23]	155	333	56	140	60	53	7	2	36	22	25	14
Oishi 2009[24]	64	502	20	330	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Portolani 2011[25]	175	276	113	182	68	75	12	13	47	73	37	35
Mirici-Cappa 2010[8]	43	142	37	133	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lee 2012[26]	61	90	39	29	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yamada 2012[27]	11	267	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Faber 2013[28]	63	78	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hirokawa 2013[10]	100	120	49	69	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ide 2013[29]	64	192	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Taniai 2013[31]	63	353	28	185	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ueno 2013[32]	66	186	30	107	11	7	3	6	40	81	10	15
Liu 2014[11]	129	730	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A
Mori 2014[33]	64	131	N/A	N/A	41	40	N/A	N/A	9	N/A		N/A
Nozawa 2014[34]	172	239	N/A	N/A	13	9	5	4	65	66	13	9
Wang 2014[35]	56	152	N/A	N/A	6	6	N/A	N/A	4	4	4	8
Wang H 2014[36]	207	1336	N/A	N/A	14	28	6	21	39	78	22	25
Kim 2015[37]	60	219	18	78	N/A	N/A	N/A	N/A	15	30	N/A	N/A
Kishida 2015[38]	22	82	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Motoyama 2015[39]	113	499	36	208	16	35	N/A	N/A	21	122	14	21
Sato 2015[40]	34	195	11	64	8	7	N/A	N/A	4	34	2	3
Santambrogio 2017[1	53	115	N/A	N/A	N/A	N/A	N/A	N/A	16	30	N/A	N/A
Famularo 2018[41]	92	92	65	65	20	7	4	2	21	19	15	5
Hsu 2018[42]	79	178	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Okamura 2018[43]	111	310	N/A	N/A	N/A	N/A	N/A	N/A	40	95	N/A	N/A
Yu 2018[44]	23	58	4	12	11	7	N/A	N/A	2	4	3	1
Wu 2019[45]	31	1858	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Xing 2019[46]	259	1875	169	1359	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chen 2020[47]	92	738	59	534	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Shin 2020[49]	49	184	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

N/A: no data reported; CV comorbidity: cardiovascular comorbidity

Table 5. Demographic characteristics, Child Pugh status, and prevalence of viral hepatitis in patients who underwent transarterial chemoembolization.

Study	Elderly	Non-Elderly	Male $p < 0.001$		Child Pugh A $p < 0.001$		Hepatitis B $p < 0.001$		Hepatitis C $p < 0.001$	
			Elderly	Non-Elderly	Elderly	Non-Elderly	Elderly	Non-Elderly	Elderly	Non-Elderly
Poon 1999[16]	67	317	54	272	52	262	N/A	N/A	N/A	N/A
Yau 2009[13]	197	843	143	715	165	674	112	429	21	43
Mirici-Cappa 2010[8]	158	396	117	301	113	234	19	44	94	202
Nishikawa 2013 [30]	271	604	222	446	233	453	99	316	94	210
Liu 2014[11]	66	84	34	63	53	52	0	13	47	49
Mosconi 2020[48]	80	145	45	126	69	86	5	19	53	72

N/A: no data reported; CV comorbidity: cardiovascular comorbidity

Overall Survival

There were 17 studies that reported one-year OS, 21 studies that reported three-year OS, and 29 studies that reported five-year OS. Significant heterogeneity was noted in the studies that reported one-year and five-year OS. There was no significant difference in the one-year OS (OR 0.93; 95% CI 0.71, 1.21, $p = 0.59$), three-year OS (OR 0.96; 95% CI 0.85, 1.07, $p = 0.44$), and five-year OS (OR 0.82; 95% CI 0.68, 1.00, $p = 0.05$) between elderly and non-elderly patients **(Figure 2)**.

Disease Free Survival (DFS)

There were 13 studies that reported one-year DFS, 20 studies that reported three-year DFS, and 21 studies that reported five-year DFS. Significant heterogeneity was noted in the studies that reported one-year, three-year, and five-year DFS. There was no significant difference in the one-year DFS (OR 1.15; 95% CI 0.92, 1.45, $p = 0.22$), three-year DFS (OR 1.12; 95% CI, 0.91, 1.39, $p = 0.27$), and one-year DFS (OR 1.06; 95% CI 0.87, 1.28, $p = 0.57$) between elderly and non-elderly patients **(Figure 3).**

Postoperative Complications

There were 28 studies that reported postoperative complications. There was no significant heterogeneity in the studies included. Elderly patients had significantly higher rates of postoperative complications than non-elderly patients (OR 1.16; 95% CI 1.03, 1.30, $p = 0.02$) **(Figure 4).** Common postoperative complications identified include pleural effusion, intra-abdominal infections, and pneumonia.

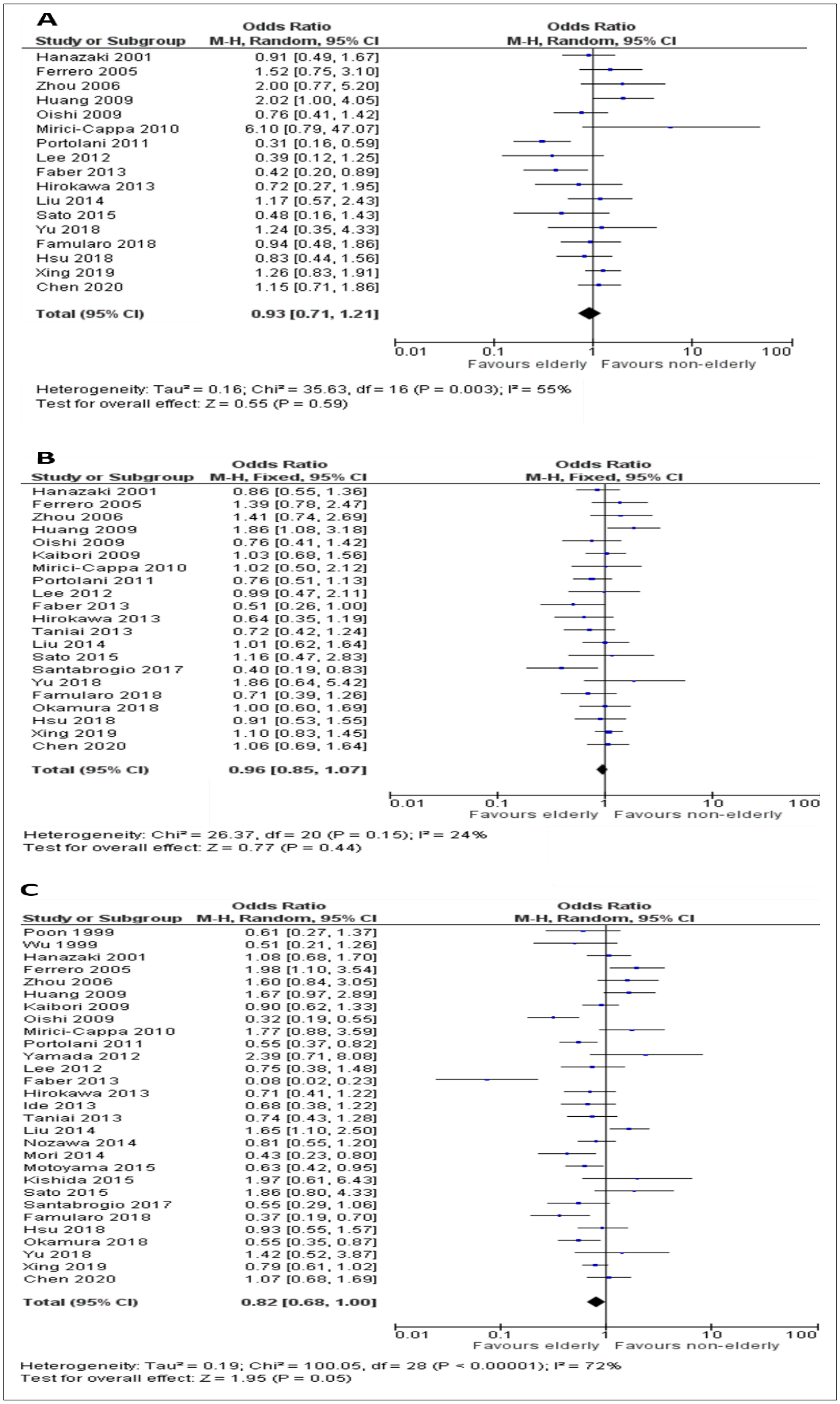

Figure 2. Overall survival (OS) of elderly vs. non-elderly HCC patients who underwent surgical resection. **A.** One-year OS. **B.** Three-year OS. **C.** Five-year OS.

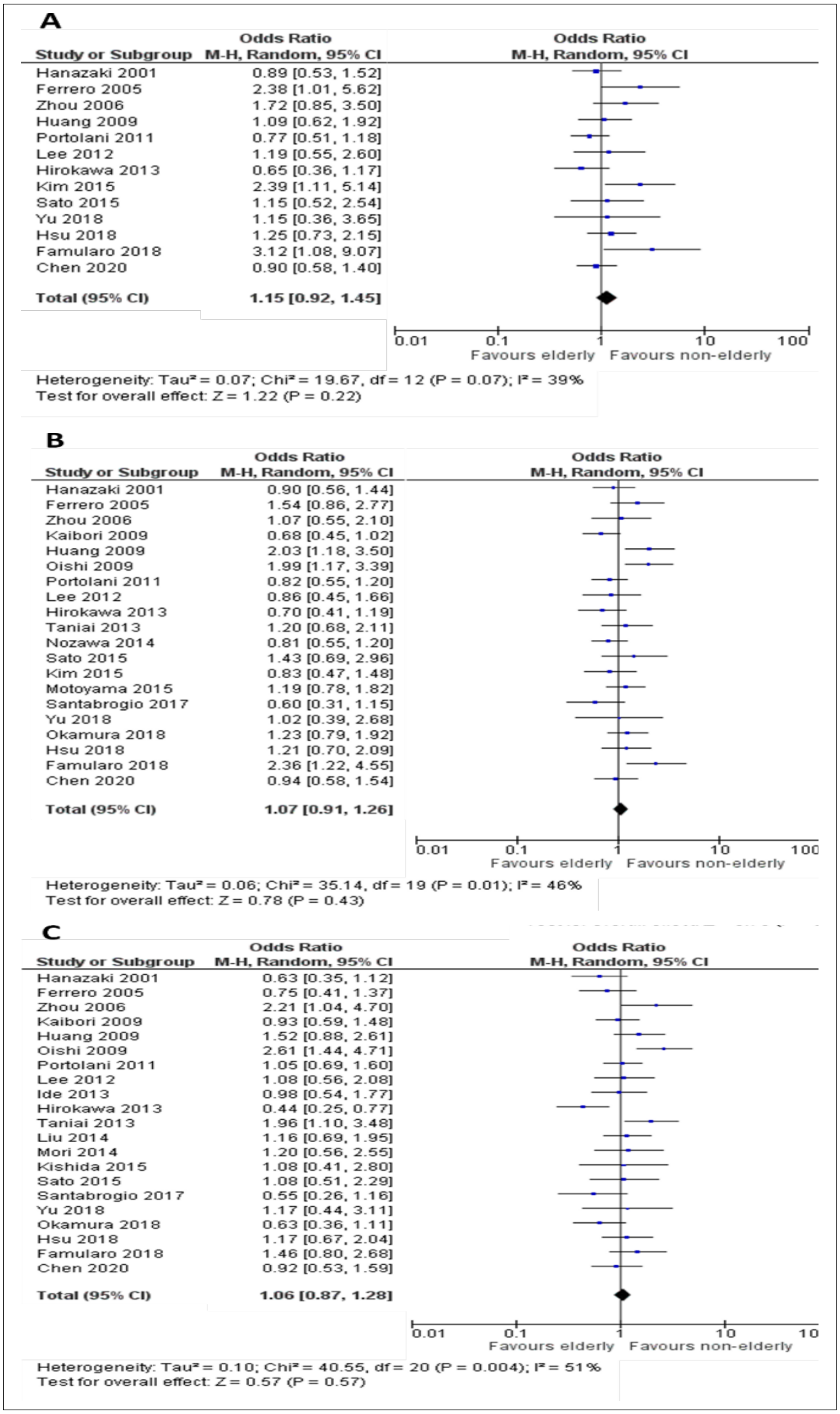

Figure 3. Disease-free survival of elderly vs. non-elderly HCC patients who underwent surgical resection. **A.** One-year DFS. **B.** Three-year DFS. **C.** Five-year DFS

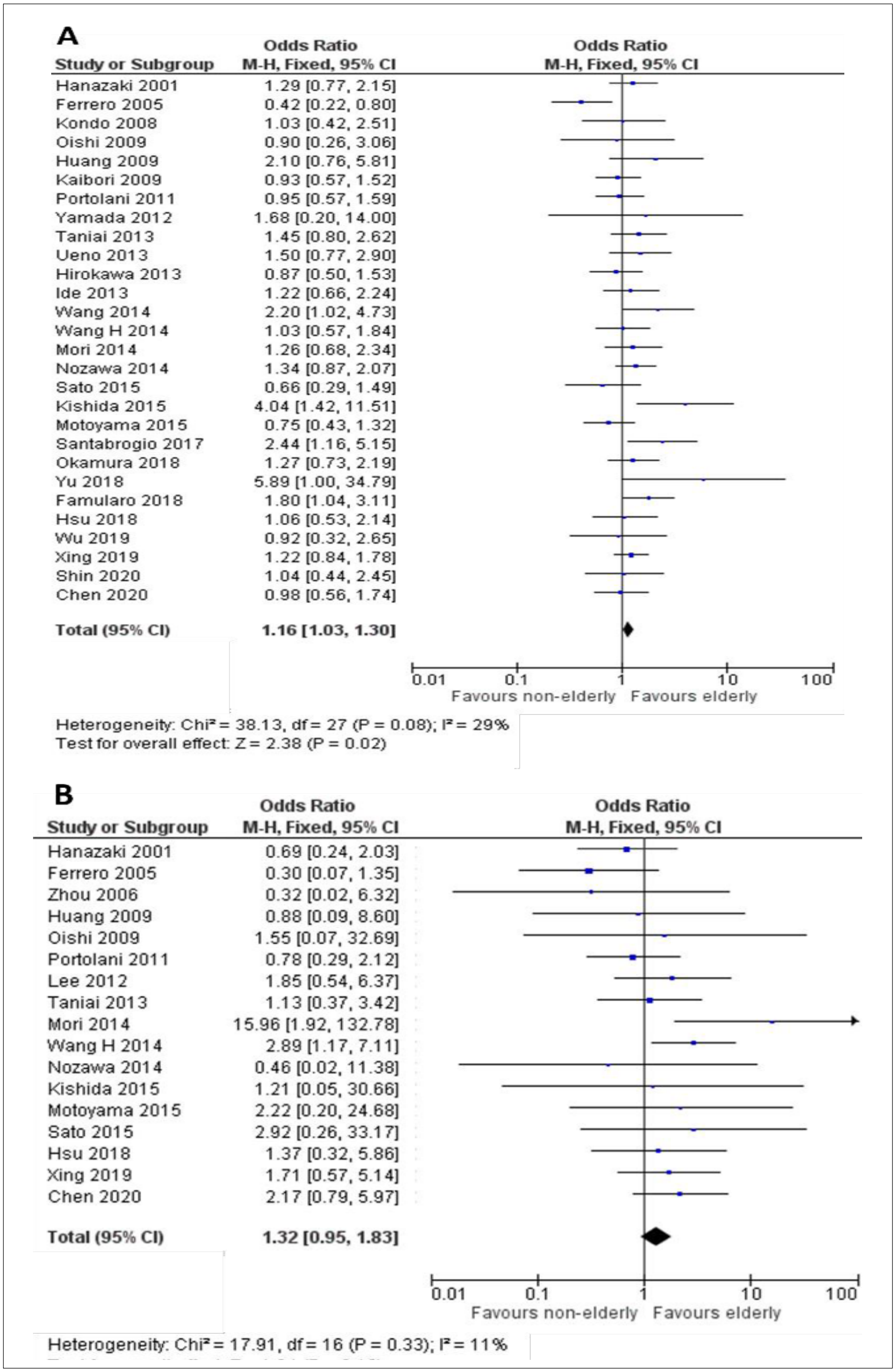

Figure 4. A. Postoperative complications of elderly vs. non-elderly HCC patients who underwent surgical resection. **B.** Postoperative mortality of elderly vs. non-elderly HCC patients who underwent surgical resection.

Postoperative Mortality

There were 17 studies that reported postoperative mortality. There was no significant heterogeneity in the studies included. There was no significant difference in postoperative mortality between elderly and non-elderly patients who underwent surgical resection (OR 1.32; 95% CI 0.95, 1.83, p = 0.10) **(Figure 4)**. Causes of postoperative mortality identified included liver failure and pneumonia.

Transarterial Chromoembolization

A total of 3,228 patients who underwent TACE were included in the meta-analysis. **Tables 4** and **5** show the clinical and demographic characteristics of patients. Significant differences were noted between the elderly and non-elderly group in terms of sex distribution, hepatitis B status, hepatitis C status, Child Pugh class, and comorbidities. More elderly patients had hepatitis C, Child Pugh A cirrhosis, and comorbidities. However, only two studies reported comorbidities. None of the included studies reported information on the Charlson comorbidity index.

Overall Survival

There were five studies that reported one-year OS, three-year OS and five-year OS. Significant heterogeneity was noted in the one-year, three-year and five-year OS. No significant difference was seen between elderly and non-elderly patients who underwent TACE in terms of one-year OS (OR 1.21; 95% CI 0.78, 1.88, p = 0.39), three-year OS (OR 1.21; 95% CI 0.79, 1.85, p = 0.37), and five-year OS (OR 0.70; 95% CI 0.40, 1.23, p = 0.22) **(Figure 5)**.

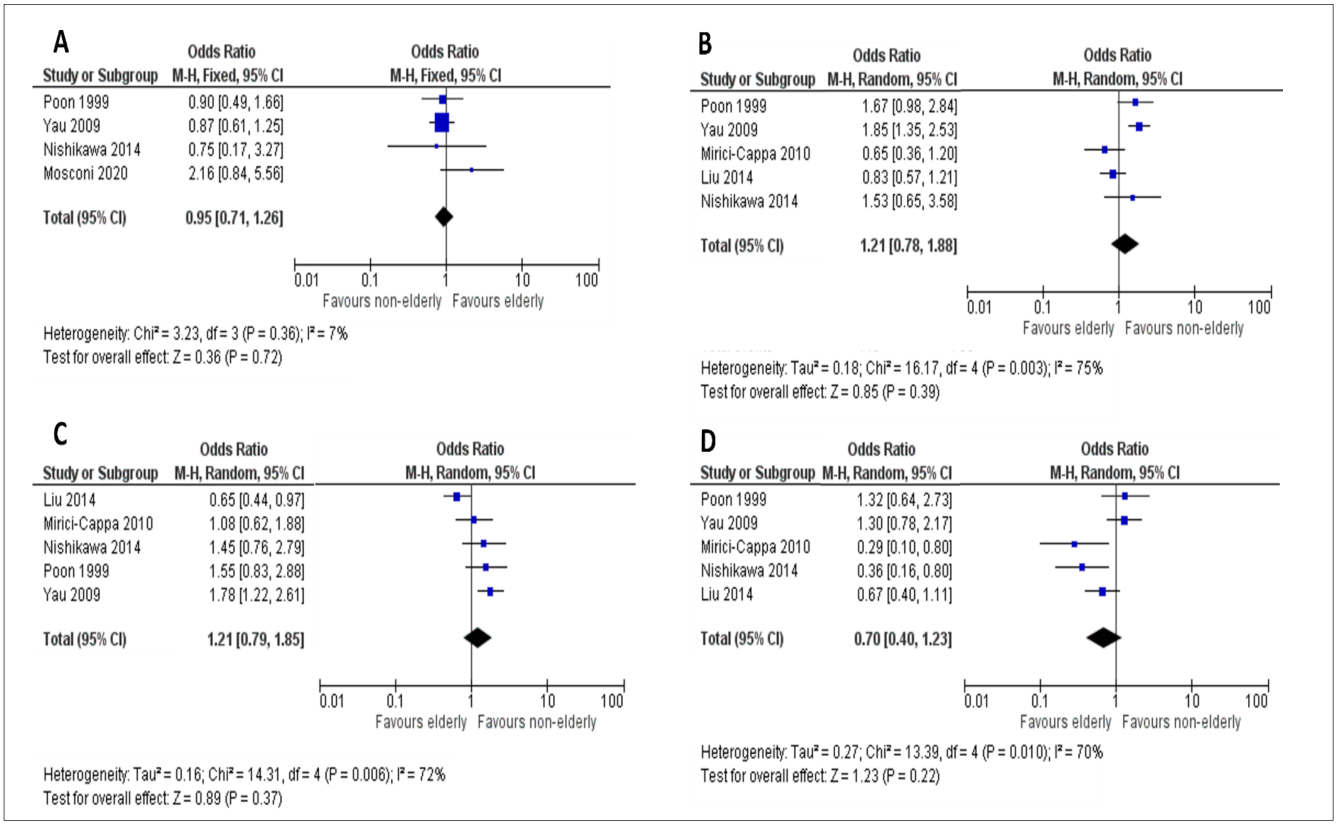

Figure 5. A. Postoperative complications of elderly vs. non-elderly HCC patients who underwent TACE.
B. One-year OS of elderly vs. non-elderly HCC patients who underwent TACE.
C. Three-year OS of elderly vs. non-elderly HCC patients who underwent TACE.
D. Five-year OS of elderly vs. non-elderly HCC patients who underwent TACE.

Post-procedure Complications

There were four studies that reported post-procedure complications. There was no significant heterogeneity in the studies included. No significant difference in post-procedure complications was seen between elderly and non-elderly patients who underwent TACE (OR 0.95; 95% CI 0.71, 1.26, p = 0.72) **(Figure 5)**. The most common complication identified post-TACE was liver function derangement, while some developed liver abscess and cholecystitis.

Publication Bias

A funnel plot was used to assess publication bias, as shown in **Figure 6.** The studies had comparative data for five-year OS in the surgical resection group. Since the funnel plot is symmetrical, there is no significant publication bias.

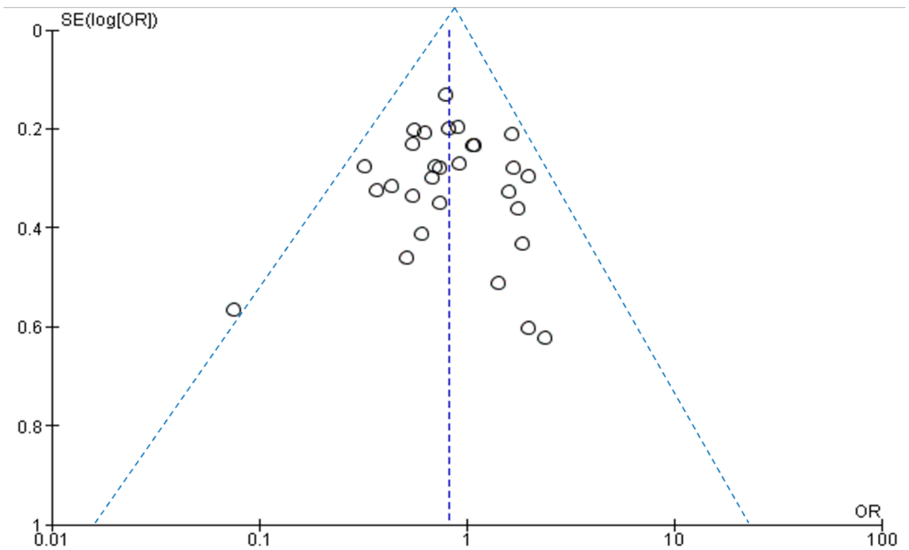

Figure 6. Funnel plot for five-year overall survival, with standard error as the Y-axis and the log of odds ratio as the X-axis.

Discussion

The results of the study showed no significant difference between elderly and non-elderly patients with HCC who underwent surgical resection in terms of one-year, three-year, and five-year overall and disease-free survival. There were higher rates of postoperative complications in the elderly than non-elderly. For those who underwent TACE, there was no significant difference in one-year, three-year, and five-year overall survival. The rate of post-procedure complications, such as liver function derangement and liver abscess, was similar between elderly and non-elderly.

Despite the higher number of comorbidities in elderly patients, long-term outcomes were similar to non-elderly patients. On the other hand, the higher number of postoperative complications in the elderly may be attributed to presence of more more comorbidities in the elderly. The significantly higher rates of Child Pugh A in elderly HCC patients in the TACE group may reflect the lack of curative therapeutic options considered for otherwise eligible elderly patients. In the TACE group, there were also more comorbidities in the elderly group, although only two studies reported comorbidities. Nevertheless, the meta-analysis revealed no significant difference in post-procedure complications and survival between elderly and non-elderly patients who underwent TACE.

There were similarities identified with a previous meta-analysis by Hung, et al.[9] Overall survival and disease-free survival after surgical resection did not differ between the elderly and non-elderly group. Although there were more studies included in our meta-analysis compared to that of Hung, et al., the results differed only in the one-year OS. Hung et al. who reported better one-year OS in the elderly. There was also significant heterogeneity in the analysis of five-year outcomes. This heterogeneity may be explained by the various age cut-off. Taking into consideration the disparity in enrollment periods of the different studies, the availability of treatment options in recent years may also account for the heterogeneity. Furthermore, elderly and non-elderly hepatocellular carcinoma patients who underwent TACE did not differ in terms of overall survival and post-procedure complications.

Among the included studies, there were differences in age cut-off, the lowest being 65 years, while the highest was 85 years. The varying age cut-off may be explained by the geographic diversity in the included studies. These reflect the increasing life expectancy and the evolving definition of being elderly.[50] There were also differences in geographic location, clinicopathologic profiles of patients, and reported outcomes in the included studies. In a systematic review by Zhao et al., Asian elderly patients had more postoperative complications, but had higher median survival time and five-year OS than non-Asian elderly patients.[51] Furthermore, the presence of cirrhosis and comorbidities have been reported to increase postoperative complications and mortality.[52] These may have contributed to the statistical heterogeneity in the analysis of the outcomes.

According to the latest Barcelona Clinic Liver Cancer (BCLC) staging, primary treatment option of early stage hepatocellular carcinoma remains to be surgical resection, regardless of age.[53] Despite this recommendation, older age has been associated with significantly lower rates of receiving HCC treatment.[54] As the population of patients with hepatocellular carcinoma age, treatment options and their outcomes must be evaluated periodically.[55] The advent of direct-acting antivirals for HCV infection has led to a change in etiology and epidemiology of HCC, with consequent changes in prognosis.[56]

As risk factors of HCC transition from a prevalence of HBV and HCV infection to obesity and diabetes[3], it is imperative that metabolic-associated risk factors are considered in future studies.

The diverse demographic, geographic, and clinical features in the included studies are limitations in this meta-analysis. Further studies that have uniformity in age cut-off, reported clinical and demographic characteristics, and reported outcomes, are recommended. Nevertheless, the results of this meta-analysis emphasize that old age should not restrict otherwise eligible hepatocellular carcinoma patients from undergoing curative resection or TACE.

Conclusion

The constant change in trends of hepatocellular carcinoma incidence warrants regularly updated studies on therapeutic options and their outcomes.

Regardless of the evolving trends, current evidence still shows that long-term outcomes are similar between elderly and non-elderly patients, despite higher rates of complications in the elderly. After appropriate pre-procedural assessment, age alone should not disqualify HCC patients from receiving curative resection, or even locoregional therapies such as TACE.

Conflicts of Interest

The authors declare no conflicts of interest or financial disclosures.

Acknowledgements

The authors acknowledge Dr. Jade Jamias, Dr. Pepito Dela Pena, Dr. Lynn Bonifacio, and Dr. Gerby Coronel for their invaluable contribution to this research and for their promotion of research endeavors in the Division of Internal Medicine at the National Kidney and Transplant Institute; Dr. Eric Yasay for providing his critical review and recommendations to this research; and the Hepatology Society of the Philippines for providing recommendations to this research.

References

[1] McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology. 2021 Jan;73:4-13.

[2] Yuen M-F, Hou J-L, Chutaputti A. Hepatocellular carcinoma in the Asia pacific region. Journal of Gastroenterology and Hepatology. 2009;24(3):346-53.

[3] Petrick JL, McGlynn KA. The changing epidemiology of primary liver cancer. Curr Epidemiol Rep. 2019;6(2):104-11.

[4] Petrick JL, Florio AA, Znaor A, Ruggieri D, Laversanne M, Alvarez CS, et al. International trends in hepatocellular carcinoma incidence, 1978-2012. Int J Cancer.

2020;147(2):317-30.
[5] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-50.
[6] Miki D, Aikata H, Uka K, Saneto H, Kawaoka T, Azakami T, et al. Clinicopathological features of elderly patients with hepatitis C virus-related hepatocellular carcinoma. J Gastroenterol. 2008;43(7):550-7.
[7] Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly". Geriatrics and Gerontology International. 2006;6.
[8] Mirici-Cappa F, Gramenzi A, Santi V, Zambruni A, Di Micoli A, Frigerio M, et al. Treatments for hepatocellular carcinoma in elderly patients are as effective as in younger patients: a 20-year multicentre experience. Gut. 2010;59(3):387-96.
[9] Hung AK, Guy J. Hepatocellular carcinoma in the elderly: Meta-analysis and systematic literature review. World J Gastroenterol. 2015;21(42):12197-210.
[10] Hirokawa F, Hayashi M, Miyamoto Y, Asakuma M, Shimizu T, Komeda K, et al. Surgical outcomes and clinical characteristics of elderly patients undergoing curative hepatectomy for hepatocellular carcinoma. J Gastrointest Surg. 2013;17(11):1929-37.
[11] Liu PH, Hsu CY, Lee YH, Hsia CY, Huang YH, Su CW, et al. Uncompromised treatment efficacy in elderly patients with hepatocellular carcinoma: a propensity score analysis. Medicine (Baltimore). 2014;93(28):e264.
[12] Santambrogio R, Barabino M, Scifo G, Costa M, Giovenzana M, Opocher E. Effect of Age (over 75 Years) on Postoperative Complications and Survival in Patients Undergoing Hepatic Resection for Hepatocellular Carcinoma. J Gastrointest Surg. 2017;21(4):657-65.
[13] Yau T, Yao TJ, Chan P, Epstein RJ, Ng KK, Chok SH, et al. The outcomes of elderly patients with hepatocellular carcinoma treated with transarterial chemoembolization. Cancer. 2009;115(23):5507-15.
[14] World Health Organization [Internet]. Ageing and health 2021 [cited 2021 4 October]. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health.
[15] Xu LN, Yang B, Li GP, Gao DW. Assessment of complications after liver surgery: Two novel grading systems applied to patients undergoing hepatectomy. J Huazhong Univ Sci Technolog Med Sci. 2017;37(3):352-6.
[16] Poon RT, Fan ST, Lo CM, Liu CL, Ngan H, Ng IO, et al. Hepatocellular carcinoma in the elderly: results of surgical and nonsurgical management. Am J Gastroenterol. 1999;94(9):2460-6.
[17] Wu CC, Chen JT, Ho WL, Yeh DC, Tang JS, Liu TJ, et al. Liver resection for hepatocellular carcinoma in octogenarians. Surgery. 1999;125(3):332-8.
[18] Hanazaki K, Kajikawa S, Shimozawa N, Shimada K, Hiraguri M, Koide N, et al. Hepatic resection for hepatocellular carcinoma in the elderly11No competing interests declared. Journal of the American College of Surgeons. 2001;192(1):38 -46.
[19] Ferrero A, Vigano L, Polastri R, Ribero D, Lo Tesoriere R, Muratore A, et al. Hepatectomy as treatment of choice for hepatocellular carcinoma in elderly cirrhotic patients. World J Surg. 2005;29(9):1101-5.
[20] Zhou L, Rui JA, Wang SB, Chen SG, Qu Q, Chi TY, et al. Clinicopathological features, post-surgical survival and prognostic indicators of elderly patients with hepatocellular carcinoma. Eur J Surg Oncol. 2006;32(7):767-72.
[21] Kondo K, Chijiiwa K, Funagayama M, Kai M, Otani K, Ohuchida J. Hepatic resection is justified for elderly patients with hepatocellular carcinoma. World J Surg. 2008;32(10):2223-9.
[22] Huang J, Li BK, Chen GH, Li JQ, Zhang YQ, Li GH, et al. Long-term outcomes and prognostic factors of elderly patients with hepatocellular carcinoma undergoing hepatectomy. J Gastrointest Surg. 2009;13(9):1627-35.
[23] Kaibori M, Matsui K, Ishizaki M, Saito T, Kitade H, Matsui Y, et al. Hepatic resection for hepatocellular carcinoma in the elderly. J Surg Oncol. 2009;99(3):154-60.
[24] Oishi K, Itamoto T, Kobayashi T, Oshita A, Amano H, Ohdan H, et al. Hepatectomy for hepatocellular carcinoma in elderly patients aged 75 years or more. J Gastrointest Surg. 2009;13(4):695-701.
[25] Portolani N, Baiocchi GL, Coniglio A, Tiberio GA, Prestini K, Gheza F, et al. Limited liver resection: a good indication for the treatment of hepatocellular carcinoma in elderly patients. Jpn J Clin Oncol. 2011;41(12):1358-65.
[26] Lee CR, Lim JH, Kim SH, Ahn SH, Park YN, Choi GH, et al. A comparative analysis of hepatocellular carcinoma after hepatic resection in young versus elderly patients. J Gastrointest Surg. 2012;16(9):1736-43.
[27] Yamada S, Shimada M, Miyake H, Utsunomiya T, Morine Y, Imura S, et al. Outcome of hepatectomy in super- elderly patients with hepatocellular carcinoma. Hepatol Res. 2012;42(5):454-8.
[28] Faber W, Stockmann M, Schirmer C, Mollerarnd A, Denecke T, Bahra M, et al. Significant impact of patient age on outcome after liver resection for HCC in cirrhosis. Eur J Surg Oncol. 2014;40(2):208-13.
[29] Ide T, Miyoshi A, Kitahara K, Noshiro H. Prediction of postoperative complications in elderly patients with hepatocellular carcinoma. J Surg Res. 2013;185(2):614-9.
[30] Nishikawa H, Kita R, Kimura T, Ohara Y, Takeda H, Sakamoto A, et al. Transcatheter arterial chemoembolization for intermediate-stage hepatocellular carcinoma: clinical outcome and safety in elderly patients. J Cancer. 2014;5(7):590-7.
[31] Taniai N, Yoshida H, Yoshioka M, Kawano Y, Uchida E. Surgical outcomes and prognostic factors in elderly patients (75 years or older) with hepatocellular carcinoma who underwent hepatectomy. J Nippon Med Sch. 2013;80(6):426-32.
[32] Ueno M, Hayami S, Tani M, Kawai M, Hirono S, Yamaue H. Recent trends in hepatectomy for elderly patients with hepatocellular carcinoma. Surg Today. 2014;44(9):1651-9.
[33] Mori S, Kita J, Shimizu T, Kato M, Shimoda M, Kubota K. Outcome of hepatectomy for hepatocellular carcinoma in elderly patients with portal hypertension. Int Surg. 2014;99(2):153-60.
[34] Nozawa A, Kubo S, Takemura S, Sakata C, Urata Y, Nishioka T, et al. Hepatic resection for hepatocellular carcinoma in super-elderly patients aged 80 years and older in the first decade of the 21st century. Surg Today. 2015;45(7):851-7.
[35] Wang WL, Zhu Y, Cheng JW, Li MX, Xia JM, Hao J, et al. Major hepatectomy is safe for hepatocellular carcinoma in elderly patients with cirrhosis. Eur J Gastroenterol Hepatol.

2014;26(4):444-51.
[36] Wang HQ, Yang J, Yan LN, Zhang XW, Yang JY. Liver resection in hepatitis B related-hepatocellular carcinoma: clinical outcomes and safety in elderly patients. World J Gastroenterol. 2014;20(21):6620-5.
[37] Kim JM, Cho BI, Kwon CH, Joh JW, Park JB, Lee JH, et al. Hepatectomy is a reasonable option for older patients with hepatocellular carcinoma. Am J Surg. 2015;209(2):391-7.
[38] Kishida N, Hibi T, Itano O, Okabayashi K, Shinoda M, Kitago M, et al. Validation of hepatectomy for elderly patients with hepatocellular carcinoma. Ann Surg Oncol. 2015;22(9):3094-101.
[39] Motoyama H, Kobayashi A, Yokoyama T, Shimizu A, Sakai H, Furusawa N, et al. Impact of advanced age on the short- and long-term outcomes in patients undergoing hepatectomy for hepatocellular carcinoma: a single-center analysis over a 20-year period. Am J Surg. 2015;209(4):733-41.
[40] Sato S, Tanaka K, Nojiri K, Kumamoto T, Mori R, Taniguchi K, et al. Hepatic Resection for Hepatocellular Carcinoma in the Elderly: Selecting Hepatectomy Procedures Based on Patient Age. Anticancer Res. 2015;35(12):6855-60.
[41] Famularo S, Di Sandro S, Giani A, Angrisani M, Lauterio A, Romano F, et al. The impact of age and ageing on hepatocarcinoma surgery: Short- and long-term outcomes in a multicentre propensity-matched cohort. Liver Int. 2019;39(5):894-904.
[42] Hsu KF, Yu JC, Yang CW, Chen BC, Chen CJ, Chan DC, et al. Long-term outcomes in elderly patients with resectable large hepatocellular carcinoma undergoing hepatectomy. Surg Oncol. 2018;27(3):595-601.
[43] Okamura Y, Sugiura T, Ito T, Yamamoto Y, Ashida R, Uesaka K. The Short- and Long-Term Outcomes in Elderly Patients with Hepatocellular Carcinoma after Curative Surgery: A Case-Controlled Study with Propensity Score Matching. Eur Surg Res. 2018;59(5-6):380-90.
[44] Yu X, Yan YC, Chen G, Yu H. The efficacy and safety of totally laparoscopic hepatectomy for non-cirrhotic hepatocellular carcinoma in the elderly. BMC Surg. 2018;18(1):118.
[45] Wu FH, Shen CH, Luo SC, Hwang JI, Chao WS, Yeh HZ, et al. Liver resection for hepatocellular carcinoma in oldest old patients. World J Surg Oncol. 2019;17(1):1.
[46] Xing H, Liang L, Wang H, Zhou YH, Pei YL, Li C, et al. Multicenter analysis of long-term oncologic outcomes of hepatectomy for elderly patients with hepatocellular carcinoma. HPB (Oxford). 2020;22(9):1314-23.
[47] Chen ZL, Zhang CW, Liang L, Wu H, Zhang WG, Zeng YY, et al. Major Hepatectomy in Elderly Patients with Large Hepatocellular Carcinoma: A Multicenter Retrospective Observational Study. Cancer Manag Res. 2020;12:5607-18.
[48] Mosconi C, Gramenzi A, Biselli M, Cappelli A, Bruno A, De Benedittis C, et al. Survival and Tolerability of Transarterial Chemoembolization in Greater Versus less than 70 Years of Age Patients with Unresectable Hepatocellular Carcinoma: A Propensity Score Analysis. Cardiovasc Intervent Radiol. 2020;43(7):1015-24.
[49] Shin IS, Kim DG, Cha SW, Kang SH, Kim SH, Kim MY, et al. Hepatocellular carcinoma in old age: are there any benefits of liver resection in old age? Ann Surg Treat Res. 2020;99(2):65-71.
[50] World Health Organization [Internet]. Organization WH. Life expectancy and leading causes of death and disability by sex by country and by region 2000 - 2019 2020 [cited 2021 Oct 15]. Available from: https://www.who.int/data/stories/world-health-statistics-2021-a-visual-summary.
[51] Zhao LY, Huo RR, Xiang X, Torzilli G, Zheng MH, Yang T, et al. Hepatic resection for elderly patients with hepatocellular carcinoma: a systematic review of more than 17,000 patients. Expert Rev Gastroenterol Hepatol. 2018;12(10):1059-68.
[52] Zhou Y, Zhang X, Zhang Z, Liu X, Wu L, Li Y, et al. Hepatectomy in elderly patients: does age matter? World J Surg. 2013;37(12):2899-910.
[53] Reig M, Forner A, Rimola J, Ferrer-Fábrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. Journal of Hepatology.
[54] Yan M, Ha J, Aguilar M, Liu B, Frenette CT, Bhuket T, et al. Older Patients With Hepatocellular Carcinoma Have More Advanced Disease, Lower Rates of Treatment, and Lower Survival. J Clin Gastroenterol. 2017;51(4):378-83.
[55] Chu KKW, Chok KSH. Is the treatment outcome of hepatocellular carcinoma inferior in elderly patients? World J Gastroenterol. 2019;25(27):3563-71.
[56] Meringer H, Shibolet O, Deutsch L. Hepatocellular carcinoma in the post-hepatitis C virus era: Should we change the paradigm? World J Gastroenterol. 2019;25(29):3929-40.