Supplementary materials

Benefits and harms of screening for hepatocellular carcinoma in high-risk populations: a systematic review and meta-analysis

Jichun Yang, Zhirong Yang, Xueyang Zeng, Shuqing Yu, Le Gao, Yu Jiang, Feng Sun

Supplementary Table 1.

Search strategy.

Search strategy of Pubmed (English database)	
#1	(((((((Carcinoma[ti] OR tumor[ti] OR cancer[ti] OR neoplasm[ti])) AND (Liver[ti] OR hepatocellular[ti] OR hepatic[ti]))) OR (Hcc[ti] OR hepatoma[ti])) OR "Liver Neoplasms"[Mesh]) OR "Carcinoma, hepatocellular"[Mesh])
#2	((("Mass Screening"[Mesh]) OR "Early Detection of Cancer"[Mesh]) OR (screening[ti] OR screen[ti] OR screened[ti] OR surveillance[ti] OR "early detection"[ti]))
#3	(((((("Tomography, X-Ray Computed"[Mesh]) OR ("Computed tomography"[ti] OR "CT"[ti]))) OR (((DCP[ti] OR "Des-gamma carboxyprothrombin"[ti] OR PIVKA*[ti] OR PIVKA-II[ti] OR "PIVKA II"[ti] OR "Protein induced by vitamin K absence*"[ti])) OR (AFP-L3[ti] OR "AFP L3"[ti] OR "Lens culinaris agglutinin-reactive alpha-fetoprotein"[ti] OR "lectin-bound AFP"[ti] OR "L3 fraction"[ti] OR "L3-fraction"[ti] OR "glycosylated AFP"[ti]))) OR (("alpha-Fetoproteins"[Mesh]) OR (alpha-fetoproteins[ti] OR alpha-fetoprotein[ti] OR "alpha fetoprotein"[ti] OR AFP[ti] OR alpha-1-fetoprotein[ti] OR "alpha1fetoprotein"[ti] OR "alpha 1 fetoprotein"[ti] OR alpha-fetoglobulin[ti] OR "alpha fetoglobulin"[ti]))) OR (("Magnetic Resonance Imaging"[Mesh]) OR ("Magnetic resonance imaging"[ti] OR "MRI"[ti]))) OR (((ultrason*[ti] OR ultrasound*[ti] OR ultrasonography[ti] OR echograph*[ti] OR echotomograph*[ti] OR doppler*[ti] OR B-mode[ti] OR B-scan[ti] OR grey*scale[ti] OR sonogram[ti] OR sonography[ti])) OR "Ultrasonography"[Mesh]))))
#4	#2 and #3
#5	#1 and #4
#6	(Animals[Mesh] NOT humans[Mesh])
#7	#5 NOT#6
Search strategy of Embase (English database)	
#1	(liver:ti OR hepatocellular:ti OR hepatic:ti) AND (carcinoma:ti OR tumor:ti OR cancer:ti OR neoplasm:ti) OR hcc:ti OR hepatoma:ti OR 'liver neoplasms'/exp OR 'hepatocellular carcinoma'/exp
#2	screening:ti OR screen:ti OR screened:ti OR surveillance:ti OR 'early detection':ti OR 'mass screening'/exp OR 'early detection of cancer'/exp
#3	ultrason*:ti OR ultrasound*:ti OR ultrasonography:ti OR echograph*:ti OR echotomograph*:ti OR doppler*:ti OR 'b mode':ti OR 'b scan':ti OR grey*scale:ti OR 'sonogram':ti OR sonogram:ti OR 'sonography':ti OR sonography:ti OR 'ultrasonography'/exp OR 'alpha-fetoproteins':ti OR 'alpha-fetoprotein':ti OR 'alpha fetoprotein':ti OR afp:ti OR 'alpha-1-fetoprotein':ti OR 'alpha1fetoprotein':ti OR 'alpha 1 fetoprotein':ti OR 'alpha fetoglobulin':ti OR 'alpha-fetoproteins'/exp OR 'afp l3':ti OR 'lens

	culinaris agglutinin-reactive alpha-fetoprotein':ti OR 'lectin-bound afp':ti OR 'l3 fraction':ti OR 'l3-fraction':ti OR 'glycosylated afp':ti OR dcp:ti OR 'des-gamma carboxyprothrombin':ti OR pivka*:ti OR 'pivka ii':ti OR 'protein induced by vitamin k absence*':ti OR 'computed tomography':ti OR 'ct':ti OR 'tomography, x-ray computed'/exp OR 'magnetic resonance imaging':ti OR 'mri':ti OR 'magnetic resonance imaging'/exp
#4	#2 and #3
#5	#1 and #4
#6	[humans]/lim AND ('english':la OR 'chinese':la)
#7	#5 and #6
Search strategy of the Cochrane library (English database)	
#5	#1 MeSH descriptor: [Liver Neoplasms] explode all trees #2 MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees #3 Hcc:ti or hepatocellular:ti (Word variations have been searched) #4 ((Carcinoma or tumor or cancer or neoplasm) and (Liver or hepatocellular or hepatic)):ti (Word variations have been searched) #5 #1 or #2 or #3 or #4
#9	#6 MeSH descriptor: [Mass Screening] explode all trees #7 MeSH descriptor: [Early Detection of Cancer] explode all trees #8 (Screening or screen or screened or surveillance or "early detection"):ti (Word variations have been searched) #9 #6 or #7 or #8
#15	#10 MeSH descriptor: [Ultrasonography] explode all trees #11 (ultrason* or ultrasound* or ultrasonography or echograph* or echotomograph* or doppler* or 'b mode' or 'b scan' or grey*scale or 'sonogram' or sonogram or 'sonography' or sonography):ti (Word variations have been searched) #12 #10 or #11 #13 MeSH descriptor: [alpha-Fetoproteins] explode all trees #14 (alpha-fetoproteins or alpha-fetoprotein'or 'alpha fetoprotein' or afp or 'alpha 1 fetoprotein' or 'alpha 1 fetoprotein' or 'alpha fetoglobulin'):ti (Word variations have been searched) #15 #13 or #14 #16 (AFP-L3 or "AFP L3" or "Lens culinaris agglutinin-reactive alpha-fetoprotein" or "lectin-bound AFP" or "L3 fraction" or "L3-fraction" or "glycosylated AFP"):ti (Word variations have been searched) #17 (DCP or "Des-gamma carboxyprothrombin" or PIVKA* or PIVKA-II or "PIVKA II" or "Protein induced by vitamin K absence*"):ti (Word variations have been searched) #18 ("Magnetic resonance imaging" or "MRI"):ti (Word variations have

	been searched) #19 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees #20 #18 or #19 #21 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees #22 ("Computed tomography" or "CT"):ti (Word variations have been searched) #23 #21 or #22 #24 #12 or #15 or #16 or #17 or #20 or #23
#26	#24 AND #9
#27	#5 AND#26
Search strategy of Clinicaltrials.gov (English database)	
#1	liver cancer OR liver neoplasm OR liver tumour OR liver carcinoma OR hepatocellular carcinoma OR hepatic cancer OR hepatic carcinoma OR HCC | screen OR surveillance OR 'early detection of cancer' OR 'mass screening' **Applied Filters:** Completed
Search strategy of Web of science (English database)	
#1	((TI=(Liver OR hepatocellular OR hepatic) AND TI=(Carcinoma OR tumor OR cancer OR neoplasm)) OR TI=(Hcc OR hepatoma)) AND (TI=(screening OR screen OR screened OR surveillance OR "early detection")) AND (TI=("Tomography, X-Ray Computed" OR "Computed tomography" OR "CT" OR DCP OR "Des-gamma carboxyprothrombin" OR PIVKA* OR PIVKA-II OR "PIVKA II" OR "Protein induced by vitamin K absence*" OR AFP-L3 OR "AFP L3" OR "Lens culinaris agglutinin-reactive alpha-fetoprotein" OR "lectin-bound AFP" OR "L3 fraction" OR "L3-fraction" OR "glycosylated AFP" OR alpha-fetoproteins OR alpha-fetoprotein OR "alpha fetoprotein" OR AFP OR alpha-1-fetoprotein OR "alpha1fetoprotein" OR "alpha 1 fetoprotein" OR alpha-fetoglobulin OR "alpha fetoglobulin" OR "Magnetic Resonance Imaging" OR "Magnetic resonance imaging" OR "MRI" OR ultrason* OR ultrasound* OR ultrasonography OR echograph* OR echotomograph* OR doppler* OR B-mode OR B-scan OR grey*scale OR sonogram OR sonography))
Search strategy of Google scholar (English database)	
#1	allintitle: (("liver cancer" OR "liver neoplasm" OR "liver tumour" OR "liver carcinoma" OR "hepatocellular carcinoma" OR “hepatic cancer” OR “hepatic carcinoma” OR “HCC”) AND (“screen” OR “surveillance” OR “early detection”))
Search strategy of CNKI (Chinese database)	

#1 (Chinese)	SU =("肝癌"+"肝肿瘤"+"肝细胞癌"+"原发性肝癌"+"肝脏肿瘤")*("筛查"+"监测"+"早期检测")*("超声"+"甲胎蛋白"+"AFP"+"AFP-L3"+"甲胎蛋白-L3"+"甲胎蛋白异质体"+"异常凝血酶原"+"DCP"+CT+MRI+"核磁")
Translation	SU = ("hepatocellular carcinoma"+"liver cancer"+"hepatocellular carcinoma "+"primary liver cancer"+" liver tumor ") * ("screening"+"surveillance"+" early detection ") * ("ultrasonography" + "alpha fetal protein" + "AFP" + "alpha fetal proteinL-3" + "AFP-L3" + "molecular heterogenetic of AFP" + "abnormal prothrombin" + "DCP+CT+MRI+"Magnetic resonance imaging")
Search strategy of WanFang (Chinese database)	
#1 (Chinese)	主题:("肝癌"+"肝肿瘤"+"肝细胞癌"+"原发性肝癌"+"肝脏肿瘤")*(主题:（"筛查"+"监测"+"早期检测") *主题: ("超声"+"甲胎蛋白"+"AFP"+"AFP-L3"+"甲胎蛋白-L3"+"甲胎蛋白异质体"+"异常凝血酶原"+"DCP"+CT+MRI+"核磁")
Translation	Theme: ("hepatocellular carcinoma"+"liver cancer"+"hepatocellular carcinoma "+"primary liver cancer"+" liver tumor ") * ("screening"+"surveillance"+" early detection ") * ("ultrasonography" + "alpha fetal protein" + "AFP" + "alpha fetal proteinL-3" + "AFP-L3" + "molecular heterogenetic of AFP" + "abnormal prothrombin" + "DCP+CT+MRI+"Magnetic resonance imaging")
Search strategy of WanFang (Chinese database)	
#1 (Chinese)	(M=肝癌 OR M=肝肿瘤 OR M=肝细胞癌 OR M=原发性肝癌 OR M=肝脏肿瘤) AND (M=筛查 OR M=监测 OR M=早期检测) AND (M=超声 OR M=甲胎蛋白 OR M=AFP OR M=AFP-L3 OR M=甲胎蛋白-L3 OR M=甲胎蛋白异质体 OR M=异常凝血酶原 OR M=DCP OR M=CT OR M=MRI OR M=核磁)
Translation	*(M= liver cancer OR M= liver cancer OR M= hepatocellular carcinoma OR M= primary liver cancer OR M= liver tumor) AND (M= screening OR M= surveillance OR M= early detection) AND (M= ultrasound OR M= alpha-fetoprotein OR M=AFP OR M=AFP-L3 OR M= alpha-fetoprotein -L3 OR M= molecular heterogenetic of AFP OR M= abnormal prothrombin OR M=DCP OR M=CT OR M=MRI OR M= Magnetic resonance imaging)*
Search strategy of Sinomed (Chinese database)	
#1 (Chinese)	("肝癌"[中文标题:智能]) OR ("肝肿瘤"[中文标题:智能]) OR ("肝细胞癌"[中文标题:智能]) OR ("原发性肝癌"[中文标题:智能]) OR ("肝脏肿瘤"[中文标题:智能])
Translation	*("liver cancer ["Chinese title: intelligent]) OR ("liver tumors"[Chinese title: intelligent]) OR ("hepatocellular carcinoma ["Chinese title: intelligent]) OR ("primary liver cancer"[Chinese title: intelligent]) OR (" liver tumor ["Chinese title: intelligent])*
#2 (Chinese)	"肝肿瘤"[不加权:扩展]

Translation	*"Liver tumor ["unweighted: extended]*
#3	#1 OR #2
#4 (Chinese)	("筛查"[中文标题:智能]) OR ("监测"[中文标题:智能]) OR ("早期检测"[中文标题:智能])
Translation	(" screening "[Chinese title: intelligent]) OR (" surveillance" [Chinese title: intelligent]) OR (" early detection "[Chinese title: intelligent])
#5 (Chinese)	("超声"[中文标题:智能]) OR ("甲胎蛋白"[中文标题:智能]) OR "AFP"[中文标题:智能]) OR ("AFP-L3"[中文标题:智能]) OR ("甲胎蛋白-L3"[中文标题:智能]) OR ("甲胎蛋白异质体"[中文标题:智能]) OR "异常凝血酶原"[中文标题:智能]) OR ("DCP"[中文标题:智能]) OR ("CT"[中文标题:智能]) OR ("MRI"[中文标题:智能]) OR ("核磁"[中文标题:智能])
Translation	*("ultrasonic ["Chinese title: intelligent]) OR ("AFP"["Chinese title: intelligent]) OR "alpha-fetoprotein"["Chinese title: intelligent]) OR ("AFP - L3 ["Chinese title: intelligent]) OR ("AFP - L3"["Chinese title: intelligent]) OR ("molecular heterogenetic of AFP ["Chinese title: intelligent]) OR"abnormal prothrombin ["Chinese title: intelligent]) OR (" DCP"["Chinese title: intelligent]) OR ("CT ["Chinese title: intelligent]) OR ("MRI"["Chinese title: intelligent]) OR ("Magnetic resonance imaging ["Chinese title: intelligent])*
#6	#4 and #5

Supplementary Table 2

Characteristics of included studies.

Included studies	Study location	Study design	Screening	Comparators	Screening population (S/C)	HCC (S/C)	Proportion of Child-Pugh C	Adjusted lead-time	Proportion male（%）	Age	Outcomes
Chen JG, et al. 2003. 5y[1]	China	RCT	AFP/6M	No-Screening	HBV (3,172/1,896)	217/117	NA	No	100.00	41.15	①②③④⑤
Zhang BH, et al. 2004. 5y[2]	China	RCT	AFP+US/6M	No-Screening	HBV (9,373/9,433)	86/67	NA	No	NA	41.50	①②③④⑤
Lu J. 2001. 5y[3]	China	RCT	AFP+US/3M	No-Screening	HBV (278/149)	92/34	NA	No	73.80	45.60	①②③④
Ji MF, et al. 2018. 4y[4]	China	RCT	AFP+US/6M	No-Screening	HBV (17,966/50,544)	57/104	NA	No	NA	44.50	①⑤
Ando et al. 2006. 5y[5]	Japan	Cohort study	AFP+US/NA	No-Screening	Cirrhosis	392/182	36.40%	No	65.30	64.40	①④③
Bui et al. 2019. 5y[6]	USA	Cohort study	AFP or US/NA	No-Screening	Cirrhosis (3,376/2,755)	91/54	NA	No	NA	68.25	⑤
Caumes et al. 2007. 3y[7]	France	Cohort study	US/NA	No-Screening	CLD	30/76	37.70%	No	93.40	66.35	①
Chaiteerakij et al. 2017. 1y[8]	Thailand	Cohort study	US > 12M	No-Screening	CH	103/343	1.12%	No	78.70	58.40	①

Chen TH, et al. 2002. 7y[9]	China	Cohort study	US/6M	No-Screening	CLD (4,385/458)	877/100	NA	No	76.90	NA	③⑤
Cheung et al. 2006. 3y[10]	China	Cohort study	AFP+US/NA	No-Screening	CH	97/126	23.32%	No	80.30	64.00	①
Chen JG, et al. 2017. 5y[11]	China	Cohort study	AFP+US/6M	No-Screening	HBV (3,712/1,869)	186/82	NA	No	100.00	41.15	②④③
Chin et al. 2016. 7y[12]	Australia	Cohort study	US/6M	No-Screening	Cirrhosis	54/58	NA	No	NA	NA	①
Chinnaratha et al. 2019. 1y[13]	Australia	Cohort study	US/6M	No-Screening	CLD	24/106	NA	No	NA	NA	① ② ③
Costentin et al. 2016. 4y[14]	France	Cohort study	US/6M	No-Screening	Cirrhosis	113/74	NA	No	NA	58.00	③
Davila et al. 2007. 5y[15]	USA	Cohort study	AFP or US/12M	No-Screening	CLD	44/113	36.31%	No	NA	57.50	②③
Demma et al. 2016. 3y[16]	UK	Cohort study	US/6M	No-Screening	Cirrhosis	108/97	NA	No	NA	NA	②
Dixon et al. 2018. 3y[17]	UK	Cohort study	AFP or US/6M	No-Screening	CLD	25/76	5.00%	No	75.00	71.00	①③
El-Serag et al. 2011. 5y[18]	USA	Cohort study	AFP+US/6-12 M	No-Screening	HCV	580/332	NA	No	NA	58.10	②④③
El-Zayadi et al. 2010. 5y[19]	Egypt	Cohort study	AFP+US/6M	No-Screening	Cirrhosis	122/473	50.08%	No	84.90	54.55	①

Eltabbakh et al. 2015. 5y[20]	Egypt	Cohort study	AFP+US/6M	No-Screening	Cirrhosis	102/155	5.80%	No	NA	55.05	①
Farrell et al. 2015. 4y[21]	UK	Cohort study	US/6M	No-Screening	Cirrhosis	31/400	NA	No	NA	NA	①
Gaba et al. 2013. 4y[22]	USA	Cohort study	US/6-12M	No-Screening	CLD	97/70	NA	No	80.80	61.00	①②③
Garcia et al. 1995. 3y[23]	Spain	Cohort study	US/NA	No-Screening	Cirrhosis	34/65	27.27%	No	NA	NA	①
Gellert et al. 2007. 5y[24]	Australian	Cohort study	AFP or US/NA	No-Screening	CLD	27/122	NA	No	79.90	NA	① ② ④
Im S, et al. 2019. 4y[25]	Korea	Cohort study	AFP or US/6M	No-Screening	CLD	127/192	16.9%	Yes	NA	NA	① ⑤
Jeffrey et al. 2015. 2y[26]	USA	Cohort study	AFP or US/6M	No-Screening	Cirrhosis	162/126	NA	No	78.10	58.50	①
Jou et al. 2010. 1y[27]	USA	Cohort study	US/6M-12M	No-Screening	Cirrhosis	98/221	10.03%	No	77.50	NA	①
Kemp et al. 2005. 12y[28]	Australian	Cohort study	AFP+US/6M	No-Screening	CLD	41/55	18.75%	No	82.30	60.00	②③
Khalaf et al. 2016. 1y[29]	USA	Cohort study	US/NA	No-Screening	Cirrhosis	145/373	NA	No	99.40	65.70	①
Kim et al. 2018. 5y[30]	Korea	Cohort study	AFP+US/6M	No-Screening	HBV	834/464	3.50%	Yes	NA	57.70	①

Kuo et al. 2010. 3y[31]	USA	Cohort study	AFP+US/6-12 M	No-Screening	Cirrhosis	318/1,118	20.90%	No	74.40	59.55	①③
Leykum et al. 2007. 6y[32]	USA	Cohort study	AFP or US 6-12M	No-Screening	HCV	16/56	NA	No	NA	56.40	①③
Mart ńez et al. 1993. 1y[33]	Spain	Cohort study	AFP+US/NA	No-Screening	Cirrhosis	43/92	NA	No	NA	NA	①
Miquel et al. 2012. 7y[34]	USA	Cohort study	AFP+US/NA	No-Screening	Cirrhosis	56/54	NA	No	NA	NA	①
Mittal R, et al. 2016. 2y[35]	USA	Cohort study	US/6M	No-Screening	HBV	94/50	NA	Yes	79.90	NA	①
Mittal S, et al. 2016. 5y[36]	USA	Cohort study	AFP or US/6M	No-Screening	CLD	412/475	18.28%	No	99.90	58.50	①
Noda et al. 2010. 6y[37]	Japan	Cohort study	US/6M	No-Screening	HCV	124/37	NA	No	66.50	71.25	①②④③
Nusbaum et al. 2015. 2y[38]	USA	Cohort study	AFP or US/12M	No-Screening	Cirrhosis	126/162	NA	No	NA	NA	①
Pascual et al. 2008. 1y[39]	USA	Cohort study	US/6M-12M	No-Screening	Cirrhosis	117/173	14.48%	No	75.20	68.50	①
Pi ñero et al. 2019. 5y[40]	Argentina	Cohort study	US/6M	No-Screening	Cirrhosis	345/208	4.70%	No	77.60	NA	① ④
Poh et al. 2015. 2y[41]	USA	Cohort	AFP+US/6M	No-Screening	CH	87/24	NA	No	82.00	66.50	②

		study									
Rich et al. 2017. 8y[42]	USA	Cohort study	AFP+US/NA	No-Screening	Cirrhosis	359/573	NA	No	NA	NA	①
Rodr ́guez et al. 2011. 2y[43]	Spain	Cohort study	AFP+US/NA	No-Screening	CLD	86/50	NA	No	71.30	66.50	①
Sarkar et al. 2012. 11y[44]	USA	Cohort study	AFP+US/6-12 M	No-Screening	HBV	14/37	NA	No	78.40	50.00	①③
Silveira et al. 2008. 7y[45]	USA	Cohort study	AFP+US/6-12 M	No-Screening	Cirrhosis	17/16	NA	No	36.10	69.00	①③
Singal et al. 2021. 2y[46]	USA	Cohort study	AFP or US /6-12M	No-Screening	Cirrhosis（614/189）	16/10	16.31%	No	74.30	60.95	①②⑦
Stravitz et al. 2008. 8y[47]	USA	Cohort study	US/6-12M	No-Screening	Cirrhosis	172/107	5.40%	No	86.00	57.00	①③
Stroffolini et al. 2011. 1y[48]	Italy	Cohort study	US/6-12M	No-Screening	Cirrhosis	257/154	21.91%	No	72.30	67.50	①
Tanaka H, et al. 2006. 12y[49]	USA	Cohort study	US/6M	No-Screening	HCV	182/202	2.60%	No	69.30	65.00	①④③
Tanaka S et al. 1990. 1y[50]	Japan	Cohort study	US/3-6M	No-Screening	CLD	22/83	NA	No	NA	NA	①
Taura et al. 2005. 1y[51]	Japan	Cohort study	AFP+US/NA	No-Screening	CLD	178/93	5.9%	No	71.22	59.60	②

Thein et al. 2015. 10y[52]	USA	Cohort study	US/6M	No-Screening	CH	302/540	NA	Yes	81.10	NA	② ④ ③
Tong MJ. 2017. 5y[53]	USA	Cohort study	AFP+US/6-12 M	No-Screening	CH	175/158	4.55%	Yes	NA	61.65	①②④ ③
Tong et al. 2010. 6y[54]	Asian-American	Cohort study	AFP+US/6M	No-Screening	HBV	26/52	5.10%	Yes	82.10	57.20	①②④ ③
Toyoda H. 2018. 5y[55]	Japan	Cohort study	AFP+US/NA	No-Screening	CLD	2,108/1,791	6.54%	Yes	72.40	68.75	①
Toyoda K, et al. 2006. 5y[56]	Japan	Cohort study	US/3-6M	No-Screening	Cirrhosis	1050/591	36.00%	No	25.20	64.3	①③
Trevisani F, et al. 2004. 3y[57]	Italy	Cohort study	AFP+US/6M	No-Screening	CLD	158/138	3.04%	Yes	64.50	74.4	①
Trevisani F, et al. 2007. 6y[58]	USA	Cohort study	AFP+US/6-12 M	No-Screening	Cirrhosis	252/356	22.88%	Yes	74.80	62.88	①②③ ④
Van Meer et al. 2015. 5y[59]	USA	Cohort study	AFP+US/6M	No-Screening	CLD	295/779	NA	Yes	75.80	62	① ② ③ ④
Van Vlierberghe et al. 2005. 1y[60]	Belguim	Cohort study	US/NA	No-Screening	Cirrhosis	47/84	NA	Yes	NA	NA	① ②
Wong G et al. 2008. 2y[61]	China	Cohort study	AFP+US/6M	No-Screening	CH	79/393	NA	Yes	81.20	59.10	①

Wong L et al. 2000. 5y[62]	Asian	Cohort study	AFP+US/6M	No-Screening	CLD	16/19	NA	No	68.60	61.15	①②③
Yang JD, et al. 2011. 3y[63]	USA	Cohort study	US/6-12M	No-Screening	Cirrhosis	136/307	10.61%	No	72.00	62.00	①③
Yeh et al. 2014. 2y[64]	China	Cohort study	US/3-6M	No-Screening	HBV (8,962/2,152)	16/18	NA	No	NA	NA	⑤
Yerokun et al. 2016. 1y[65]	USA	Cohort study	AFP+US/NA	No-Screening	Cirrhosis	160/220	NA	No	75.00	59.80	①
Youk et al. 2003. 6y[66]	USA	Cohort study	AFP+US/6M	No-Screening	CLD	64/183	3.64%	No	82.20	57.50	①②③
Zapata et al. 2010. 2y[67]	USA	Cohort study	US/6M	No-Screening	Cirrhosis	40/45	25.88%	No	87.10	63.00	①
Atiq et al. 2017. 3y[68]	USA	Case series	AFP or US/12M	NA	Cirrhosis (680)	48	NA	No	NA	NA	⑥
Konerman et al. 2019. 2y[69]	USA	Case series	AFP+US/6-12M	NA	Cirrhosis (999)	69	NA	No	53.60	58.00	⑥
Frey et al. 2015. 2y[70]	Switzerland	Case series	AFP+US/8M	NA	cirrhosis (285)	9	NA	No	63.0	55.00	⑥

Outcomes of benefits: Outcomes of bene (①, proportion of early HCC; ②, 1-year survival rate; ③, 3-year survival rate; ④, 5-year survival rate; ⑤, mortality); Outcomes of harms (⑥, proportion of physiological harms); S/C = screening/comparator.

Abbreviations: AFP, alpha-fetoprotein; CH, chronic hepatitis (chronic hepatitis included hepatitis B, hepatitis C, alcoholic liver disease and so on); CLD, chronic liver disease (chronic liver disease included chronic hepatitis and cirrhosis); CT, computed tomography; HBV, hepatitis B; HCC, hepatocellular

carcinoma; HCV, hepatitis C; M, screening interval is x months (eg., 3M means screening interval was 3 months); MRI, magnetic resonance imaging; NA, not reported; RCT, random clinical trial; UK, The United Kingdom; US, ultrasound; USA, The United States of America.

Supplementary Table 3

Risk-of-bias assessment of RCT (CROB).

Included studies	①	②	③	④	⑤	⑥	⑦	Total
Chen JG, et al. 2003. 5y. RCT[1]	1	0	NA	NA	0	1	NA	2
Zhang BH, et al. 2004. 5y. RCT[2]	1	0	NA	NA	0	1	NA	2
Lu J. 2001. 5y. RCT[3]	NA	0	NA	NA	NA	1	NA	1
Ji MF, et al. 2018. 4y. RCT[4]	1	0	0	0	1	1	NA	2

①, random sequence generation; ②, allocation concealment; ③, blinding of participants and personnel; ④, blinding of assessment; ⑤, complete outcome data; ⑥, selective reporting; ⑦, other bias.

1, low risk; 0, high risk; NA, not available.

Abbreviations: CROB, Cochrane Collaboration's tool; RCT, random clinical trial.

Supplementary Table 4

Risk-of-bias assessment of cohort study (NOS).

Included studies	selection				Comparability	Outcome			Total
	①	②	③	④	⑤	⑥	⑦	⑧	
Ando et al. 2006. 5y[5]	1	1	0	1	1	0	1	0	5
Bui et al. 2019. 5y[6]	1	1	0	1	1	0	1	1	6
Caumes et al. 2007. 3y[7]	1	0	0	1	1	1	1	0	5
Chaiteerakij et al. 2017. 1y[8]	1	1	0	1	2	1	1	0	7
Chen TH, et al. 2002. 7y[9]	1	1	1	1	2	0	1	1	8
Cheung et al. 2006. 3y[10]	1	1	0	1	1	0	1	0	5
Chen JG, 2017. 8y[11]	1	0	1	1	1	0	1	0	5
Chin et al. 2016. 7y[12]	1	1	0	1	2	0	1	0	6
Chinnaratha et al. 2019. 1y[13]	1	1	1	1	1	1	0	0	6
Costentin et al. 2016. 4y[14]	0	1	1	1	1	0	1	0	5
Davila et al. 2007. 5y[15]	1	1	1	1	1	1	1	0	7
Demma et al. 2016. 3y[16]	1	1	0	1	1	1	1	0	6
Dixon et al. 2018. 3y[17]	1	1	0	1	1	1	1	0	6
El-Serag et al. 2011. 5y[18]	1	1	1	1	1	1	1	0	7
El-Zayadi, at al. 2010. 5y[19]	1	1	1	1	2	1	1	0	8
Eltabbakh et al. 2015. 5y[20]	1	0	1	1	2	0	1	0	6
Farrell et al. 2015. 4y[21]	0	1	1	1	1	1	1	0	6
Gaba et al. 2013. 4y[22]	1	1	1	1	1	1	1	0	7
Garcia et al. 1995. 3y[23]	1	1	1	1	1	0	1	0	6
Gellert et al. 2007. 10y[24]	1	1	1	1	1	1	1	0	7
Im S, et al. 2019. 4y[25]	1	1	1	1	2	1	1	0	8
Jeffrey et al. 2015. 2y[26]	1	1	1	1	1	1	1	1	8
Jou et al. 2010. 1y[27]	1	1	1	1	2	1	1	0	8
Kemp et al. 2005. 12y[28]	1	1	1	1	2	1	1	0	8
Khalaf et al. 2016. 1y[29]	0	1	1	1	1	0	1	0	5
Kim et al. 2018. 5y[30]	1	1	1	1	1	1	1	1	8
Kuo et al. 2010. 3y[31]	1	1	1	1	1	1	1	0	7
Leykum et al. 2007. 6y[32]	1	1	1	1	1	1	1	0	7
Martínez et al. 1993. 1y[33]	1	1	0	1	1	0	1	0	5
Miguel et al. 2012. 7y[34]	1	1	0	1	1	0	1	0	5
Mittal R, et al. 2016. 2y[35]	1	1	1	1	1	0	1	0	6
Mittal S, et al. 2016. 5y[36]	1	1	1	1	1	1	1	1	8
Noda et al. 2010. 6y[37]	1	0	1	1	2	1	1	0	7
Nusbaum et al. 2015. 2y[38]	1	1	1	1	1	1	1	1	8
Pascual et al. 2008. 1y[39]	1	1	1	1	1	1	1	0	7
Piñero et al. 2019. 5y[40]	1	1	1	1	1	1	1	0	7
Poh et al. 2015. 2y[41]	1	1	1	1	1	1	0	0	6
Rich et al. 2017. 8y[42]	1	1	0	1	1	0	1	0	5

Rodríguez et al. 2011. 2y[43]	1	1	1	1	2	1	1	0	8
Sarkar et al. 2012. 11y[44]	1	1	0	1	1	0	1	1	6
Silveira et al. 2008. 7y[45]	0	1	1	1	1	0	1	0	5
Singal et al. 2021. 2y[46]	1	1	1	1	1	1	1	0	7
Stravitz et al. 2008. 8y[47]	1	0	0	1	2	0	1	0	5
Stroffolini et al. 2011. 1y[48]	1	0	1	1	1	1	1	0	6
Tanaka H, et al. 2006. 12y[49]	1	1	1	1	1	1	1	1	8
Tanaka S, et al. 1990. 1y[50]	1	0	1	1	1	0	1	0	5
Taura et al. 2005. 1y[51]	1	1	1	1	1	0	1	0	6
Thein et al. 2015. 10y[52]	0	1	1	1	1	1	1	1	7
Tong MJ, 2017. 5y[53]	1	1	1	1	1	1	1	1	8
Tong et al. 2010. 6y[54]	1	1	1	1	1	0	1	0	6
Toyoda H. 2018. 10y[55]	1	1	1	1	2	1	1	0	8
Toyoda et al. 2006. 5y[56]	1	1	1	1	1	1	1	0	7
Trevisani F. 2004. 3y[57]	1	1	1	1	1	0	1	0	6
Trevisani et al. 2007. 6y[58]	0	1	0	1	2	1	1	1	7
Van Meer, et al. 2015. 5y[59]	1	1	1	1	1	1	1	0	7
Van Vlierberghe, et al. 2005. 1y[60]	1	0	0	1	1	0	1	0	4
Wong G, et al. 2008. 2y[61]	1	1	1	1	1	1	1	0	7
Wong L, et al. 2000. 5y[62]	1	1	0	1	1	0	1	0	5
Yang JD, et al. 2011. 3y[63]	0	1	1	1	1	1	1	1	7
Yeh et al. 2014. 2y[64]	1	1	1	1	1	1	1	0	7
Yerokun et al. 2016. 1y[65]	1	0	1	1	1	1	1	0	6
Youk et al. 2003. 6y[66]	1	1	1	1	1	1	1	0	7
Zapata et al. 2010. 2y[67]	0	1	1	1	1	0	1	0	5

①, representativeness of the exposed cohort; ②, selection of the non-exposed cohort; ③, ascertainment of exposure; ④, demonstration that outcome of interest was not present at start of study; ⑤, comparability of cohorts on the basis of the design or analysis; ⑥, assessment of outcome; ⑦, follow-up long enough for outcomes to occur; ⑧, adequacy of follow-up of cohorts.

Abbreviation: NOS, Newcastle-Ottawa Scale.

Supplementary Table 5

Risk-of-bias assessment of case series studies (NICE).

Included study	NICE items	Score
Atiq et al. 2017. 3y[68]	1. Case series collected in more than one centre, i.e. multi-centre study?	1
	2. Is the hypothesis/aim/objective of the study clearly described?	1
	3. Are the inclusion and exclusion criteria (case definition) clearly reported?	1
	4. Is there a clear definition of the outcomes reported?	1
	5. Were data collected prospectively?	0
	6. Is there an explicit statement that patients were recruited consecutively?	1
	7. Are the main findings of the study clearly described?	1
	8. Are outcomes stratified? (e.g., by disease stage, abnormal test results, patient characteristics)	0
	Total	6
Konerman et al. 2019. 2y[69]	1. Case series collected in more than one centre, i.e. multi-centre study?	0
	2. Is the hypothesis/aim/objective of the study clearly described?	1
	3. Are the inclusion and exclusion criteria (case definition) clearly reported?	1
	4. Is there a clear definition of the outcomes reported?	1
	5. Were data collected prospectively?	0
	6. Is there an explicit statement that patients were recruited consecutively?	1
	7. Are the main findings of the study clearly described?	1
	8. Are outcomes stratified? (e.g., by disease stage, abnormal test results, patient characteristics)	0
	Total	7
Frey et al. 2015. 2y[70]	1. Case series collected in more than one centre, i.e. multi-centre study?	0
	2. Is the hypothesis/aim/objective of the study clearly described?	1
	3. Are the inclusion and exclusion criteria (case definition) clearly reported?	1
	4. Is there a clear definition of the outcomes reported?	0

	5. Were data collected prospectively?	1
	6. Is there an explicit statement that patients were recruited consecutively?	1
	7. Are the main findings of the study clearly described?	1
	8. Are outcomes stratified? (e.g., by disease stage, abnormal test results, patient characteristics)	0
	Total	5

1, yes; 0, no; 8, total score.

Abbreviation: NICE, National institute for clinical excellence.

Supplementary Table 6

Subgroup analyses of 1-year survival rate.

Variables	Subgroup	Number of Study	HCC-S	HCC-C	Test of Heterogeneity		Results of meta-analysis		*P* between Subgroups
					I^2	*P*-value	RR (95% CI)	*P*-value	
RCTs									
Total	-	3	451	228	72.5	0.012	1.72 (1.13-2.61)	< 0.001	-
Screening modalities	AFP	1	257	117	-	-	2.52 (1.38-4.62)	0.003	0.41
	AFP+US	2	178	101	0.0	0.41	1.91 (1.42-2.56)	< 0.001	
Cohort studies									
Total	-	22	2,714	3,753	58.9	0.001	1.47 (1.35-1.59)	< 0.001	-
Screening modalities	AFP or US	3	96	311	0.0	0.48	1.77 (1.38-2.27)	< 0.001	0.30
	AFP+US	12	1,916	2,589	59.3	0.005	1.43 (1.31-1.57)	< 0.001	
	US	7	859	1,070	57.0	0.03	1.45 (1.25-1.69)	< 0.001	
Screening population	HBV	2	212	134	70.1	0.07	1.37 (1.04-1.80)	0.03	0.91
	HCV	2	704	369	0.0	0.65	1.55 (1.32-1.81)	< 0.001	
	Cirrhosis	4	564	754	61.5	0.05	1.56 (1.28-1.90)	< 0.001	
	CH	4	580	1,178	77.9	0.004	1.43 (1.17-1.75)	< 0.001	
	CLD	9	787	1,510	53.6	0.03	1.47 (1.29-1.69)	< 0.001	

Screening intervals	≤ 6m	13	1,314	2,425	58.1	0.004	1.42 (1.29-1.56)	< 0.001	0.01
	6-12m	5	1,261	1,133	0.0	0.63	1.40 (1.29-1.51)	< 0.001	
	> 12m	1	44	113	-	-	1.39 (0.99-2.41)	0.03	
	NA	3	252	299	0.0	0.98	2.25 (1.73-2.92)	< 0.001	
Adjusting lead-time bias	Yes	7	1,284	2,468	62.5	0.001	1.36 (1.23-1.50)	< 0.001	0.04
	No	15	1,587	1,502	42.8	0.04	1.54 (1.39-1.71)	< 0.001	
Location of study	Asia	6	609	676	63.6	0.02	1.58 (1.30-1.91)	< 0.001	0. 10
	USA	10	1,990	2,835	9.2	0.36	1.31 (1.24-1.38)	< 0.001	
	Europe	3	180	257	0.0	0.61	1.94 (1.54-2.44)	< 0.001	
	Other	3	92	202	7.7	0.33	1.67 (1.34-2.09)	0.001	
Study period	2000-2010	9	748	1,418	63.1	0.01	1.64 (1.40-1.92)	< 0.001	0.08
	2010-2021	13	2,123	2,552	40.8	0.06	1.57 (1.27-1.78)	< 0.001	
Proportion of Child Pugh C	< 10%	5	468	562	55.9	0.06	1.38 (1.20-1.59)	< 0.001	0.49
	≥ 10%	5	518	766	0.0	0.77	1.41 (1.28-1.56)	< 0.001	
	NA	12	1,885	2,642	68.3	< 0.001	1.53 (1.35-1.74)	< 0.001	
Age	40-50	1	186	82	-	-	1.59 (1.25-2/10)	< 0.001	0.25
	50-60	6	971	1,166	78.5	< 0.001	1.54 (1.27-1.87)	< 0.001	
	60-70	8	1,057	1,741	0.0	0.67	1.32 (1.24-1.41)	< 0.001	

≥ 70	2	149	113	0.0	0.58	1.54 (1.20-1.97)	< 0.001
NA	5	1.73	508	77.9	0.001	1.73 (1.24-2.40)	< 0.001

Abbreviations: AFP, alpha-fetoprotein; CH, chronic hepatitis (chronic hepatitis included hepatitis B, hepatitis C, alcoholic liver disease and so on); CI, confidence interval; CLD, chronic liver disease (chronic liver disease included chronic hepatitis and cirrhosis); HBV, hepatitis B; HCV, hepatitis C; HCC-S, number of patients with hepatocellular carcinoma in screening group; HCC-C, number of patients with hepatocellular carcinoma in non-screening group; m, months; NA, not reported; RCT, random clinical trial; RR, risk ratio; US, ultrasound; USA, The United States of America.

Supplementary Table 7

Subgroup analyses of 3-year survival rate.

Variables	Subgroup	Numbers of Study	HCC-S	HCC-C	Test of Heterogeneity		Results of meta-analysis		*P* between Subgroups
					I^2	*P*-value	RR (95% CI)	*P*-value	
RCTs									
Total	-	3	435	218	10.1	0.33	2.86 (1.78-4.58)	< 0.001	-
Screening modalities	AFP	1	257	117	-	-	2.05 (1.07-3.92)	0.03	0.18
	AFP+US	2	178	101	0.0	0.51	3.76 (2.04-6.93)	< 0.001	
Cohort studies									
Total	-	26	5,499	6,064	68.9	< 0.001	1.58 (1.42-1.76)	< 0.001	-
Screening modalities	AFP or US	3	85	245	3.2	0.36	2.05 (1.30-3.21)	0.002	0.44
	AFP+US	13	2,376	3,369	41.3	0.06	1.59 (1.42,1.78)	< 0.001	
	US	10	3,038	2,450	71.0	< 0.001	1.51 (1.24-1.85)	< 0.001	
Screening population	HBV	3	226	171	0.0	0.47	2.11 (1.57-2.84)	< 0.001	0.36
	HCV	4	902	627	50.5	0.11	1.56 (1.21-2.00)	0.001	
	Cirrhosis	8	2,411	2,790	84.3	< 0.001	1.48 (1.23-1.78)	< 0.001	
	CH	2	447	698	82.5	0.02	1.68 (1.10-2.56)	0.02	

	CLD	10	1,483	1,778	0.0	0.547	1.56 (1.35-1.80)	< 0.001	
Screening intervals	≤ 6m	14	3,286	3,212	54.6	0.007	2.19 (1.79-2.68)	< 0.001	0.57
	6-12m	10	1,777	2,557	75.1	< 0.001	1.59 (1.31-1.95)	< 0.001	
	> 12m	1	44	113	-	-	1.56 (0.89-2.75)	0.12	
	NA	1	392	182	-	-	1.64 (1.34-2.00)	< 0.001	
Adjusting lead-time bias	Yes	5	1,098	1,946	57.1	0.05	1.51 (1.28-1.78)	< 0.001	0.04
	No	21	4,401	4,118	72.2	< 0.001	1.62 (1.42-1.85)	< 0.001	
Location of study	Asia	8	2,685	1,458	0.0	0.73	1.83 (1.66-2.01)	< 0.001	< 0.001
	USA	14	2,650	4,337	66.2	< 0.001	1.44 (1.28-1.62)	< 0.001	
	Europe	2	99	189	67.9	0.08	1.64 (0.66-4.09)	0.29	
	Other	2	65	80	0.0	0.90	2.20 (1.28-3.76)	0.03	
Study period	2000-2010	12	3,123	2,338	46.6	0.04	1.63 (1.43-1.85)	< 0.001	0.53
	2010-2021	14	2,376	3,726	72.6	< 0.001	1.55 (1.34-1.79)	< 0.001	
Proportion of Child C	< 10%	7	644	778	69.0	0.01	1.63 (1.25-2.13)	< 0.001	0.39
	≥ 10%	8	2,257	2,747	84.5	< 0.001	1.53 (1.25-1.88)	< 0.001	
	NA	11	2,598	2,539	32.6	0.13	1.59 (1.40-1.81)	< 0.001	
Age	40-50	1	186	82	-	-	1.59 (1.25-2/10)	< 0.001	0.04
	50-60	9	1,308	2,111	40.8	0.09	1.45 (1.25-1.69)	< 0.001	

60-70	10	2,401	2,379	82.3	< 0.001	1.56 (1.27-1.91)	< 0.001
≥ 70	3	401	469	0.0	0.40	1.53 (1.41-2.38)	< 0.001
NA	3	1,203	1,023	39.6	0.19	1.56 (1.27-1.93)	< 0.001

Abbreviations: AFP, alpha-fetoprotein; CH, chronic hepatitis (chronic hepatitis included hepatitis B, hepatitis C, alcoholic liver disease and so on); CI, confidence interval; CLD, chronic liver disease (chronic liver disease included chronic hepatitis and cirrhosis); HBV, hepatitis B; HCV, hepatitis C; HCC-S, number of patients with hepatocellular carcinoma in screening group; HCC-C, number of patients with hepatocellular carcinoma in non-screening group; m, months; NA, not reported; RCT, random clinical trial; RR, risk ratio; US, ultrasound; USA, The United States of America.

Supplementary Table 8

Subgroup analyses of 5-year survival rate.

Variables	Subgroup	Numbers of Study	HCC-S	HCC-C	Test of Heterogeneity		Results of meta-analysis		*P*-value between Subgroup
					I^2	*P*-value	RR (95% CI)	*P*-value	
RCTs									
Total	-	3	435	218	28.3	0.25	2.76 (1.37-5.54)	< 0.001	-
Screening modalities	AFP	1	257	117	-	-	1.38 (0.44-4.38)	0.58	0.07
	AFP+US	2	175	101	0.0	0.43	2.11 (1.23-11.29)	< 0.001	
Cohort studies									
Total	-	12	2,886	3050	14.0	0.31	1.62 (1.47-1.79)	< 0.001	-
Screening modalities	AFP or US	1	27	122	-	-	2.71 (0.69-10.66)	0.15	0.10
	AFP+US	7	1,906	1,941	39.3	0.13	1.80 (1.46-2.12)	< 0.001	
	US	4	953	987	0.0	0.87	1.53 (1.37-1.72)	< 0.001	
Screening population	HBV	2	212	134	0.0	0.54	2.01 (1.35-2.99)	0.001	0.42
	HCV	3	886	571	0.0	0.48	1.40 (1.15-1.71)	0.001	
	Cirrhosis	3	989	746	0.0	0.53	1.58 (1.38-1.80)	< 0.001	
	CH	2	477	698	80.6	0.02	1.98 (1.13-3.44)	0.02	
	CLD	2	322	901	0.0	0.50	1.70 (1.40-2.07)	< 0.001	

Screening intervals	≤ 6m	7	1,460	1,900	0.0	0.79	1.59 (1.44-1.75)	< 0.001	0.82
	6-12m	3	1,007	846	75.8	0.02	1.90 (1.11-3.26)	0.02	
	NA	2	419	304	0.0	0.43	1.58 (1.18-2.11)	0.002	
Adjusting lead-time bias	Yes	4	1,024	1,833	48.8	0.12	1.83 (1.46-2.28)	< 0.001	0.17
	No	8	1,862	1,217	0.0	0.65	1.54 (1.38-1.72)	< 0.001	
Location of study	Asia	4	728	353	0.0	0.66	1.71 (1.37-2.14)	< 0.001	0.79
	USA	6	1,786	2,367	50.2	0.07	1.64 (1.37-1.96)	< 0.001	
	Other	2	372	330	0.0	0.43	1.56 (1.34-1.83)	< 0.001	
Study period	2000-2010	5	1,039	944	0.0	0.58	1.59 (1.34-1.88)	< 0.001	0.73
	2010-2021	7	1,847	2,106	39.0	0.13	1.65 (1.43-1.91)	< 0.001	
Proportion of Child Pugh C	< 10%	4	728	620	61.2	0.05	1.76 (1.36-2.29)	< 0.001	0.79
	≥ 10%	2	644	538	9.6	0.29	1.67 (1.24-2.24)	0.001	
	NA	6	1,514	1,892	0.0	0.57	1.60 (1.40-1.82)	< 0.001	
Age	40-50	1	186	82	-	-	1.59 (1.25-2/10)	< 0.001	0.58
	50-60	2	606	384	61.8	0.11	1.59 (1.36-1.77)	< 0.001	
	60-70	4	1,044	1,321	54.1	1.10	1.70 (1.38-2.09)	< 0.001	
	≥ 70	2	376	393	0.0	0.73	2.06 (1.32-3.21)	< 0.001	
	NA	3	674	870	0.0	0.72	1.55 (1.36-1.77)	< 0.001	

Abbreviations: AFP, alpha-fetoprotein; CH, chronic hepatitis (chronic hepatitis included hepatitis B, hepatitis C, alcoholic liver disease and so on); CI, confidence interval; CLD, chronic liver disease (chronic liver disease included chronic hepatitis and cirrhosis); HBV, hepatitis B; HCV, hepatitis C; HCC-S, number of patients with hepatocellular carcinoma in screening group; HCC-C, number of patients with hepatocellular carcinoma in non-screening group; m, months; NA, not reported; RCT, random clinical trial; RR, risk ratio; US, ultrasound; USA, The United States of America.

Supplementary Table 9

Subgroup analyses of proportion of early HCC.

Variables	Subgroup	Numbers of study	HCC-S	HCC-C	Test of Heterogeneity		Results of meta-analysis		*P* between Subgroup
					I^2	*P*-value	RR (95% CI)	*P*-value	
RCTs									
Total	-	4	492	322	50.4	0.11	2.68 (1.77-4.06)	< 0.001	-
Screening modalities	AFP	1	257	117	-	-	4.94 (2.35-10.39)	< 0.001	0.08
	AFP+US	3	235	205	19.8	0.29	2.35 (1.66-3.33)	< 0.001	
Cohort studies									
Total	-	50	9,908	12,433	81.6	< 0.001	2.16 (1.99-2.33)	< 0.001	-
Screening modalities	AFP or US	7	849	1,245	74.3	0.001	1.89 (1.58-2.27)	< 0.001	0.31
	AFP+US	21	5,934	7,174	84.7	< 0.001	2.24 (1.99-2.53)	< 0.001	
	US	22	3,266	4,121	76.7	< 0.001	2.15 (1.91-2.45)	< 0.001	
Screening population	HBV	4	968	603	0.0	0.62	2.41 (2.09-2.77)	< 0.001	0.53
	HCV	3	322	295	66.1	0.05	2.27 (1.48-3.48)	< 0.001	
	CH	3	375	627	0.0	0.93	2.37 (2.08-2.71)	< 0.001	

	Cirrhosis	25	4,739	6,550	86.7	< 0.001	2.08 (1.83-2.36)	< 0.001	
	CLD	15	3,645	4,465	73.3	< 0.001	2.20 (1.94-2.50)	< 0.001	
Screening intervals	≤ 6m	26	4,652	5,927	84.0	< 0.001	2.19 (1.94-2.46)	< 0.001	0.82
	6-12m	12	1,646	2,870	73.9	< 0.001	2.21(1.90-2.57)	< 0.001	
	NA	12	3,751	3,843	79.3	< 0.001	2.07 (1.77-2.41)	< 0.001	
Adjusting lead-time bias	Yes	9	4,097	4,059	85.7	< 0.001	2.15 (1.83-2.54)	< 0.001	0.89
	No	41	5,952	8,581	80.1	< 0.001	2.17 (1.98-2.38)	< 0.001	
Location of study	Asia	13	5,067	4,322	82.7	< 0.001	2.35 (2.04-2.72)	< 0.001	0.59
	USA	23	3,699	6,216	84.0	< 0.001	2.09 (1.86-2.35)	< 0.001	
	Europe	9	711	1,135	73.6	< 0.001	2.23 (1.73-2.87)	< 0.001	
	Other	5	572	967	81.2	< 0.001	2.05 (1.48-2.86)	< 0.001	
Study period	1990-2000	3	99	240	0.0	0.68	3.04 (2.11-4.37)	< 0.001	0.16
	2000-2010	15	2,784	2,820	63.5	< 0.001	2.19 (1.94-2.47)	< 0.001	
	2010-2021	32	7,166	9,580	85.4	< 0.001	2.11 (1.91-2.33)	< 0.001	
Proportion of Child Pugh C	< 10%	12	4,294	3,877	79.6	< 0.001	2.20 (1.94-2.50)	< 0.001	0.85
	≥ 10%	17	3,653	4,877	82.4	< 0.001	2.22 (1.91-2.57)	< 0.001	
	NA	21	2,102	3,886	80.7	< 0.001	2.10 (1.83-2.40)	< 0.001	
Age	50-60	13	2,469	3,845	80.2	< 0.001	2.34 (2.00-2.73)	< 0.001	0.02

60-70	18	5,632	5,669	85.5	< 0.001	2.17 (1.90-2.49)	< 0.001
≥ 70	3	307	251	38.6	< 0.001	2.11 (1.60-2.79)	< 0.001
NA	17	1,640	2,875	79.7	< 0.001	2.02 (1.74-2.34)	< 0.001

Abbreviations: AFP, alpha-fetoprotein; CH, chronic hepatitis (chronic hepatitis included hepatitis B, hepatitis C, alcoholic liver disease and so on); CI, confidence interval; CLD, chronic liver disease (chronic liver disease included chronic hepatitis and cirrhosis); HBV, hepatitis B; HCV, hepatitis C; HCC-S, number of patients with hepatocellular carcinoma in screening group; HCC-C, number of patients with hepatocellular carcinoma in non-screening group; m, months; NA, not reported; RCT, random clinical trial; RR, risk ratio; US, ultrasound; USA, The United States of America

Supplementary Table 10

Results of Sensitivity analysis.

Outcomes	RR (95% CI)	High risk bias studies excluded
Proportion of early HCC	(1) Before exclude RR = 2.16 (2.00-2.34) (2) After exclude RR = 2.12 (1.94-2.31)	Ando et al. 2006. 5y[5] Caumes et al. 2007. 3y[7] Cheung et al. 2006. 3y[10] Khalaf et al. 2016. 1y[29] Martínez et al. 1993. 1y[33] Miguel et al. 2012. 7y[34] Rich et al. 2017. 8y[42] Stravitz et al. 2008. 8y[47] Tanaka S, et al. 1990. 1y[50] Van Vlierberghe, et al. 2005. 1y[60] Wong L, et al. 2000. 5y[62] Zapata et al. 2010. 2y[67]
1-year survival rate	(1) Before exclude RR = 1.47 (1.35-1.59) (2) After exclude RR = 1.40 (1.30-1.51)	Wong L, et al. 2000. 5y[62] Van Vlierberghe, et al. 2005. 1y[60] Chen JG, et al. 2017. 5y[11]

3-year survival rate	(1) Before exclude RR = 1.58 (1.42-1.76) (2) After exclude: RR = 1.53 (1.37-1.70)	Ando et al. 2006. 5y[5] Chen JG, et al. 2017. 5y[11] Costentin et al. 2016. 4y[14] Silveira et al. 2008. 7y[45] Stravitz et al. 2008. 8y[47] Wong L, et al. 2000. 5y[62]
5-year survival rate	(1) Before exclude RR = 1.62 (1.47-1.79) (2) After exclude: RR = 1.63 (1.45-1.79)	Ando et al. 2006. 5y[5] Chen JG, et al. 2017. 5y[11]

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; RR, risk ratio.

Supplementary Table 11

Results of the quality of evidence.

Outcomes	Study design	NO. study	Rating down quality of evidence				Rating up quality of evidence				Quality of evidence
			Limitation	Inconsistency	Indirection	Imprecision	Reporting bias	Large effect	Plausible confounding	Dose response	
HCC mortality	RCTs	3	-2	-2	0	-1	NA	-	-	-	Very low
	Cohort studies	3	0	-1	0	-1	NA	0	0	0	Very low
1-year survival rates	RCTs	3	-2	-2	0	-1	NA	-	-	-	Very low
	Cohort studies	22	0	-1	0	-1	-1	0	0	0	Very low
3-year survival rates	RCTs	3	-2	0	0	-2	NA	-	-	-	Very low
	Cohort studies	26	0	-2	0	-1	0	0	0	0	Very low
5-year survival rates	RCTs	3	-2	0	0	-1	NA	-	-	-	Very low
	Cohort studies	12	0	0	0	-1	0	0	0	0	Very low
Proportion of early HCC	RCTs	4	-2	-1	0	-1	NA	-	-	-	Very low
	Cohort studies	50	0	-2	0	-1	-2	+1	0	0	Very low

Notes:

Based on the GRADE guidelines, we considered rating down the quality of evidence of each outcome in the meta-analysis on five dimensions (limitation, inconsistency, indirections, imprecision, reporting bias) or rating up the quality of evidence on three dimensions (large effect, plausible confounding, dose response).

(1) Rating down the quality of evidence:

① Limitation: We evaluated the limitation of each pooled outcome according to the risk of bias of included studies. All the RCTs had high risk of bias, most of cohort studies had low risk of bias. Therefore, the limitations of pooled outcome across RCTs were considered very serious, the limitations downgraded 2 levels, limitation of pooled outcome across cohort studies did not downgrade.

② Inconsistency: We evaluated the inconsistency of each pooled outcome according to the heterogeneity across included studies. If the I^2 was under 30%, the inconsistency was not considered downgrade; if the range of I^2 was 30%-60%, the inconsistency was considered to downgrade 1 level; if the I^2 was over 60%,

the inconsistency was considered downgrade 2 levels.

③ Indirection: Head-to-head meta-analyses were conducted to compare respectively screening to non-screening group, different screening intervals and screening modalities. Therefore, there was no indirect comparison in the meta-analysis.

④ Imprecision: We evaluated the imprecision of each pooled outcome according to the 95% confidence intervals (CIs) and optimal information size (OIS). We found total number of events or patients exceeds the OIS criterion in the all outcomes. If the 95% CI includes appreciable benefit or harm (RR/HR/OR of under 0.75 or over 1.25), rating down for imprecision was considered.

⑤ Reporting bias: We evaluated the reporting bias according to publication bias. Considering the availability of the Egger's test for the symmetry of funnel plots, we only analyzed the publication bias of the pooled outcomes was included the more than 10 studies. Therefore, the publication bias of pooled outcomes included 1-9 studies was not evaluated. If the publication bias was significant, reporting bias was considered to downgrade.

(2) Increase quality of evidence:

According to the GRADE guidelines, increasing quality of evidence was be applied generally to the observational studies.

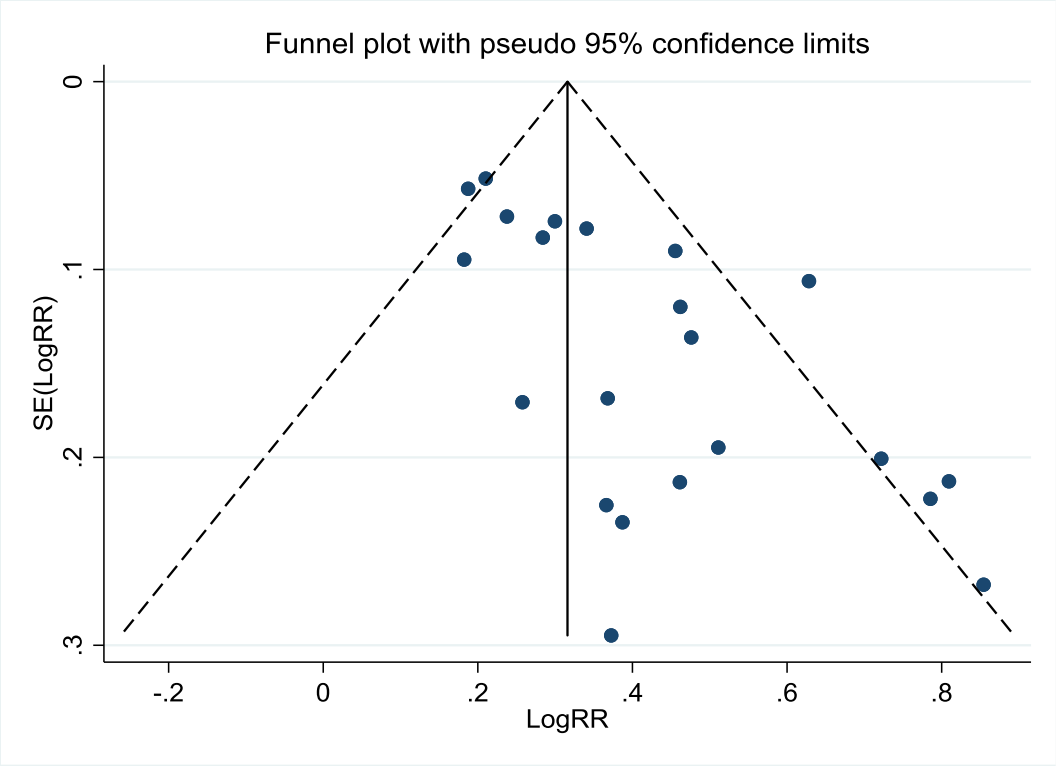
① Large effect: If the RR of under 0.5 or over 2 based on consistent evidence from at least 2 studies, considering to upgrade 1 level; If the RR of under 0.2 or over 5 based on direct evidence with no major threats to validity, considering to upgrade 2 levels.

② Plausible confounding: We only pooled the outcome rates of the screening group and the non-screening group without adjusting plausible confounding. Therefore, we did not upgrade GRADE levels because adjusting plausible confounding factors all the pooled outcomes.

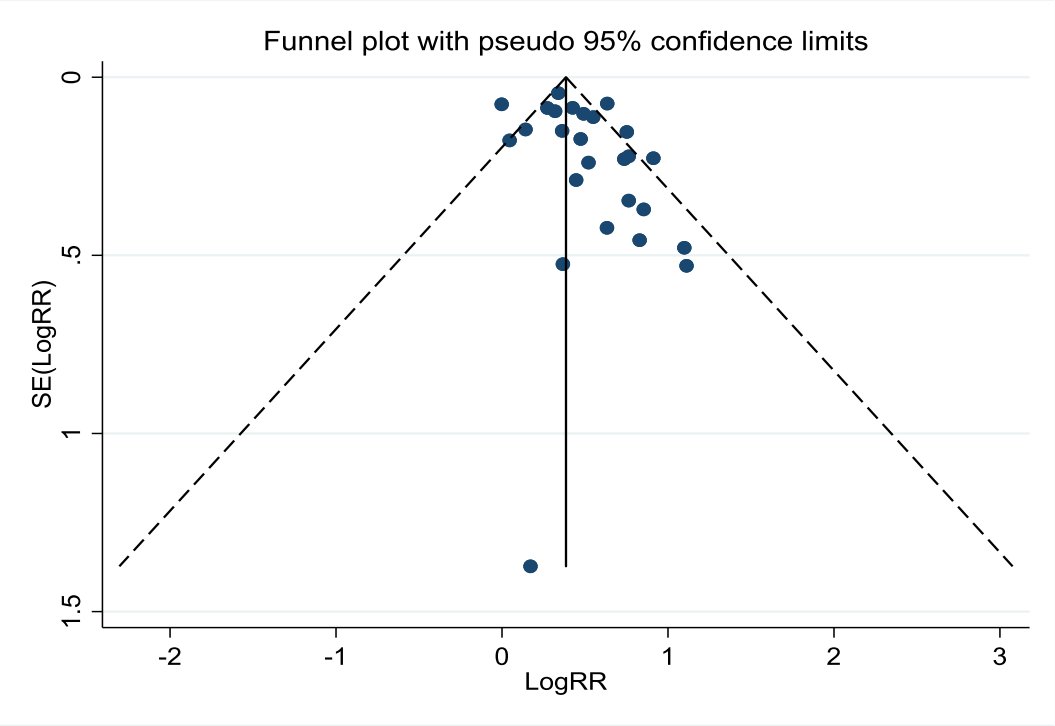
③ Dose response: There was no dose response among all the pooled outcomes

Proportion of physiological harm: GRADE is only for pooled evidence from comparative studies such as RCTs and cohort studies, while the proportion of physiological harm was provided by non-comparative studies. Therefore, it was not evaluated using GRADE. However, there is a great heterogeneity in pooled proportion of physiological harm so it is necessary to be cautious in quoting it.

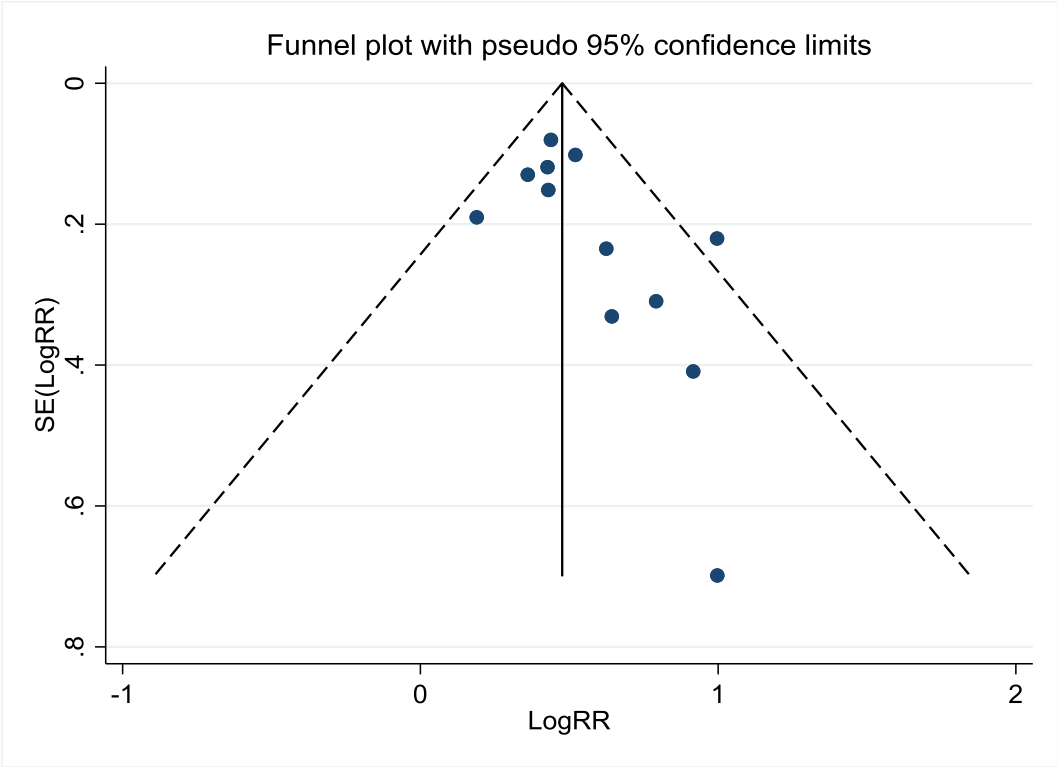
Abbreviations: HCC, hepatocellular carcinoma; NA, not reported; RCT, random clinical trial.



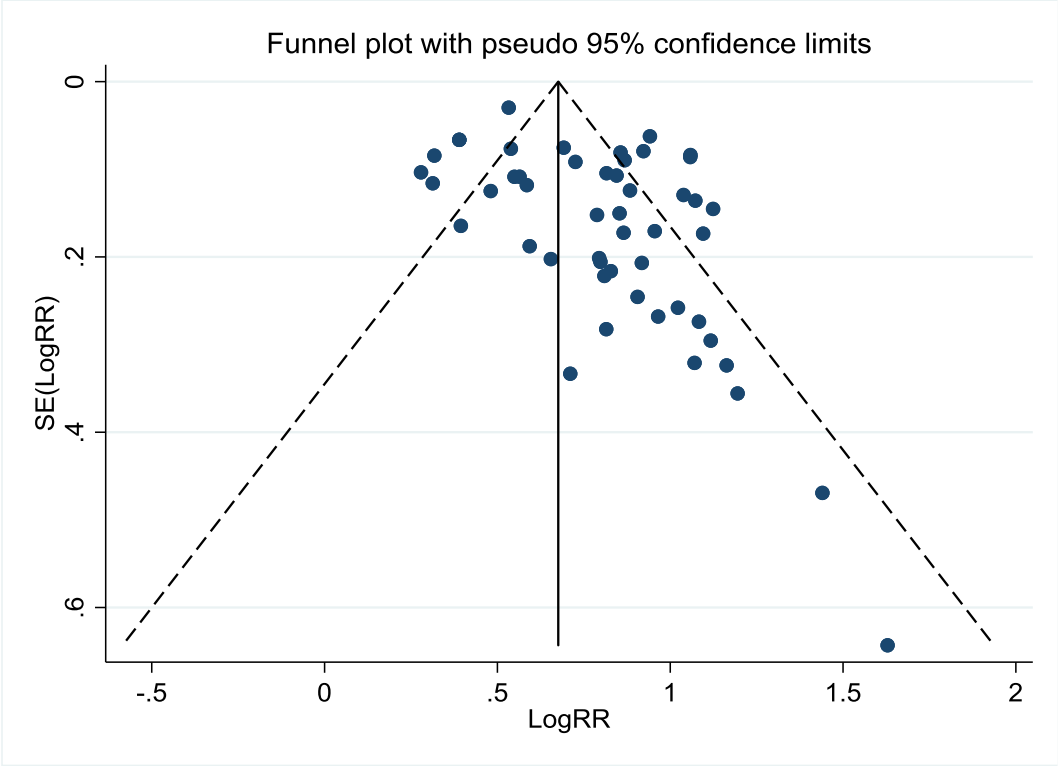
Supplementary Fig. 1. Funnel plot of pooled 1-year survival rate of cohort studies. *P* of Egger's test ≤ 0.001.



Supplementary Fig. 2. Funnel plot of pooled 3-year survival rate of cohort studies. *P* of Egger's test = 0.06.



Supplementary Fig. 3. Funnel plot of pooled 5-year survival rate of cohort studies. *P* of Egger's test = 0.07.



Supplementary Fig. 4. Funnel plot of pooled proportion early HCC of cohort studies. *P* of Egger's test = 0.002.

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