

**Table 4. Assessment of study methods for potential sources of bias in cohort studies of screening for hepatocellular carcinoma in patients with chronic liver disease**

Author, Year, Setting Years of enrollment	How was the screening group distinguished from non-screening?	Was this definition objective and replicable?	Loss to follow-up, difference in loss to follow-up between screened and unscreened?	Selection bias - are screening and nonscreening groups drawn from similar populations?	Ascertainment of outcomes adequately described and similar between surveilled and non-surveilled groups?
Bolondi, 2001 <sup>32</sup> Europe: Italy	Screening group were patients prospectively enrolled in a screening program. Non-screening group was referred - possible that some of these patients were screened, but no data	Yes, for the screening group, not for the non-screening group.	Data for screening group only: Mean follow-up months: 56 7.7% lost to follow-up	Compared patients at an institution to referral patients.	Unclear
Chen, 2002 <sup>33</sup> Asia: Taiwan	Those undergoing screening vs those who refused	Objective, but not valid.	NR	No - non-screening group were those that refused intervention.	Probably yes (national death registry)
El-Serag, 2011 <sup>35</sup> U.S. (national VA HCV registry) 1998-2007	Used lab data and CPT codes to determine receipt of AFP or ultrasounds. Used an algorithm to determine whether AFP or US were performed for HCC screening based on lab data and ICD-CM codes.	Yes	NR, but unlikely that there was differential or high loss to follow-up as included all VA patients and they conducted sensitivity analyses using Medicare data for older patients	Yes	Yes - the date of death was obtained from the VA vital status file.
Davila, 2007 <sup>34</sup> U.S - 3 VAMCs (Houston, Tennessee Valley, Kansas City)	Receipt of screening defined as having AFP, US, or CT within 3 years prior to HCC diagnosis. Detailed chart review used to assess intent of test. Tests performed for acute symptoms, during hospitalization, or to assess a mass were not considered screening.	Yes	NR	Yes	Yes
Giannini, 2000 <sup>36</sup> Europe: Italy	Screening group defined as those who were receiving follow-up for cirrhosis. Control patients were referred patients or had tests done at "non-scheduled intervals"	No	NR	Unclear - control patients had tests done at "non-scheduled intervals" but it was unclear whether this meant they were enrolled in cirrhosis clinic but failed to present for testing or were not enrolled in a screening program.	No
Kemp, 2005 <sup>37</sup> 1994-2002	Screening group were those treated by gastroenterology unit, which used regular screening. Unclear how unit of treatment was determined	No - it is not clear how patients were chosen for treatment by gastroenterology unit	Unclear	No - groups defined by treating unit which may treat different patient populations.	Unclear
Kuo, 2010 <sup>38</sup> Asia: Taiwan	Screening group had AFP and US done as part of screening program and repeated within one year. Control group had HCC diagnosed because of symptoms or as part of another work-up, but it is not clear how they differentiated groups based on chart review	No	NR	Unclear - not enough detail about both groups. Unclear whether control patients were referred from outside institutions and why they would not have received screening.	Yes - national mortality dataset
Leykum, 2007 <sup>39</sup> US. Michael DeBakey VAMC, Houston TX	Chart review. Screening group were those who received AFP or imaging in year prior to diagnosis and no alternative reason for testing was apparent from chart review.	Yes	NR, but unlikely that there was differential or high loss to follow-up as included all VA patients	Yes	Yes - VA patients

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Pascual, 2008 <sup>40</sup> Europe: Spain 1996-2005	Screening group were patients seen in Liver Unit and diagnosed as part of their regular screening program. Non-screening group were either patients with cirrhosis diagnosed with HCC because of symptoms, or diagnosed with HCC at the time of cirrhosis diagnosis	No, it is unclear why some patients attending a screening program and others didn't. Also unclear procedures for cirrhosis work-up.	28 out of 290 patients were lost to follow-up but did not differentiate between screened and unscreened	No - some non-screening patients were referred from outside institutions and others at the institution did not attend screening program for unclear reasons.	Yes, through registry
Tanaka, 2006 <sup>41</sup> Asia: Japan 1991-2003	Unclear - screening group patients were part of a screening program. Non-screening patients had HCC detected because of symptoms (12%), as a result of initial screening (11%), incidentally during other work-up (20%), and referred from outside hospitals (57%)	No - unclear how symptomatic detection was determined retrospectively and unclear how referral patients were surveilled.	None	Unclear - probably not, the majority of non-screening patients were referred from outside institutions with little detail about care at these institutions.	Unclear
Taura, 2005 <sup>42</sup> Asia: Japan 1991 - 2001	Unclear - non-screening group presented with symptoms, but unclear how this was determined in retrospective review	No	Loss to follow-up - unclear Median follow-up months: 41.3 vs 29.6	Unclear - does not specify whether these were consecutive patients with HCC. All were from single institution, but unclear why some patients received routine screening while others did not.	Unclear
Tong, 2010 <sup>43</sup> U.S. Pasadena, CA 1991-2008	Unclear: Non-screening group was referred from elsewhere. No info on screening among non-screening group.	NR	NR	Unclear - non-screening patients presented to clinic with HCC. No information about their prior care.	Source of death data NR
Trevisani, 2002 <sup>44</sup> Europe: Italy 1988-1998	Unclear how symptomatic presentation was defined.	No	5 vs 4 vs 9	No - Most patients treated at study center were part of screening program, while referral patients were not.	unclear
2004 <sup>45</sup> Europe: Italy 1988-2001	Unclear - no details about how symptomatic or incidental HCC diagnoses were categorized in the registry.	No	0 vs 2 vs 2	No - Most patients treated at study center were part of screening program, while referral patients were not. In fact, treating center was independently associated with survival.	unclear
Wong, 2008 <sup>46</sup> Asia: China (Hong Kong) 2003-2005	Screening group pts enrolled in a screening program. Non-screening group was referred - possible that some of these patients were screened, but no data. "We assumed that these patients did not receive regular follow-up or screening with AFP or USG while the HCC was an incidental finding."	No	NR Data for screening group only: median duration of follow-up 184 weeks (range 61-363 weeks).	No - non-screening group defined as being all referral patients	Unclear
Yu, 2004 <sup>47</sup> Asia: Taiwan 1996-1997	No details reported. Screening group: tumors were found during routine follow-up US, no details on frequency. The nonscreening group consisted of the opportunistic and symptomatic groups. Opportunistic group: tumors were found by incidental health checkup or other nonhepatic reasons without liver-associated symptoms Symptomatic group - visited hospital because of liver-associated symptoms.	No	NR	Unclear - not enough information about how groups were defined	Yes - linked to Taiwan mortality data