

Appendix 3. Summary of included studies with study design information

Author	Country and year	Study type	Population	Sample size	Participant characteristics	Study setting	Target population for surveillance	Surveillance approach(es)/intervention	Outcome measures
Patients with viral hepatitis									
McMahon et al ¹	USA, 2000	Prospective cohort	HBV-positive Alaska 'Natives'	1487	Native Alaskans, many living in isolated villages; mean age at first AFP: 20 years, HBV positive	Village Community Health Aides, regional HCP	All HBV-positive patients	6-monthly: AFP; if elevated repeat AFP, if elevated US + LFTs Elevated AFP: Pre-1993: >25 ng/mL; subsequently >15 ng/mL	HCC diagnosed in 32 participants, AFP elevated in 97% of these; mean age at diagnosis 24 years. 83% detected through surveillance were at a resectable stage; 5-year survival rate 42%
Leykum et al ²	USA, 2007	Retrospective chart review	HCV + HCC patients	72	HCV positive; racially diverse	South Texas Veteran Health Care System; PCPs and other specialities	n/a	AFP + US/CT; no time frequency of surveillance reported	For all HCPs: 22% of patients were screened prior to HCC diagnosis; all screen-identified HCC were detected at early stages; improved survival for screened patients: average survival: 19.8 months vs 8.5 months. Decreased risk of HCC death associated with PCP care delivered in a tertiary setting (unadjusted: HR 1.47; 95% CI: 1.01, 2.14), but no associations in adjusted analysis
Sarkar et al ³	USA, 2012	Retrospective cohort	CHB patients	1431; 947 meeting surveillance criteria	Mostly uninsured patients, HBV positive; Asian Americans	11 primary care clinics in San Francisco safety net healthcare system	Males >40 years and females >50 years and patients with cirrhosis	>1 AFP and/or US annually	67% screened in first year after HBV diagnosis; 47% in second year, 24% in 10th year. HCC diagnosed in 51 patients. Screened patients more likely to be diagnosed at an early stage of HCC (79% vs 19%) and receive curative treatment (71% vs 30%). Median survival was associated with curative treatment (HR 0.3; 95% CI: 0.1, 0.9).

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Sarkar et al ⁴	USA, 2014	Retrospective cohort	CHB patients	12,016	Mean age 49 years, 51% male, 83% Asian ethnicity	Kaiser Permanente Medical Care Program	CHB patients: - with cirrhosis - females aged >50 years - males aged >40 years - clinical diagnosis of alcohol abuse	US and/or AFP 6- to 12-monthly	Imaging within 18 months: 56% overall; 73% for PCPs vs 92% for gastroenterologists Imaging + AFP: 49% overall; PCPs 65% vs gastroenterologists 87%. AFP only: PCPs 13% vs 5%
Wu et al ⁵	USA, 2014	Retrospective cohort	CHB patients	962, with 696 meeting surveillance guidelines	Median age 45 years, 43% female, racially diverse	Medical centre and satellite clinics	HBV patients	Abdominal imaging ± AFP at least once per 12 months (+3-month grace period)	55% received surveillance at least once per 15 months; 35% ≤ every 15 months (mean surveillance interval 3.9 years); 10% received no surveillance. Greater odds of timely HCC surveillance when managed by a gastroenterologist versus PCP: OR 6.87 (95% CI: 4.5, 9.7)
Allard et al ⁶	Australia, 2017	Retrospective cohort	CHB patients	67	Predominantly male, racially diverse, median age 38 years	Community health centre (Victoria) in a multicultural setting	Cirrhosis, first-degree family history of HCC, Asian men aged >40 years, Asian women aged >50 years, African people aged >20 years, Aboriginal and Torres Strait Islander people aged >50 years	US ± AFP 6-monthly Surveillance was supported by specialist nurses: contacting patients lost to follow-up; strengthening standard recall and reminder systems by mailing radiology/pathology requests, regular review and telephone calls to patients not attending	Follow-up 4.5 years: 'good adherence' 27%, suboptimal adherence 43%, poor adherence 30%

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O'Leary et al ⁷	Australia, 2018	Quasi-experimental	High risk CHB patients: Asian males >40 years; Asian females >50 years; those with cirrhosis or a family history of HCC	Intervention: 30 Control: 60	Intervention: 63% female; mean age 56 years; 80% Asian ethnicity; 83% 'high risk' for HCC surveillance Control: 63% female; mean age 55 years; 80% Asian ethnicity; 83% 'high risk' for HCC surveillance	Intervention group: Primary care settings with high numbers of CHB patients Control group: Matched 2:1 on gender, age, ethnicity treated in a tertiary liver clinic	High risk CHB patients	'B in IT' program: Primary care-based CHB care including HCC surveillance for high-risk patients. Links primary care with specialist hepatologists/gastroenterologists Surveillance: US 6-monthly	Receipt of 2 US over 12 months: Before intervention: 26% Intervention: 88% Controls: 10%
DeSilva et al ⁸	USA, 2022	Quasi-experimental	CHB patients	Intervention (PCP): 213 GI: 656 PCP: 4003	Intervention arm: 72% Asian, 27% African American GI arm: 60% Asian, 30% African American PCP: 38% Asian, 38% African American respectively; 18% White	Intervention group: Primary care serving foreign-born patients GI: Primary care patients not having a regular PCP PCP: Patients with a regular PCP	CHB patients	Abdominal imaging + AFP across three groups: Intervention: CHB registry with workflows with reminder system, support staff following up with patients GI and PCP groups: Usual care	6 months prior to baseline (ie introduction of the intervention): Surveillance uptake: intervention (PCP) group 27%, GI 22%; PCP 3% 6 months subsequent to introduction of intervention: Intervention (PCP) group 34%, GI 15%; PCP 2%

Patients with CHB and HCPs

Burman et al ⁹	USA, 2014	Cross-sectional survey and clinical audit	PCPs and CHB patients	148 HCPs; 1727 patients	HCPs: 71% female, 59% Caucasian, 70% medical doctors Patients: 54% male, mean age 51 years, 67% Asian/Pacific Islander	Community Health Network	HBV patients	n/a	HCP survey: 96% of HCPs reported regular HCC surveillance in the centre; 43% were not familiar with guidelines Audit: 51% of patients had some form of surveillance in preceding 12 months, of these, 51% had AFP, 13% imaging, 36% AFP + imaging
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Author	Country and year	Study type	Population	Sample size	Participant characteristics	Study setting	Target population for surveillance	Surveillance approach(es)/intervention	Outcome measures
Gowda et al ¹⁰	USA, 2017	Mixed methods: Quantitative quasi-experimental with HBV patients allocated to primary care physician, gastroenterologist or infectious diseases physician Qualitative: Focus groups with HCPs	Physicians and patients Focus groups consisted of PCPs, and nurses and physicians from gastroenterology and infectious diseases	201 patients; 19 providers	Patients: HBV	Veteran's Health Services		AASLD guidelines: HBV patients at high risk of HCC: US 6-12 months. High risk: - cirrhosis - aged >40 years + ALT elevation and/or high HBV DNA level > 2000 IU/mL - HCC family history - African Americans aged > 20 years - Asian men aged >40 years and women aged >50 years	Adherence to surveillance guidelines: 15% of patients had US surveillance at 6- to 12-month intervals No statistical difference on surveillance adherence rates for provider type, however PCP had a slightly lower rate
Patients with cirrhosis									
David et al ¹¹	USA, 2010	Retrospective cohort of patients and their providers	HCC patients with previously diagnosed cirrhosis	1873	Medicare recipients aged 65+ years diagnosed with HCC 1994-2002; 66% male, predominantly White	Administrative data from SEER program	Patients with cirrhosis	US and/or AFP 'Regular' surveillance: Annual US and/or AFP in 2 of the last 3 years prior to HCC diagnosis; 'Inconsistent': ≥1 US and/or AFP in prior 3 years	Overall: 17% patients had regular surveillance, 38% inconsistent Regular surveillance group: 52% US+AFP; 46% AFP, 2% US 9.8% of cirrhosis + ALD patients screened; 29% of cirrhosis + HBV/HCV; 32% of cirrhosis + ALD + HBV/HCV; 5% of cirrhosis only
Patwardhan et al ¹²	USA, 2011	Retrospective cohort	Patients with cirrhosis	156 patients	Aetiologies: 29% HCV; 11% HBV; 26% alcohol; 17% NAFLD 63% regularly seen by gastroenterologist; 37% by internists or surgeons	Primary care and outpatient gastroenterology	Patients with cirrhosis	Imaging (US, CT, MRI) ± AFP ≥12-monthly	Overall, 51% received recommended surveillance Surveillance in context of ≥12-monthly follow-up with gastroenterologist: 67% of patients screened. For primary care only patients: 23% were screened

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Author	Country and year	Study type	Population	Sample size	Participant characteristics	Study setting	Target population for surveillance	Surveillance approach(es)/intervention	Outcome measures
Del Poggio et al ¹³	Italy, 2015	Quasi-experimental: pre intervention 1994–2005 and post intervention (2006–2013) and control groups	HCC patients with previously diagnosed cirrhosis	566	Across all groups (ie pre and post for intervention and controls): Predominantly males, Child-Pugh A, with viral aetiology	Primary care centres	Patients with cirrhosis	Training program for PCPs: Opportunistic surveillance of all patients at risk of cirrhosis, refer to hepatologist for confirmation, conduct regular US	Pre-intervention: 35% diagnosed through surveillance; postintervention 55% HCC diagnosed at early stage (BCLC-A) increased from 48% to 64% in the intervention group, and from 38% to 43% in the control Survival: 5-year survival increased in the intervention group: 20% to 40%; in the control group this remained unchanged: 20%
Beste et al ¹⁴	USA, 2015	Quasi-experimental	Patients with cirrhosis	2884: 790 in intervention site; 2094 control sites	>96% male, predominantly White	8 VA facilities in the Pacific Northwest, intervention facility has tertiary and primary care centres	Patients with cirrhosis	Point-of-care computerised clinical reminder (for the physician) for cirrhosis patients with no US/CT/MRI in preceding 6 months	Reminders: 26% were up-to-date, ie no reminder required; reminder 'ignored' in 30%, reminder completed in 45% Adequate surveillance was defined as ≥2 US/CT/MRI more than 6 months apart over 18 months. Overall, adequate surveillance was 28% for intervention site vs 18% at control sites
Ahmed Mohammed et al ¹⁵	USA, 2017	Retrospective cohort	Patients with cirrhosis	369	Median age 58 years, 91% White, mixed aetiologies	Mayo Clinic Health System	Patients with cirrhosis	6-monthly US, CT or MRI	14% received 100% of recommended biannual surveillance, 16% received 75–99%, 29% received 50–74%, 21% received 25–49%, 13% received 1–24%, 7% received no surveillance

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Author	Country and year	Study type	Population	Sample size	Participant characteristics	Study setting	Target population for surveillance	Surveillance approach(es)/intervention	Outcome measures
Atiq et al ¹⁶	USA, 2017	Retrospective cohort	Patients with cirrhosis	680	Mean age 54 years, 65% male, racially diverse, mixed aetiologies	Safety net health system (Dallas), low income	Patients with cirrhosis	Typical surveillance consists of US ± AFP, less commonly CT, MRI (time frame not specified) Follow-up 3 years, mean follow-up 26.7 months	Over 3 years 26.3% had ≥3 US, 1.6% had ≥6 US Benefits of surveillance: <ul style="list-style-type: none">• 70.2% of HCC detected at an early stage cf. 40.0% with no surveillance• 22.9% of patients eligible for curative treatment cf. 0% not receiving surveillance Harms of surveillance: <ul style="list-style-type: none">• 27.5% of follow-up tests for false positive or indeterminate results
Singal et al ¹⁷	USA, 2017	Retrospective cohort	Patients with cirrhosis	1137 1053 with ≥12 months of follow-up	Multi-racial, median age 60 years, 51% male, mixed aetiologies	An integrated healthcare delivery system (Washington state); PCPs, gastroenterologists, hepatologists	Patients with cirrhosis	US 6-monthly	Surveillance over 2 years: 2% received consistent surveillance, 33% inconsistent surveillance, and 65% no surveillance
Goldberg et al ¹⁸	USA, 2017	Retrospective cohort	Patients with cirrhosis	26,577	Veterans Health Administration database	Care provided across primary care, local specialist and tertiary care settings	Patients with cirrhosis	US/CT/MRI 6-monthly	Up-to-date with surveillance over median of 4.7 years: 18% for US/MRI/CT
Singal et al ¹⁹	USA, 2019	Randomised trial	Documented or suspected cirrhosis	1800	Racially diverse, socioeconomically disadvantaged, mixed aetiologies	Large safety net health system (Dallas)	Documented or suspected cirrhosis	Mailed US outreach, mailed US outreach + patient navigation, usual care Navigation involved staff working with patients to identify barriers and encouragement of surveillance decliners to be screened, reminder calls, rescheduling of appointments	Surveillance over 2 years: Mailed US outreach: 18%; mailed US outreach + patient navigation: 23%, usual care: 7% HCC diagnosed in 1.8% of outreach/navigation, 1.0% of outreach, 2.3% of usual care

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Author	Country and year	Study type	Population	Sample size	Participant characteristics	Study setting	Target population for surveillance	Surveillance approach(es)/intervention	Outcome measures
Rodriguez Villalvazo et al ²⁰	USA, 2020	Retrospective cohort	Patients with cirrhosis	61,770	Mean age 61 years, 97% male, 68% White	Veterans Health Administration Medical Centres	Patients with cirrhosis	Initial surveillance consisting of: US/MRI/CT ± AFP within 12 months of index date	Patients living >60 miles away were less likely to be screened (any imaging: HR 0.83; 95% CI: 0.79, 0.88) compared to those living 10–30 miles away (HR 1.05; 95% CI: 1.00, 1.11) Patients living in large/small rural towns or isolated areas were less likely to receive surveillance
Yeo et al ²¹	USA, 2021	Retrospective cohort	Patients with cirrhosis	82,427	55% male, 53% aged >55 years	Data sourced from Truven Health MarketScan Research Database, patients managed by PCP, gastroenterologist/hepatologists	Patients with compensated and decompensated cirrhosis	US/CT/MRI Categories as no testing, testing 6–12 months, 12–24 months, >24 months	Surveillance across all HCPs: 6–12 months: 8.8% 12–24 months: 25.3% >24 months: 40.5% No testing: 45.4% Being seen by a PCP (rather than a gastroenterologist) was negatively associated with surveillance: OR 0.48; 95% CI: 0.46, 0.52

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Appendix 3. Summary of included studies with participant characteristics (cont'd)

Author	Country and year	Study type	Population	Sample size	Participant characteristics	Study setting	Target population for surveillance	Surveillance approach(es)/intervention	Outcome measures
HCC patients, aetiology not specified up-front									
Toyoda et al ²²	Japan, 2006	Retrospective cohort	HCC patients	1641	Patients diagnosed: 1968-80 1981-90 1991-2000 2001-04	Surveillance at tertiary centre or primary care	No surveillance 1968-80 1981-90: Surveillance with limited understanding of risk factors 1991-2000: Surveillance with HCV as a risk factor 2000-04: Surveillance with risk factors HCV and HBV	Tertiary setting: 1968-80: patients with symptoms (eg abdominal pain, hepatomegaly); liver scintigraphy, US, CT, with 6-monthly follow-up with US/CT. Only at author's tertiary setting 1981-1990: Cirrhotic patients US/CT 3- to 6-monthly 1991-2004: Patients with cirrhosis and severe fibrosis: US + AFP 3-monthly + CT/MRI 6-monthly Primary care: 'depended on respective physician'	Tertiary-based surveillance: 33.4% of HCC diagnosed at Stage 1, 35.8% at Stage 2; 52.7% Class A Child-Pugh Primary care-based surveillance: 13.3% of HCC diagnosed at Stage 1, 31.1% at Stage 2; 46.4% Class A Child-Pugh No surveillance: 3.6% of HCC diagnosed at Stage 1, 16.1% at Stage 2; 34.4% Class A Child-Pugh Survival 2001-04: Surveillance in tertiary and primary care: 5-year survival 35.9%, for no surveillance 18.6%
HCPs									
Nguyen et al ²³	USA, 2007	Cross-sectional survey	Family practice, internists, gastroenterology, nephrology	459	60% male, mean age 45 years, 53% Asian ancestry and 43% White, 64% general internists, 22% family practice, <14% gastroenterologists, nephrologists	n/a	n/a	n/a	Any surveillance undertaken in high risk patients: Gastroenterologists: 100% General Internists: 88.4% Family practice: 84.2% Nephrologists: 75.0%
Ferrante et al ²⁴	USA, 2008	Cross-sectional survey	Primary care physicians (ie family physicians)	215	47% female, predominantly White, 75% practicing in community-based group clinics, racially diverse patients	Community clinics	n/a	n/a	Self-report: 25% reported they would order AFP for HBV patients with normal LFTs

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Author	Country and year	Study type	Population	Sample size	Participant characteristics	Study setting	Target population for surveillance	Surveillance approach(es)/intervention	Outcome measures
Khalili et al ²⁵	USA, 2011	Cross-sectional survey	PCPs and specialty providers providing care to Asian Americans	109 HCPs: 87% PCPs	65% female; 61% White and 31% Asian/Pacific Islander	Community clinics in a safety net healthcare system	n/a	n/a	88% self-reported using abdominal imaging and AFP 6- to 12-monthly 66% (of all providers) screened ≥75% of HBV patients for HCC, and 94% self-reported HCC surveillance for HBV patients 27% were unfamiliar with guidelines
El-Serag et al ²⁶	USA, 2013	Cross-sectional survey	HCP in VA medical facilities	268	140 physicians (including PCPs), 65 nurse practitioners, 14 registered nurses, 11 physician assistants, 38 pharmacists, and certified nurse specialists	VA Medical Centres	n/a	n/a	70.9% self-reported surveillance in line with recommendations, experience with management of HCV patients. Physicians and HCP working in gastroenterology/hepatology specialities were more likely to recommend guideline-concordant HCC surveillance than other groups
Han et al ²⁷	USA, 2014	Qualitative	PCPs	20	Self-identified as Korean, Chinese, Egyptian or Russian; fluent in native language, 65% of practice in same ethnic community	Community	n/a	n/a	Patient barriers and facilitators of surveillance (from the perspective of PCPs)
McGowan et al ²⁸	USA, 2015	Cross-sectional survey	PCPs	389	60% male; 81% in private practice; 89% had patients with cirrhosis	n/a	n/a	~ two-thirds of PCPs used US + AFP ~ two-thirds screened 12-monthly	Of the PCPs who had patients with cirrhosis, 45% recommended surveillance
Dalton-Fitzgerald et al ²⁹	USA, 2015	Cross-sectional survey	Primary care physicians with ≤1 cirrhosis patient/week	77	56% female, racially diverse, 66% based in community and 33% in tertiary clinics	Tertiary hospital	Patients with cirrhosis	n/a	Self-reported surveillance: Median annual US surveillance 65%, median biannual surveillance 15% 86% used US ± AFP US-based surveillance conducted by ~33% biannually and ~67% annually

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Mukhtar et al ³⁰	USA, 2017	Cross-sectional survey	PCPs	277	59% female; 50% White, 31% Asian	148 from safety net systems, 129 for non-safety net systems	HBV patients	Predominantly US + AFP; small proportion using CT or MRIs	Half the participants reported surveillance >75% of CHB patients; AFP and US the most frequent used
Fitzgerald et al ³¹	USA, 2018	Cross-sectional survey	Primary care physicians working with migrants from Africa and China	109	Working in areas with high concentrations of patients who are migrants from Africa and China	Community clinics and primary care centres	n/a	n/a	92% responded surveillance should be carried out using US; and 64% reported this should occur every 6–12 months For HBV patients, 68% recommended surveillance; 78% responded that HBV patients from China and Africa should be screened
Simmons et al ³²	USA, 2019	Cross-sectional survey	PCPs	100	PCPs who had ≥1 cirrhosis patient annually; median age 41 years, 65% female, racially diverse	University-affiliated tertiary care referral medical centres	Patients with cirrhosis	n/a	67% conducted surveillance, 33% referred to specialist care for this Of those conducting surveillance: >90% US ± AFP CT/MRI more commonly used for patients with NASH/obesity or decompensated cirrhosis 36.8% reported not performing surveillance in healthy patients aged >80 years with compensated cirrhosis 62% screened HCV patients without cirrhosis

AASLD, American Association for the Study of Liver Disease; AFP, α -fetoprotein; ALD, alcoholic liver disease; ALT, alanine transaminase; BCLC, Barcelona Clinic Level Cancer; CHB, chronic hepatitis B; CI, confidence interval; CT, computed tomography; GI, gastroenterologist; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCP, healthcare provider; HCV, hepatitis C virus; HR, hazard ratio; LFT, liver function test; MRI, magnetic resonance imaging; n/a, not available; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio; PCP, primary care provider; SEER, Surveillance, Epidemiology, and End Results; US, ultrasound; VA, Veterans Affairs.

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