# Supplementary material

**Risk prediction models for liver cancer in adults: a systematic review and meta-analysis**

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**Contents**

[Supplementary panel 1. Search strategy used in PubMed](#_bookmark0)

[Supplementary panel 2. Search strategy used in Web of Science](#_bookmark1)

[Supplementary panel 3. Search strategy used in Cochrane Library](#_bookmark2)

[Supplementary panel 4. Search strategy used in Embase](#_bookmark3)

Supplementary Table 1. Overview of the basic information of the prediction models for liver cancer

[PRISMA Checklist](#_bookmark4)

Supplementary Table 2. Quality assessment of the prediction models based on Prediction model Risk of Bias Assessment Tool (PROBAST).

**Supplementary panel 1.** Search strategy used in PubMed

|  |  |
| --- | --- |
| #1 | ((((((Liver Neoplasms[MeSH Terms]) OR (liver cancer[Title/Abstract])) OR (Carcinoma, Hepatocellular[Title/Abstract])) OR (Hepatocellular Carcinoma[Title/Abstract])) OR (liver tumor[Title/Abstract])) OR (liver tumour[Title/Abstract])) OR (HCC[Title]) |
| #2 | ((((((((((((((((((((((((risk assessment[MeSH Terms]) OR (risk prediction[Title/Abstract])) OR (risk score[Title/Abstract])) OR (risk calculation[Title/Abstract])) OR (prediction model[Title/Abstract])) OR (predict index[Title/Abstract])) OR (decision rule[Title/Abstract])) OR (discrimination[Title/Abstract])) OR (ROC Curve[Title/Abstract])) OR (calibration[Title/Abstract])) OR (AUC[Title/Abstract])) OR (area under the curve[Title/Abstract])) OR (machine learning[Title/Abstract])) OR (neural networks computer[Title/Abstract])) OR (artificial intelligence[Title/Abstract])) OR (Risk estimation[Title/Abstract])) OR (Nomogram[Title/Abstract])) OR (Scoring System[Title/Abstract])) OR (outcome prediction[Title/Abstract]) ) OR (risk classification[Title/Abstract])) OR (forecasting[Title/Abstract])) OR (forecast[Title/Abstract])) OR (decision tree[Title/Abstract])) OR (predictive score[Title/Abstract])) OR (validat\*[Title/Abstract]) |
| #3 | (((meta-analysis[Title]) OR (review[Title])) OR (systematic review[Title]) OR ((((((comment[Publication Type]) OR interview[Publication Type]) OR review[Publication Type]) OR letter[Publication Type]) OR editorial[Publication Type]) OR Meta-Analysis[Publication Type]) OR Systematic review[Publication Type]) OR (Guideline[Publication Type]) |
| #4 | #1 And #2 Not #3 |

**Supplementary panel 2.** Search strategy used in Web of Science

|  |  |
| --- | --- |
| #1 | TOPIC: ((Liver Neoplasms)  OR  TOPIC:  (liver cancer)  OR  TOPIC:  (Carcinoma, Hepatocellular)  OR  TOPIC:  (Hepatocellular Carcinoma)  OR  TOPIC:  (liver tumor)  OR  TOPIC:  (liver tumour)  OR  TOPIC:  (HCC) ) |
| *Indexes=CPCI-S Timespan=All years* |
| #2 | TOPIC:  (risk assessment)  *OR*  TOPIC:  (risk prediction)  *OR*  TOPIC:  (risk score)  *OR*  TOPIC:  (risk calculation)  *OR*  TOPIC:  (prediction model)  *OR*  TOPIC:  (predict index)  *OR*  TOPIC:  (decision rule)  *OR*  TOPIC:  (discrimination)  *OR*  TOPIC:  (ROC Curve)  *OR*  TOPIC:  (calibration)  *OR*  TOPIC:  (AUC)  *OR*  TOPIC:  (area under the curve)  *OR*  TOPIC:  (machine learning)  *OR*  TOPIC:  (neural networks computer)  *OR*  TOPIC:  (artificial intelligence)  *OR*  TOPIC:  (Risk estimation)  *OR*  TOPIC:  (Nomogram)  *OR*  TOPIC:  (Scoring System)  *OR*  TOPIC:  (outcome prediction)  *OR*  TOPIC:  (risk classification)  *OR*  TOPIC:  (forecasting)  *OR*  TOPIC:  (forecast)  *OR*  TOPIC:  (decision tree)  *OR*  TOPIC:  (predictive score)  *OR*  TOPIC:  (validat\*) |
| *Indexes=CPCI-S Timespan=All years* |
| #3 | (#2 AND #1)  *AND* DOCUMENT  TYPES:  (Article) |
| *Indexes=CPCI-S Timespan=All years* |

**Supplementary panel 3.** Search strategy used in Cochrane Library

|  |  |
| --- | --- |
| #1 | (Liver Neoplasms):ti,ab,kw OR (liver cancer):ti,ab,kw OR (Carcinoma, Hepatocellular):ti,ab,kw OR (Hepatocellular Carcinoma):ti,ab,kw OR (liver tumor):ti,ab,kw (Word variations have been searched) |
| #2 | (liver tumour):ti,ab,kw OR (HCC):ti,ab,kw (Word variations have been searched) |
| #3 | #1 OR #2 |
| #4 | (risk assessment):ti,ab,kw OR (risk prediction):ti,ab,kw OR (risk score):ti,ab,kw OR (risk calculation):ti,ab,kw OR (prediction model):ti,ab,kw (Word variations have been searched) |
| #5 | (predict index):ti,ab,kw OR (decision rule):ti,ab,kw OR (discrimination):ti,ab,kw OR (ROC Curve):ti,ab,kw OR (calibration):ti,ab,kw (Word variations have been searched) |
| #6 | (AUC):ti,ab,kw OR (area under the curve):ti,ab,kw OR (machine learning):ti,ab,kw OR (neural networks computer):ti,ab,kw OR (artificial intelligence):ti,ab,kw (Word variations have been searched) |
| #7 | (Risk estimation):ti,ab,kw OR (Nomogram):ti,ab,kw OR (Scoring System):ti,ab,kw OR (outcome prediction):ti,ab,kw OR (risk classification):ti,ab,kw (Word variations have been searched) |
| #8 | (forecasting):ti,ab,kw OR (forecast):ti,ab,kw OR (decision tree):ti,ab,kw OR (predictive score):ti,ab,kw OR (validat\*):ti,ab,kw (Word variations have been searched) |
| #9 | #4 OR #5 OR #6 OR #7 OR #8 |
| #10 | #3 AND #9 |

**Supplementary panel 4.** Search strategy used in Embase

|  |  |
| --- | --- |
| #1 | 'liver neoplasms':ab,ti OR 'liver cancer':ab,ti OR 'carcinoma, hepatocellular':ab,ti OR 'hepatocellular carcinoma':ab,ti OR 'liver tumor':ab,ti OR 'liver tumour':ab,ti OR hcc:ab,ti |
| #2 | 'risk assessment':ab,ti OR 'risk prediction':ab,ti OR 'risk score':ab,ti OR 'risk calculation':ab,ti OR 'prediction model':ab,ti OR 'predict index':ab,ti OR discrimination:ab,ti OR 'roc curve':ab,ti OR calibration:ab,ti OR auc:ab,ti OR 'area under the curve':ab,ti OR 'machine learning':ab,ti OR 'neural networks computer':ab,ti OR 'artificial intelligence':ab,ti OR 'risk estimation':ab,ti OR nomogram:ab,ti OR 'scoring system':ab,ti OR 'outcome prediction':ab,ti OR 'risk classification':ab,ti OR forecasting:ab,ti OR forecast:ab,ti OR 'decision tree':ab,ti OR 'predictive score':ab,ti OR validat\*:ab,ti |
| #3 | #1 AND #2 |
| #4 | #3 AND 'article'/it |

**Supplementary Table 1.** Overview of the basic information of the prediction models for liver cancer

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Author, year | Participants characteristic | Number of Events | EPV | Model performance | Handling of missing data | Model presentation |
| Yuen 20091 | 1. Patients were positive for hepatitis B surface antigen for at least 6 months 2. Had baseline ultrasound findings and platelet counts. | 40 | 3.33 | Discrimination | NR | Full equation |
| Wong 20102 | Patients with positive HBsAg for ≥ 6 months and a life expectancy of more than 2 years | 105 (45)† | 10.50 | Discrimination | NR | 0-5 score: low risk,  5-19: score medium risk,  ≥19 score: high risk |
| Yang 20113 | Residents with positive HBV | 131 | 26.20 | Discrimination, calibration | NR | 0-17 score |
| Michikawa 20124 | Participants aged 40 to 69 years without a history of liver cancer and without missing data | 104 | 11.55 | Discrimination, calibration | Exclusion | 0-17 score |
| Wen 20125 | 1. Free of cancer; 2. Aged over 20 years or older | 416 | 37.82 | Discrimination, calibration | NR | 0-39 score |
| Tseng 20136 | HBsAg-positive patients aged >28 years | 128 | 25.60 | Discrimination | NR | \_\_\_\_\_\_\_ |
| Lee 20137 | HBsAg-seropositive and anti-HCV-seronegative participants | 164 | 18.22 | Discrimination | Keep | 0-19 score |
| Singal 20138 | Chronic HCV infection with advanced fibrosis or cirrhosis without decompensation and had failed to achieve SVR after previous interferon treatment | 41 | 6.83 | Discrimination, calibration | NR | Low-risk and high- risk group |
| El-Serag 20149 | HCV-related cirrhosis | 987 | 89.73 | Discrimination; calibration | NR | Full equation |
| Flemming 201410 | Patients aged over 18 years with cirrhosis | 1116 (844) | 85.85 | Discrimination; calibration | Exclusion | Full equation |
| Lee 201411 | Aged between 30–65 years seropositive for antibodies against HCV but seronegative for HBsAg | 91(52) | 22.75 | Discrimination | NR | <13 score: low-risk,  13–18 score: medium risk,  ≥19 score: high-risk |
| Hung 201512 | 1. Men ages 30-65 years; 2. HBsAg-positive men and women ages 20-75 years; 3. Men and women ages 20-80 years | 387 | 55.28 | Discrimination, calibration | NR | Prediction algorithm |
| Ganne-Carrié 201613 | Patients with HCV-compensated cirrhosis | 103 (39) | 4.48 | Discrimination; calibration | NR | 0-3 score: low risk,  3-8 score: medium risk  > 8 score: high risk |
| Rau 201614 | Patients newly diagnosed with type II diabetes who did not have a history of cancer | 515 | 51.50 | Discrimination | NR | Web-application |
| Aoki 201715 | 1. Follow-up duration more than 1 year. 2. No previous history of HCC. 3. HCC surveillance performed during the follow-up period. 4. Diagnosis of HCC more than 1 year after the start of the follow-up period. 5 without missing data or at least one time of VTQ examination\* | 49 | 6.13 | Discrimination | Exclusion | 0-1, low-score group; 2-3, intermediate-score group; 4-5, high-score group |
| Chung 201716 | Chronic hepatitis B patients age over 18 years | 113 (109) | 7.53 | Discrimination; calibration | Imputation | Nomogram |
| Zhang 201917 | 1. Patients with cirrhosis 2. Adhere to at least six-month follow-ups | 76 | 19.00 | Discrimination | Exclusion | low-risk as < 120, intermediate-risk as 120–240 and high-risk as > 240 |
| Demirtas 202018 | Patients were the age of 18 years or older, the presence of cirrhosis, absence of history, or suspicion of HCC and adherence to at least 6 monthly follow-ups for at least 1-year period | 57 | 14.25 | Discrimination |  | \_\_\_\_\_\_\_\_\_ |
| Ioannou 202019 | Patients with ALD-cirrhosis or NAFLD-cirrhosis | 1278 | 51.12 | Discrimination; calibration | Exclusion | Web-based risk estimating tools |
| Sinn 202020 | 1. Individuals aged over 20 years without chronic HBV or HCV infection 2. Without heavy alcohol use 3. Without diagnosed with cirrhosis 4. Without history of cancer | 236 | 21.45 | Discrimination | NR | 0-19 Score |
| Abbreviations: EPV, events per variable; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NR, not reported; HCV, hepatitis C virus; SVR, sustained virologic response; HCC, hepatocellular carcinoma; VTQ, Virtual touch quantification; ALD, alcohol-related liver disease; NAFLD, nonalcoholic fatty liver disease. †: information for validation set | | | | | | |

# PRISMA Checklist

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page**  **#** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 01 |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 03 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 05 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 05 |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 05 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow- up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 05-06 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 06 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 06-07 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 06-07 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 06-07 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 06-07 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 08 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 08-09 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | NA |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | NA |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 09 |

|  |  |  |  |
| --- | --- | --- | --- |
| **RESULTS** | | |  |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 09-11 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 09-11 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 09-11 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 09-11 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 09-11 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | NA |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | NA |
| **DISCUSSION** | | |  |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12-15 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of | 12-15 |
|  |  | identified research, reporting bias). |  |

|  |  |  |  |
| --- | --- | --- | --- |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 15-16 |
| **FUNDING** | | |  |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 01 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097r more information, visit: [**www.prisma-statement.org**.](http://www.prisma-statement.org/)

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 2.** Quality assessment of the prediction models based on Prediction model Risk of Bias Assessment Tool (PROBAST) | | | | | | | | | | | | | | | | | | | | | |
| Models | **Domain 1: Participant** | | **Domain 2:**  **Predictors** | | | **Domain 3:**  **Outcome** | | | | | | **Domain 4:**  **Analysis** | | | | | | | | | |
| **1.1** | **1.2** | **2.1** | **2.2** | **2.3** | **3.1** | **3.2** | **3.3** | **3.4** | **3.5** | **3.6** | **4.1** | **4.2** | **4.3** | **4.4** | **4.5**† | **4.6** | **4.7** | **4.8**† | **4.9**† |
| Yuen 20091 | Y | PY | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | PY | PY | NI | Y | N | Y | Y | Y |
| Wong 20102 | Y | Y | Y | Y | Y | Y | NI | Y | Y | Y | Y | N | N | Y | N | N | N | N | N | Y |
| Yang 20113 | Y | PY | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | PY | PY | NI | Y | N | Y | Y | Y |
| Michikawa 20124 | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | PY | N | Y | N | Y | N | Y |
| Wen 20125 | Y | PY | Y | Y | Y | Y | PY | Y | Y | Y | Y | Y | Y | PY | NI | Y | N | Y | Y | NI |
| Tseng 20136 | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | PY | NI | N | N | N | N | Y |
| Lee 20137 | Y | Y | NI | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | N | N | N | N | Y |
| Singal 20138 | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | PY | NI | N | N | Y | N | Y |
| El-Serag 20149 | Y | PY | Y | Y | Y | PY | N | Y | Y | Y | NI | Y | Y | PY | NI | Y | N | Y | Y | NI |
| Flemming 201410 | Y | PY | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | N | N | Y | N | Y |
| Lee 201411 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | PY | N | Y | Y | N | N | Y |
| Hung 201512 | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | N | Y |
| Ganne-Carrié 201613 | Y | PY | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Rau 201614 | N | PY | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | PY | NI | N | N | N | N | Y |
| Aoki 201715 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | PY | N | N | Y | N | Y | N | Y |
| Chung 201716 | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | N | N | Y | N | Y |
| Zhang 201917 | N | PY | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | - | N | Y | - | - |
| Demirtas 202018 | Y | Y | Y | Y | Y | Y | PY | Y | Y | Y | Y | N | Y | Y | Y | - | Y | N | - | - |
| Ioannou 202019 | Y | PY | Y | Y | Y | PY | Y | Y | Y | Y | Y | Y | PY | Y | N | Y | N | Y | Y | PY |
| Sinn 202020 | Y | PY | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | PY | NI | N | N | N | N | Y |

Y, yes; N, no; NI, no information; PY, probably yes; †: Development only.

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