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SYSTEMATIC REVIEW **Open Access**

Risk prediction models for targeted testing of HIV, hepatitis B and hepatitis C: a systematic review and meta-analysis

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Abstract

Background Diagnosing human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections in general population settings is challenging. We conducted a systematic review and meta-analysis of prediction tools designed to help identify individuals at risk of these blood-borne viruses.

Methods We included studies on individuals of any age at risk of blood-borne viruses from healthcare, community settings, and national databases. We searched the Web of Science, MEDLINE, EMBASE, and CENTRAL databases (from database inception to 2023) and used the Prediction model Risk Of Bias ASsessment Tool (PROBAST) to evaluate the quality and systematic risk of bias of these studies. We extracted model accuracy using the area under the receiver operating characteristic curve (AUC), sensitivity, and specificity. A mixed-effects model (for AUC) and bivariate random-effects model (for sensitivity/specificity) were used to generate pooled values for these studies.

Results Of the 41,585 records, 71 were included, covering over 31 million participants and more than 65,000 cases of blood-borne viruses. We examined 67 models: 47 for HIV, 13 for HCV, 5 for HBV, and 2 from studies that assessed multiple viruses separately. The studies were conducted in 41 low- and middle-income and 30 high-income countries. They covered 11 different populations (including men who have sex with men, the general population, and women), 8 types of settings (including sexual health, secondary care, and primary care) and 7 types of risk factors (behavioural, clinical, and demographic). The methods comprised traditional regression ($n = 50$), machine-learning models ($n = 17$), and others ($n = 4$). The risk of bias was high in 64 studies and low in seven. Among 33 studies reporting mean and 95% CI, pooled AUC values were 0.73 (95% CI:0.67–0.80, $I^2 = 74\%$) across HIV studies (including 8 machine-learning models), 0.80 (0.73–0.86, $I^2 = 86\%$) for HCV (including 2 machine-learning models) and 0.79 (0.76–0.81, $I^2 = 93\%$) for HBV (including 3 machine-learning models).

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Conclusions Significant heterogeneity exists in blood-borne virus prediction accuracy across diverse settings and populations, with a high risk of bias. Contributions from primary care were limited, and evaluation and reporting were inconsistent. Developing and evaluating effective models for the combined risk assessment of HIV, HBV, and HCV in general population settings remains a priority.

Keywords Blood-borne virus, Predictive algorithm, Primary care screening, Hepatitis B, Hepatitis C, Human immunodeficiency virus

Background

Identifying individuals with undiagnosed blood-borne virus infections, Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), and Hepatitis C (HCV), remains a challenge in the UK, where one in 20 people living with HIV [1], and up to two in three people living with chronic HCV [2] or chronic HBV remain undiagnosed [3]. Undiagnosed blood-borne virus infection is associated with an increased risk of ill health, onward transmission, and death [1–3]. Following acute infection, HIV may remain clinically latent for approximately 10 to 15 years before the onset of symptoms. In adults, hepatitis B and hepatitis C progress to chronic infection in an estimated 5% and 55–85% of cases, respectively. While hepatitis C is curable with direct-acting antiviral (DAA) therapy, both HIV and hepatitis B require lifelong antiviral treatment to suppress viral replication and prevent disease progression. Left untreated, HIV infection invariably leads to AIDS, whereas hepatitis B and hepatitis C may lead to cirrhosis and liver cancer [1–3]. Early diagnosis is essential for the effective treatment and prevention of transmission.

All three blood-borne viruses share common routes of transmission, and co-infection rates are notable among HIV care recipients [4, 5]. Co-infection in people with HIV worsens health outcomes, underscoring the importance of early detection to improve outcomes and manage disease progression [4, 5]. Social determinants of health, such as substance use, homelessness, and migration status, worsened by recent austerity policies and the COVID-19 pandemic [6, 7], amplify the need for early blood-borne virus diagnosis to mitigate health inequalities.

Early identification of blood-borne viruses requires effective testing strategies [8]. Despite national guidance recommending combined testing, these viruses are frequently not concurrently tested for [8, 9]. Instead, current testing initiatives in the general population focus on single viruses and have low specificity [8, 10], leading to the identification of large numbers of uninfected people, avoidable costs, service inefficiency, and constraints. A targeted approach using combined testing in a general population setting is likely to be more effective and efficient for improving early diagnosis. The European Centre for Disease Prevention and Control (ECDC) recommends integrating digital technologies, such as computerised clinician decision tools, in healthcare and community settings to enhance early detection and management of blood-borne virus and other sexually transmitted infections [11].

From personalised risk assessment and early diagnosis to targeted treatment and follow-up care, the digitalisation of healthcare, augmented by artificial intelligence (AI) and predictive models, offers new opportunities to transform care delivery toward a more tailored, patient-centered approach [12]. Advances in genomic viral testing have improved treatment outcomes for people with HIV [13] and hepatitis C virus [14] in specialist settings, enabling clinicians to select the most effective and least toxic therapies. Extending these precision medicine principles into primary care - by using digital technologies to identify individuals at increased risk of undiagnosed blood-borne virus infections - could drive earlier diagnosis and more equitable access to personalised care across the healthcare system [15].

Diagnostic prediction models are statistical tools designed to identify individuals most at risk of having a given condition [16, 17]. Although multiple models have been proposed for blood-borne virus diagnosis, no single ‘gold standard’ risk score exists for individual or combined blood-borne virus infection, unlike well-established models in other areas like cardiovascular disease [18, 19] and diabetes (QDiabetes) [20] in primary care in England.

The Prediction model Risk Of Bias ASsessment Tool (PROBAST) has been developed to appraise the risk of bias and applicability of prediction models across four domains: Participants, Predictors, Outcome and Analysis [21]. Its recent update, (PROBAST+AI), emphasizes diversity, inclusivity and generalisibility when applying AI and machine-learning to digital health data [22].

This systematic review evaluated both the predictive accuracy (area under the receiver operating characteristic curve [AUC], sensitivity, and specificity) and the risk of bias (using PROBAST) of published prediction models in healthcare and community settings from 1946[1] to 2023. Using the evidence from this review, we aimed to develop and evaluate a predictive tool for blood-borne virus screening in primary care settings.

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[1] The databases were searched from their inception with the oldest record in MEDLINE dating back to 1946.

Methods

Search strategy and selection criteria

We searched for published prediction models for identifying people at risk of the blood-borne viruses HIV, HBV, and HCV across age groups and settings, published in the English language. Using Web of Science, MEDLINE, EMBASE and CENTRAL, each database was searched from their inception to 2023 (details in the supplementary material) adhering to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guidelines [23]. Initial and repeat searches were conducted on 10 January 2022 and 9 March 2023, respectively, to capture all relevant studies.

The following inclusion criteria were applied to the studies:

- **Participants/population:** Patients in healthcare and community settings, and national databases
- **Condition:** Blood-borne virus diagnosis status - HIV, HBV, and/or HCV
- **Intervention:** Diagnostic (current risk of undiagnosed infection) or prognostic (future infection) prediction models assessing for blood-borne viruses
- **Setting:** All settings (e.g., primary care, secondary care, sexual health centres and community settings) in all world regions. Studies published from the 1st of January 1946 to the 9th of March 2023
- **Study type:** Randomised controlled trials (RCTs), observational designs (prospective cohort, cross-sectional, case-control), and derivation/development and validation studies.

We excluded mathematical modelling studies[2] and those that did not meet the above criteria. A prediction model is defined as a mathematical or statistical function that relates a set of risk factors to an outcome, whereas an algorithm refers to the process or procedure used to develop, train, and test a model.

All records were independently screened by members of the systematic review screening team (Appendix) using the Rayyan [24] SR screening programme. After the initial title and abstract screening, two reviewers (HZF and EAD) screened the full texts, and discrepancies were resolved by a third reviewer (WL). Reference checks ensured comprehensive inclusion.

Data synthesis and assessment of study quality and bias

Data were extracted using the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) [25] and the study quality and risk of bias were assessed using the Prediction model Risk Of Bias ASsessment Tool (PROBAST) [21]. Three reviewers (HZF, WL and HL) independently analysed the full texts. WL is a clinician who developed a computer prompt (see Supplementary Materials) to assess the risk of bias using two large language models: Claude (Anthropic) was used to generate the risk of bias assessment, and ChatGPT (Microsoft/OpenAI) was used to generate a structured output in a comma-separated values format (see Supplementary Materials). HL is a health data scientist who used a manual approach. To generate a consensus, both approaches were compared, and studies were classified as either concordant (agreeing) or discordant (not agreeing). Any discrepancies between the two approaches were validated by an independent statistician (JPG).

Cluster analysis

We manually collected data on the risk factors (predictors) used in each prediction model and grouped these factors based on the healthcare settings in which the models were developed or applied. After reviewing all studies, we sorted the predictors into the following categories: behavioural, clinical, demographic, environmental, substance use, contaminated blood and other exposure. The settings were grouped into sexual health, secondary care, paediatric, primary care, registry, electronic health records and drug services. The results were visualised on a Sankey diagram using SankeyMATIC (https://sankeymatic.com/). We used Sankey diagrams instead of conventional bar or pie charts because unlike conventional charts, they are more suitable for showing the weighting of the flow and drawing attention to the largest and most significant variables within the studied system.

Statistical analysis

We calculated the mean and 95% Confidence Intervals (CIs) for accuracy measurements (AUC, sensitivity, and specificity) across studies related to HIV, HCV, and HBV. For the AUC value, we used a mixed-effects model, while for the sensitivity and specificity we used a bivariate random-effects model [26] to generate pooled values and the I^2 statistic across studies. Publication bias was evaluated using Egger's test, which compares pooled means and confidence intervals (CIs) among all studies and those that reported machine-learning models. The study protocol was prospectively registered in the PROSPERO Registry (CRD42022307844).

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[2] We defined mathematical modelling studies as those that simulated epidemiological trajectories under varying transmission dynamics or intervention scenarios, without reporting individual BBV cases or their characteristics.

Results

Data synthesis

The initial search yielded 41,585 records. After removing 7,683 duplicates, 33,901 articles remained for screening. We assessed 310 full-text articles, of which 72 were reviewed in detail. One study [27] did not report any relevant outcomes and was excluded, resulting in a final inclusion of 71 studies [27–98]. A total of 238 studies were excluded based on our predefined criteria (Fig. 1). These included 43 (61%) retrospective studies, of which 11 were secondary analyses of RCTs; 13 (18%) prospective studies, including one primary RCT; and 15 (21%) cross-sectional studies (Supplementary Table S1). A total of 31,296,475 individuals at risk of blood-borne viruses were screened, and 65,269 individuals with infections were identified. The blood-borne viruses studied included HIV only (51/71, 72%), HCV only (13/71, 18%), HBV only (5/71, 7%), and two studies that examined multiple viruses separately within the same paper - one addressing HBV and HCV and one addressing HIV, HBV, and HCV (2/71, 3% total). Most studies (66/71, 93%) investigated a single blood-borne virus infection, with 3/71 (4%) examining HCV co-infection and 2/71 (3%) examining HBV co-infection among those with HIV. None of the studies evaluated combined blood-borne virus testing. We examined 67 models: 47 for HIV, including four models that were evaluated twice, 13 for HCV, five for HBV, and two models that assessed multiple viruses separately - one addressing HBV and HCV, and one addressing HIV, HBV, and HCV (Supplementary Table S1). Among the 53 HIV-related papers, 16 focused specifically on HIV seroconversion and 27 reported general or unspecified infection status. For HBV, 7 papers were identified – 4 describing active infection and 3 reporting unspecified infection status. For HCV, 15 papers were reviewed – 2 focused on active infection, 1 on acute infection, and 12 were not specified (Supplementary Table S1).

The geographic distribution of the studies included 41 (58%) from low-to middle-income countries and 30 (42%) from high-income countries (Table 1, Supplementary Table S1). Regarding prevalence settings, sixty-eight studies (96%) were conducted in high-prevalence settings (defined as two or more positives per 1000 population) and three (4%) in low-prevalence settings, including two on HIV and one on HCV. The research settings varied across sexual health (*n* = 29, 41%), secondary care (*n* = 14, 20%), community settings (*n* = 8, 11%), registry (*n* = 6, 8%), paediatrics (*n* = 5, 7%), primary care (*n* = 5, 7%), substance use centres (*n* = 2, 3%), and electronic health records (*n* = 2, 3%) (Table 1, Supplementary Table S1).

In terms of demographics, as shown in Table 1 and Supplementary Table S1, the studies predominantly focused on men-who-have-sex-with-men (MSM) (*n* = 20, 28%), the general population (*n* = 17, 24%), women (*n* = 8, 11%), including one study on female sex workers. Smaller numbers of studies focused on other specific groups such as children, adolescents, and individuals living with HIV or affected by conditions such as tuberculosis or malignancy and key populations vulnerable to HBV. Notably, one study reported separately on MSM, female sex workers, and substance users.

Assessment of bias

The PROBAST assessment of the Analysis domain demonstrated a high risk of bias in 90% (64/71) of the studies and low risk in 10% (7/71) (Supplementary Table S2). These seven low-risk studies also maintained low risk across the three other PROBAST domains (Participants, Predictors and Outcomes). Twelve of the 64 studies that were considered to have high risk of bias were secondary analyses of behavioural RCTs. Due to the predominance of high-risk categorisation, a sub-analysis of high-quality studies was not feasible. Concordance between researcher-led and AI-assisted analyses occurred in 86% (61/71) of studies, with discordance in 14% (10/71). As shown in Supplementary Table S3, among the discordant studies, AI-assisted misclassification included six studies as 'low' risk and two as 'probably low' risk that were considered 'high risk' per consensus. In contrast, manual assessment misclassified two studies and rated them as 'high risk' when consensus was 'low risk'.

Of the seven low-risk studies, five introduced new predictive models and two performed external validations of existing models. Only one low-risk study employed a machine-learning algorithm. Within the PROBAST Analysis domain, the most common causes of high risk of bias were inadequate sample sizes (44/71 studies, 62%), as evidenced by an events-per-predictor ratio below 10–20, or fewer than 100 events in validation; a lack of performance metrics in evaluation (40 studies, 56%), often due to missing calibration data; and dependence on univariate analysis for predictor selection (30 studies, 42%). The findings are presented in Supplementary Table S2.

Cluster analysis

Of the 71 studies, 60 used 508 predictors in their final models, categorised as behavioural (*n* = 140), clinical (*n* = 126), demographic (*n* = 88), substance use (*n* = 54), environmental (*n* = 34), contaminated blood (*n* = 16), and other exposures (*n* = 50) (Fig. 2). Predictor variables were used in various population group settings, most frequently in sexual health settings (*n* = 181), followed by registries (*n* = 87), secondary care (*n* = 74), community (*n* = 60), primary care (n = 49), paediatrics (*n* = 27), and drug services (*n* = 11).

Key predictors varied, with behavioural factors prioritised in sexual health settings (*n* = 82), clinical variables

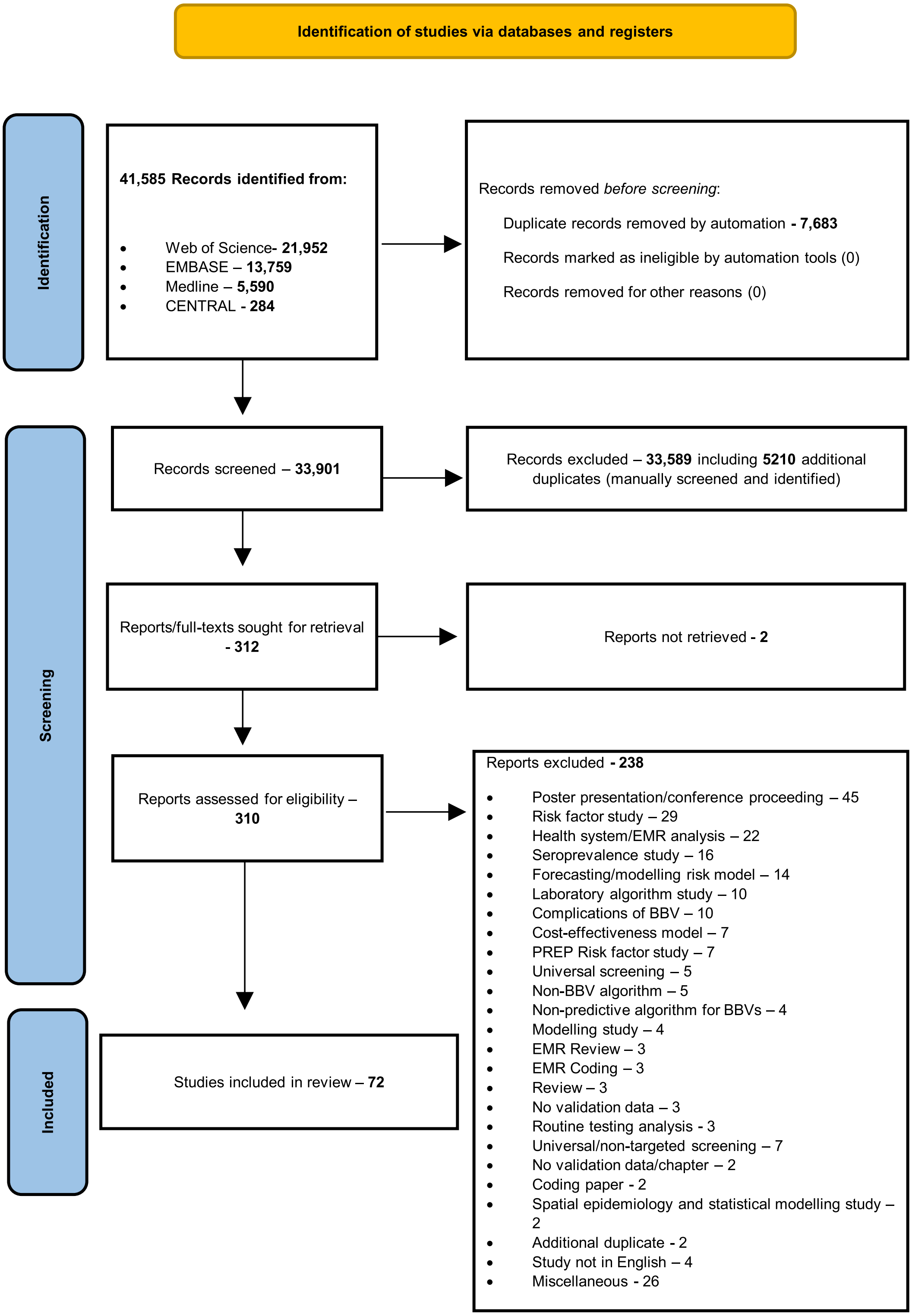

Fig. 1 Prisma diagram

in secondary care ($n = 29$) and demographic predictors in registries ($n = 23$) (Fig. 2).

Logistic regression was the predominant statistical method used in 58% (41/71) of the studies, followed by machine-learning algorithms in 24% (17/71). Cox regression and Poisson regression were used in six and three studies, respectively. Additionally, four studies employed advanced statistical analysis, including one each that

Table 1 Overview of study characteristics and distribution in systematic review of 71 published prediction model studies

Category	Value (N=)
Full Texts Assessed	310
Articles Excluded from review	238
Articles Included in review	72
Articles Excluded from final analysis	1
Articles Included in final analysis	71
Blood-borne viruses studied	
HIV	51 (72%)*
HBV	13 (18%)
HCV	5 (7%)
HIV/HBV/HCV	1 (1.5%)
HBV/HCV combined	1 (1.5%)
Study types	
Retrospective Studies	43 (61%), incl. 11 RCTs
Prospective Studies	13 (18%), incl. 1 RCT
Cross-sectional Studies	15 (21%)
Study regions	
Low-Middle Income Countries	41 (58%)
High-Income Countries	30 (42%)
Prevalence	
High Prevalence Settings	68 (96%)
Low Prevalence Settings	3 (4%)
Study setting	
Sexual health	29 (41%)
Secondary care	14 (20%)
Community	8 (11%)
Registry	6 (8%)
Paediatric	5 (7%)
Primary care	5 (7%)
Drug centres	2 (3%)
Electronic health records	2 (3%)
Study population	
MSM	20 (28%)
General population	17 (24%)
Women (incl. 1 study on female sex worker**)	8 (11%)
Children and adolescents	5 (7%)
People with HIV	4 (6%)
Substance users	4 (6%)
People with Tuberculosis	3 (4%)
Others	10 (14%)
Statistical method	
Logistic regression	41 (58%)
Machine learning	17 (24%)
Cox regression	6 (8%)
Poisson regression	3 (4%)
Other	4 (6%)
Predictive modelling	
Development with internal validation	37 (52%)
Development only	17 (24%)
External validation only	9 (13%)
Other	8 (11%)

*Four HIV models were evaluated twice (see Supplementary Table S1 for more detail), resulting in a total of 67 models across all blood-borne viruses. **One study reported separately on female sex workers, men who have sex with men (MSM) and substance users

used a generalised estimating equation, X^2 analysis and descriptive analysis (Table 1, Supplementary Table S1). Studies utilising machine-learning models were published between 2018 and 2023.

The studies included development and internal validation (52%, 37/71), development only (24%, 17/71), external validation only (13%, 9/71), and combinations of development with external or internal validation (11%, 8/71) (Table 1, Supplementary Table S1). Internal validation methods included split-sample analysis ($n = 34$), cross-validation ($n = 14$), bootstrapping ($n = 14$), and others ($n = 2$) (Supplementary Table S1).

Statistical analysis

Of the 71 studies reporting statistical results, 51 (72%) focused on HIV alone, 13 (18%) on HCV alone, five (7%) on HBV alone, and two (3%) on both HBV and HCV. One of these two studies, Kuniholm et al. [99], initially considered all three viruses but excluded HIV from the final model due to a low number of cases. Therefore, HIV, but not HBV and HCV, was excluded from statistical analysis in that paper. A larger number of studies reported at least one outcome (AUC, sensitivity, and specificity) for HIV than for HBV or HCV, with 51 studies for HIV, 15 for HCV, and seven for HBV (Table 2). Fewer studies have reported all three outcomes: 30 for HIV, nine papers for HCV and one for HBV. Most studies reported only the mean values of these outcomes instead of both the mean and range (46 vs. 25 papers). Across the three outcome metrics (AUC, sensitivity, and specificity), some studies reported only the mean values instead of both the mean and the range. For AUC as an outcome, the mean alone was reported in 28 studies, while both the mean and 95% CI were reported in 33 studies. For sensitivity as an outcome, the mean was reported in 44 studies, whereas both the mean and 95% CI were reported in 13 studies. For specificity as an outcome, the mean was reported in 39 studies, while both the mean and 95% CI were reported in 14 studies (Table 2).

Of the 61 studies reporting AUC values, 33 provided both mean and 95% confidence intervals (95% CI) (25 HIV, five HCV and three HBV) (Table 2, forest plots in Fig. 3). The remaining studies reported only the mean AUC values (18 HIV, seven HCV and three HBV). Eight HIV studies, three HCV studies, and one HBV study did not report AUC. In the 33 studies with both mean and 95% CI AUC values, the pooled AUC values were 0.73 (0.67,0.80), $I^2 = 74\%$ across HIV studies; 0.80 (0.73,0.86) $I^2 = 86\%$ across HCV studies; and 0.79 (0.76,0.81), $I^2 = 93\%$ across HBV studies (Fig. 3). Among the 43 HIV, 12 HCV and six HBV studies that reported mean or both mean and 95% CIs AUC values, the pooled AUC values were 0.74 (0.68,0.80), $I^2 = 76\%$ for HIV; 0.78 (0.73,0.86), $I^2 = 89\%$ for HCV; and 0.81 (0.78,0.85),

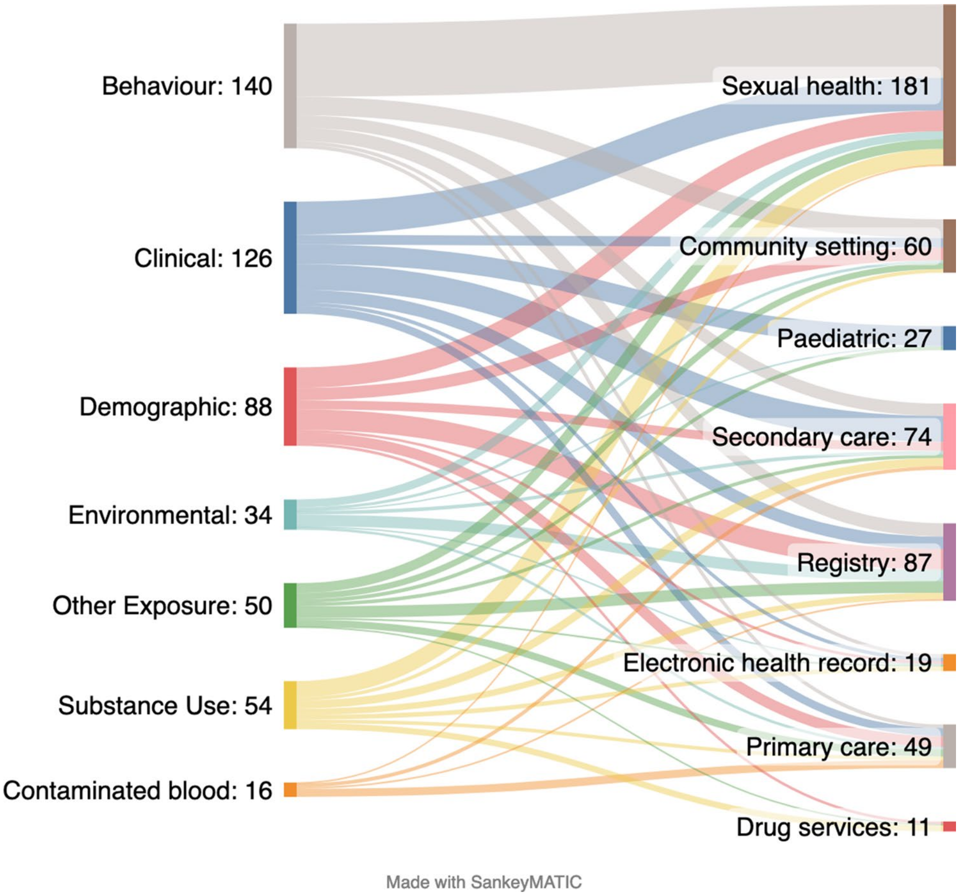

Fig. 2 Distribution of predictor variables across population group settings in 71 prediction model studies. Sankey diagram showing how 508 predictors from 60 studies were distributed across population group settings. The predictor types included behavioural, clinical, demographic, substance use, environmental, contaminated blood, and other exposures. The diagram highlights dominant patterns, such as behavioural predictors in sexual health settings and clinical predictors in secondary care. Created using SankeyMATIC (https://sankeymatic.com/)

$I^2 = 90\%$ for HBV (forest plots in the supplementary material).

Across the 25 HIV studies reporting AUC values with 95% CIs, eight used machine-learning models, showing a higher pooled mean AUC of 0.81 and tighter range (0.76–0.86) compared to 0.73 (0.67–0.80) across all studies, with reduced heterogeneity ($I^2 = 67\%$) (Supplementary Figure S1). Among the five HCV studies with 95% CIs, two used machine-learning models with reported AUCs of 0.80 and 0.81, and five of the six HBV studies utilising machine-learning models reported an AUC of 0.82 (0.78–0.87) with high heterogeneity ($I^2 = 91\%$) (Supplementary Figure S1).

Like the AUC, both sensitivity and specificity were higher among studies reporting mean and 95% CIs ranges compared to those reporting the mean with or without 95% CIs (see Supplementary Figures S2 and S3, and Supplementary Materials)

More recent studies have frequently utilised machine-learning models and reported both mean and 95% confidence intervals (CIs) for sensitivity and specificity. Of the nine HIV studies that detailed these metrics, only two recent studies (published in 2019 [28] and 2023 [68]) used machine-learning models. For HCV, none of the papers reporting the mean and 95% CIs for sensitivity and specificity used machine-learning models, whereas one HBV paper [77] did.

The funnel plot (Supplementary Figure S4) indicated no significant publication bias across the selected studies and across the blood-borne viruses, supported by an Egger's test regression intercept p-value of 0.545, suggesting no publication bias.

Discussion

This is the first comprehensive systematic review and meta-analysis to evaluate the diagnostic performance of predictive models for three globally prevalent blood-borne viruses - HIV, HBV, and HCV, across a wide range of populations and settings.

Previous reviews have focused on prediction models for HIV in sub-Saharan Africa [98] and models for HIV in adults in primary care settings in high-income countries

Table 2 Summary of AUC, sensitivity, and specificity for HIV, hepatitis B, and hepatitis C prediction models (*N* = 71)

Detail	HIV	HCV	HBV
Papers Reporting at least one Outcome (*N* = 71)*	51	15	7
Studies Reporting All Outcomes (*N* = 40)	30	9	1
Studies Reporting mean AUC Values (*N* = 61)	43	12	6
Studies Reporting Both Mean and 95% CI AUC Values (*N* = 33)	25	5	3
Studies Reporting Only Mean AUC Values (*N* = 28)	18	7	3
Studies Not Reporting AUC (*N* = 12)	8	3	1
Pooled AUC Values (Both Mean and Mean and 95% CI) (*N* = 61)	0.74 (0.68,0.80)	0.78 (0.73,0.82)	0.81 (0.78,0.85)
Pooled AUC Values (Mean and 95% CI) (*N* = 33)	0.73 (0.67,0.80)	0.80 (0.73,0.86)	0.79 (0.76,0.81)
Pooled AUC Values Across All Studies with MLAs (*N* = 15)	8 MLAs, 0.81 (0.76,0.86)	2 MLAs, only mean of 0.8 and 0.81 reported	5 MLAs, 0.82 (0.78,0.87)
Studies Reporting mean Sensitivity values (*N* = 57)	39	12	6
Studies Reporting Both Mean and 95% CI Sensitivity Values (*N* = 13)	9	3	1
Studies Reporting Only Mean Sensitivity Values (*N* = 44)	30	9	5
Studies Not Reporting Sensitivity (*N* = 16)	12	3	1
Pooled Sensitivity Values (Both Mean and Mean and 95% CI) (*N* = 61)	72.9% (68.19%,77.6%)	75.98% (63.98%,87.98%)	73.39% (52.48%, 94.29%)
Pooled Sensitivity Values (Mean and 95% CI) (*N* = 13)	74.51% (66.41%,82.61%)	64.87% (42.34%, 87.39%)	1 study, 75.6% (64.9,84.4)
Pooled Sensitivity Values Across All Studies with MLAs (*N* = 12)	7 MLAs, 78.36% (70.04%,86.68%)	1 MLA with mean of 61.2% reported	4 MLAs, 67.23% (36.11%, 98.35%)
Studies Reporting mean Specificity Values (*N* = 53)	36	12	5
Studies Reporting Both Mean and 95% CI Specificity Values (*N* = 14)	9	3	1
Studies Reporting Only Mean Specificity Values (*N* = 39)	27	9	4
Studies Not Reporting Specificity (*N* = 20)	15	3	2
Pooled Specificity Values (Both Mean and Mean and 95% CI) (*N* = 53)	63.77% (59.97%,67.67%),	77.5% (68.42%,86.59%)	71.10% (45.9%,96.3%)
Pooled Specificity Values (Mean and 95% CI) (*N* = 14)	68.69% (63.04%,74.34%)	84.8% (76.49%,93.11%)	1 study, 80.2 (79.7,80.8)
Pooled Specificity Values Across All Studies with MLAs (*N* = 11)	5 MLAs, 74.78% (57.44%,92.11%)	2 MLAs, reporting means of 98.1% and 96.3% reported	4 MLAs, 80.4% (67.64%, 92.96%)

*Two studies reported both HCV and HBV infections. AUC, area under the receiver operating characteristic curve; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus

[100]. A recent systematic review summarised machine-learning models for blood-borne viruses using narrative synthesis [29], but did not include meta-analysis and risk of bias assessment. Another review performed meta-analysis on viral hepatitis models but did not apply PROBAST to evaluate risk of bias [101]. Our review builds on these studies by comprehensively appraising and summarising all blood-borne virus prediction models published in English up to March 2023 using both meta-analysis and PROBAST.

Our analysis demonstrated that most existing models for blood-borne viruses have been developed in specialised settings, such as sexual health clinics (*n* = 29), secondary care (*n* = 14) and community settings (*n* = 8), with fewer in primary care settings (*n* = 5). However, primary care is a crucial setting for early detection of blood-borne viruses, which can significantly improve health outcomes [102–104].

Despite many studies exploring diverse methods, settings and cohorts, their conduct and measurement approaches have varied. Moreover, the performance of BBV models differs widely across populations and settings, resulting in a broad spectrum of reported AUC, sensitivity and specificity values. Pooling these heterogeneous values across all three metrics was feasible, and the wide confidence intervals reflected the large variability in these metrics across studies, particularly in the case of AUC, which was the most used prediction variable in both the methods of generation and the cohorts studied. This heterogeneity in research methods, combined with the prior lack of established standards for conducting and evaluating predictive algorithm studies, has led to inconsistent analyses and reporting across studies. Consequently, most of the studies (64/71, or 90%) were classified as high risk according to the PROBAST criteria, including secondary analyses from 12 behavioural RCTs. Although RCTs typically apply the same eligibility rules to their study participants, the inclusion criteria may be narrower, potentially reducing the predictive ability and applicability of prediction models in other populations. Therefore, all RCTs in this review were categorised as 'high risk' [105]. This highlights the challenges posed by

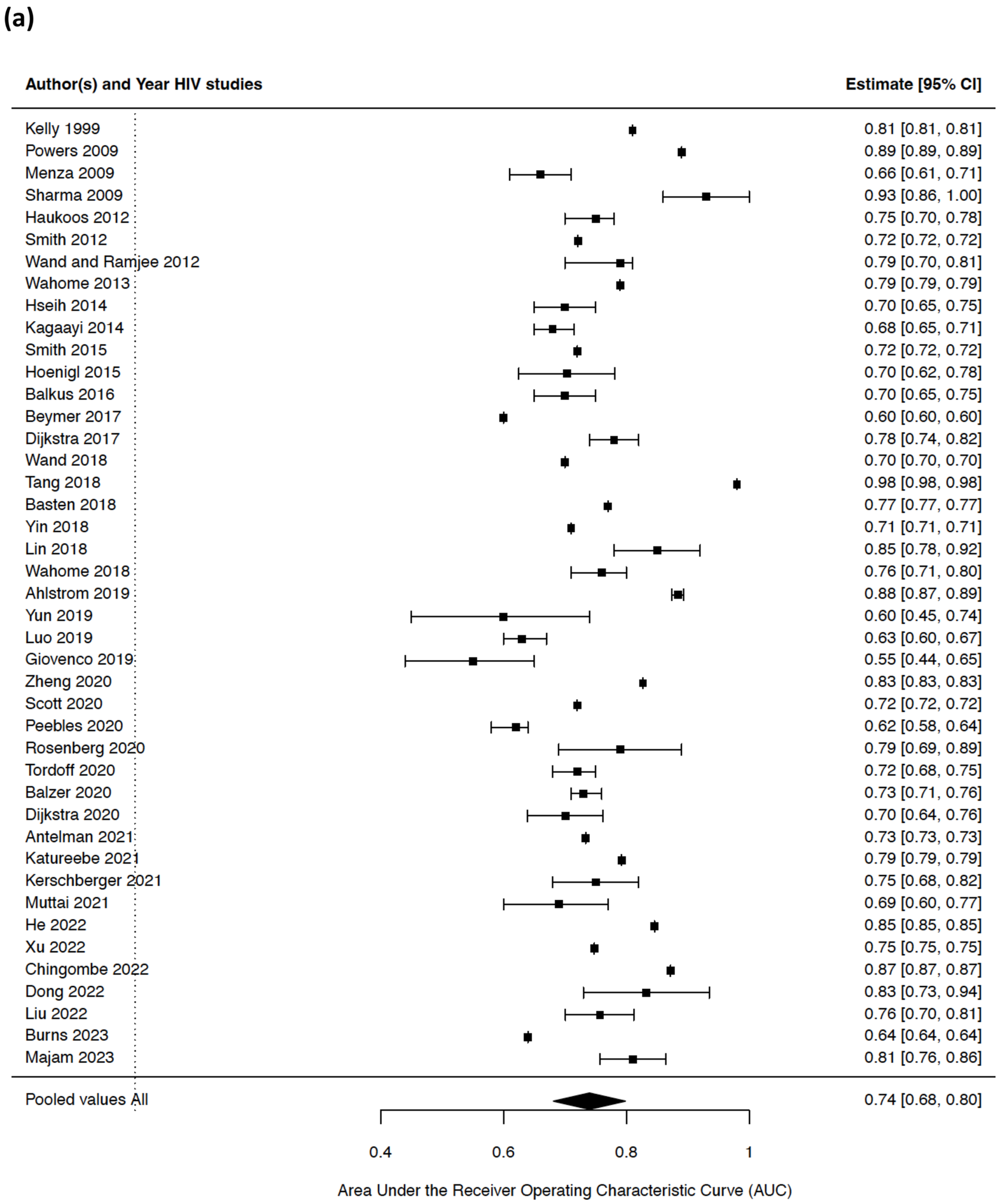

Fig. 3 (**A-C**): forest plots of AUC values from HIV, HBV, and HCV prediction model studies. Forest plots display AUC values from studies reporting either the mean alone or both the mean and range: (**a**) HIV-related studies (*n* = 43), (**b**) hepatitis C-related studies (*n* = 12) and (**c**) hepatitis B-related studies (*n* = 5). Supplementary Figures S1–S3 include additional studies with the full AUC range data

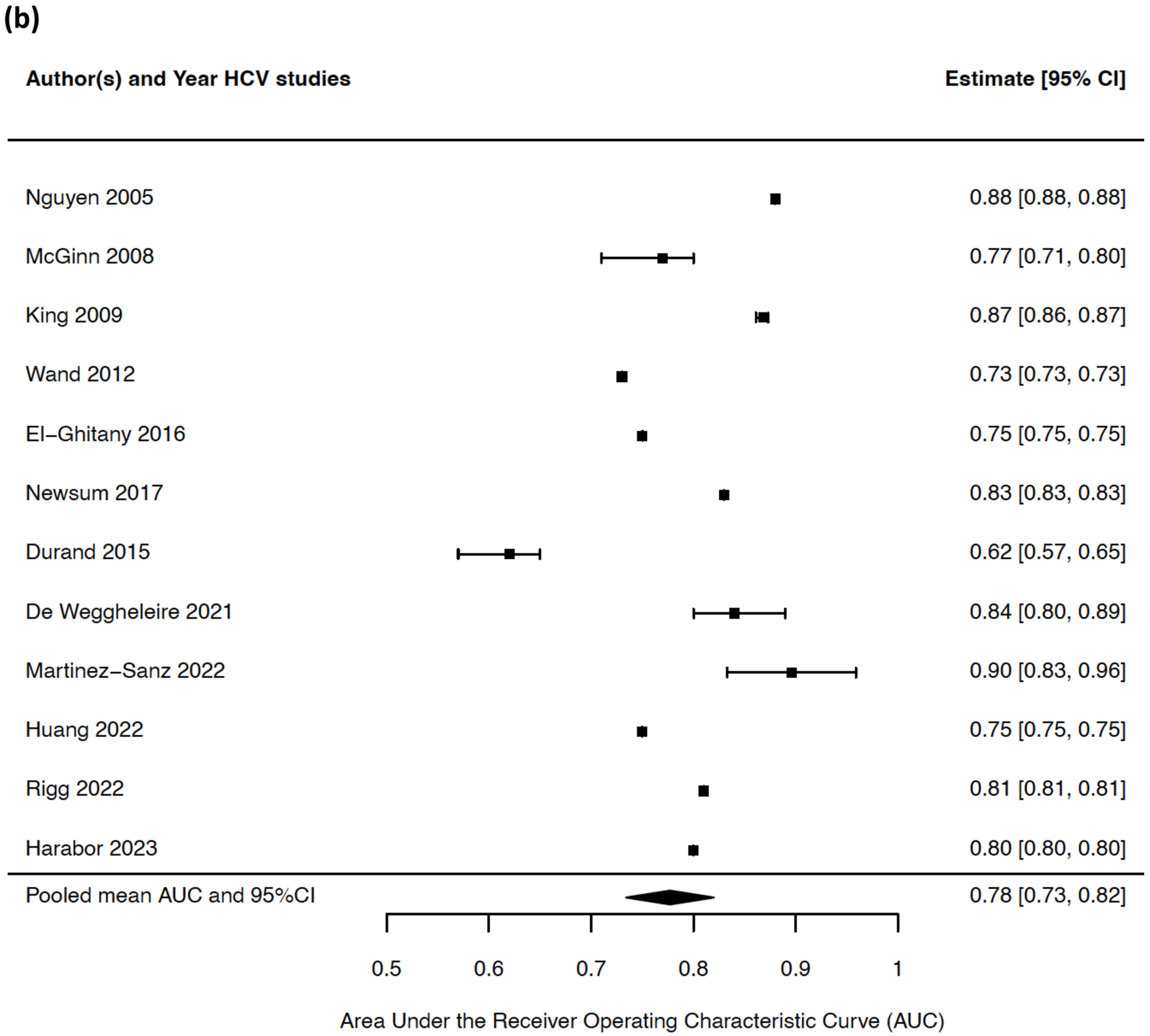

Fig. 3 (continued)

various approaches adopted in these studies, including divergent data collection methods, disparate model training and validation techniques, and inconsistent reporting practices. The absence of a standardised framework for the development and evaluation of machine-learning models up to the 2023 cut-off date of this review has also hindered the comparability of results and raised concerns regarding the reliability and robustness of the assessed models. In combination with the wide range of reported AUC values, this suggests that, despite the advent of machine learning, the quality of both data analysis and reporting among studies has remained poor. However, the recent release of the PROBAST+AI guidelines, which provide detailed instructions for assessing the risk of bias analysis and applicability in studies using artificial intelligence including machine learning, may help improve the methodologic rigour and transparency of future research in this field [22].

More recent studies have increasingly utilised machine-learning models, with 17 (24%) of the analysed studies using these techniques. Studies using machine-learning models have generally reported higher AUC values and less heterogeneity. For example, among the 25 HIV-related studies that reported both the mean and 95% CIs for AUC values, those employing machine-learning models ($n = 8$) reported improved accuracy (pooled mean AUC value of 0.81, compared to 0.73 across all 25 studies) and less heterogeneity ($I^2 = 67\%$ compared to $I^2 = 74\%$ across all HIV studies). Thus, the introduction of machine learning may enhance the data accuracy and

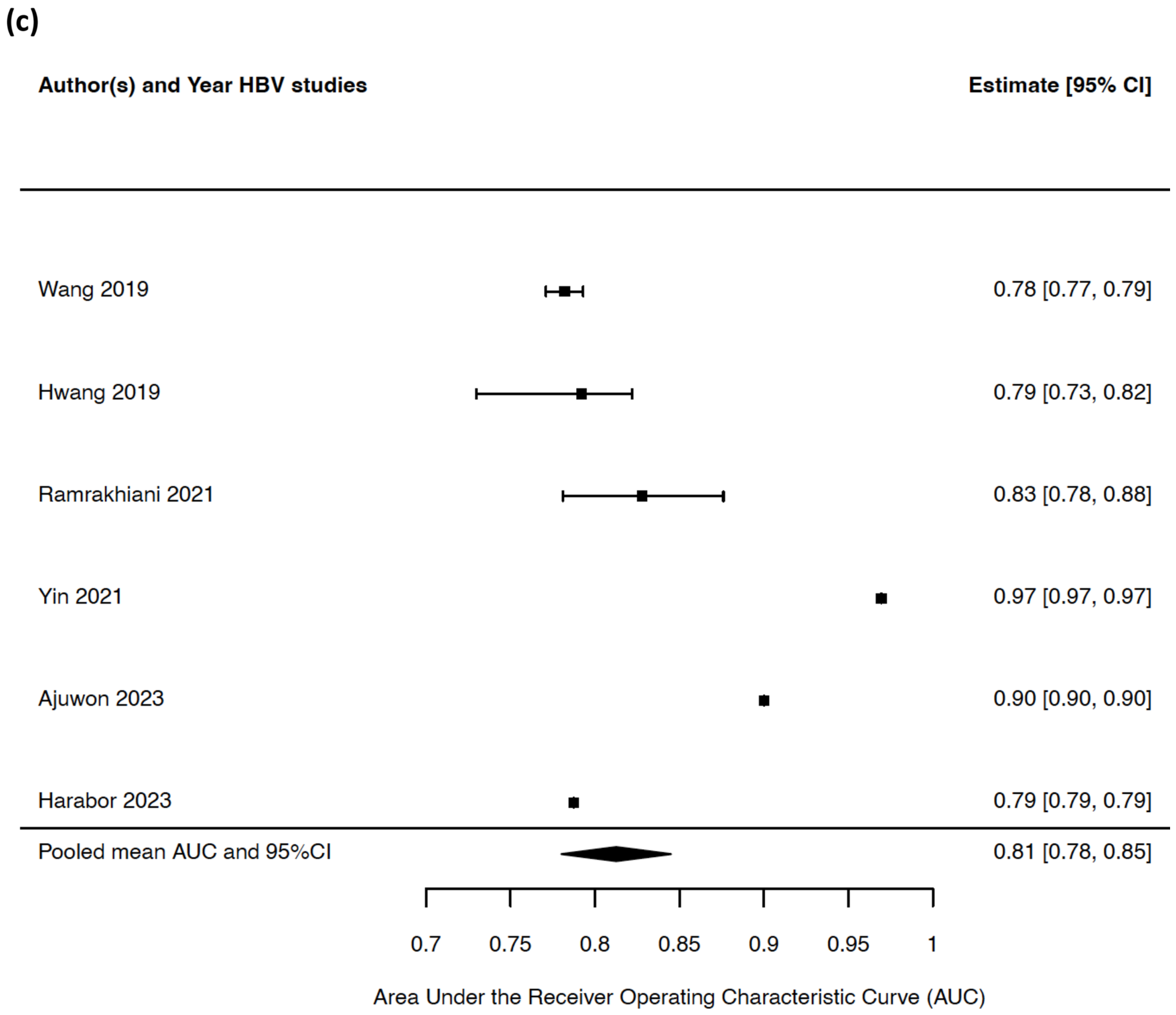

Fig. 3 (continued)

reliability. Machine-learning model-based studies also tend to include larger and more complex datasets, which may be more effective for predictions. A comparison between machine-learning models and traditional statistical methods remains challenging and requires more extensive comparative research.

This review uses the CHARMS [25] and PROBAST [21, 22, 105] frameworks for data extraction and systematic risk of bias assessment, ensuring the reliability and validity of the study findings and consistency in the evaluation process. We corroborated the validity and reliability of the PROBAST risk-of-bias results by comparing the AI-assisted approach against the judgment of a health data scientist. By extending the search to March 2023, we included more recent scientific literature, making it relevant to the readers. The primary constraints of this review and meta-analysis stem from the considerable heterogeneity among the studies, attributed to the expansive scope of the search and notable variations in the definitions and statistical methods used. Furthermore, suboptimal reference standards for machine-learning models add an additional layer of complexity to the analysis. Finally, the majority of papers across all three blood-borne viruses did not clearly define the infection stage under study, which may limit the comparability of findings and the precision of evidence synthesis.

Our review focused on collating available information on the accuracy of published studies in identifying blood-borne virus infections, emphasising descriptive characteristics and accuracy metrics, rather than comparing all possible co-variates. Hence, we did not perform a meta-regression; instead, we conducted a regression solely on the accuracy metrics by pooling the data to inform the accuracy. Undertaking a large-scale meta-regression across all possible co-variates from the studies was beyond the scope of this review.

Assessing publication bias is important in systematic reviews because it can affect the reliability of the results [106]. A common way to check for this bias is a funnel plot, which compares study effect sizes with their precision. If bias exists, the plot looks uneven or skewed [107]. Since interpreting funnel plots can be subjective, a statistical test like Egger's regression may provide more objective evidence [99]. While other more complex models exist to adjust for bias, they require assumptions that can add uncertainty [108]. For our review, we used funnel plots and Egger's test, which are widely accepted and sufficient for our purposes. The exploration of alternative methods was beyond the scope of this study.

It is striking that, despite many shared risk factors, no models currently exist for the simultaneous prediction of HIV, HBV, and/or HCV in the general population. These findings underscore the need to critically evaluate and refine existing models, not only by their performance metrics (such as AUC) but also for their feasibility, practical utility, and clinical effectiveness in real-world settings. This systematic review has informed our research programme on the improved identification of people with blood-borne viruses. With their unselected and comprehensive data, electronic health records in England's primary care system are ideal for developing and validating prediction model tools [109]. As part of a recent grant, our team developed and validated a prediction model – a statistical function that relates risk factors to blood-borne virus status - using the electronic health records of 1.2 million primary care patients registered in East London. The model was developed through an algorithmic process that is informed by evidence from this systematic review, reflects the diversity of an inner-city population and performs well across all risk groups, including marginalised communities. We will externally validate it using the national QResearch database (http://www.qresearch.org) and are currently evaluating the real-world feasibility of the model in a mixed-methods pilot study involving six general practices across the English cities of Leicester, Bristol and London. This systematic review provides insights into the current literature and identifies knowledge gaps. By integrating robust risk predictors with primary care electronic health records, we aim to deliver a precision medicine tool ready for broad adoption in the digital health era.

Conclusion

We identified large variations in the performance of the published prediction models for HIV, HCV, and HBV infections across different populations and settings. Evidence for the development and validation of prediction models from electronic health records, such as primary care, is limited. While machine-learning models are increasingly used to predict individual blood-borne virus risks, they may not necessarily outperform traditional models and often suffer from poor-quality reporting. An improved risk-score algorithm that enables targeted, combined testing of blood-borne viruses across diverse settings and at-risk populations is essential for effective testing and elimination strategies in general population health settings.

Abbreviations

HIV	Human Immunodeficiency Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus

Supplementary information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

Conceptualisation: HZF, WL, RFB, CG, JR, MP, CMO; Data curation: HZF, WL, PD, DH, SC, LG, SRH, EAD, RFB, JPG; Formal analysis: HZF, WL, JPG; Funding acquisition: WL, RFB, CG, JR, MP, HZF; Investigation: HZF, WL, DH, SC, LG, SRH, LG, RFB, JPG; Methodology: HZF, WL, JPG, HL; Supervision: CG, JR, MP, JA, CMO, GRF; Validation: WL, HZF, HL, JPG; Visualisation: HZF, WL, JPG; Roles/Writing - original draft: HZF, WL, JPG, Writing - review & editing: All authors. All authors approved the final version of the manuscript submitted.

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Data availability

The data used for CHARMS-based data extraction and PROBAST risk of bias assessments are provided in the supplementary materials. The dataset used for statistical analyses is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable to this publication.

Consent for publication

Not applicable to this publication.

Generative AI and AI-assisted technologies in the writing process

During the preparation of this work one of the authors (WL) used Paperpal (https://paperpal.com/) and ChatGPT (https://chat.openai.com) to improve language and readability. Rayyan SR software was used for paper screening, while WL employed ChatGPT (Microsoft/OpenAI) and Claude (Anthropic) for AI-assisted risk of bias assessment. After using these tools/services, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Competing interests

The authors declare no competing interests.

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