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Assessing the diagnostic accuracy of serological tests for hepatitis delta virus diagnosis: a systematic review and meta-analysis

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Hepatitis Delta Virus (HDV), a satellite virus of Hepatitis B virus, exacerbates liver damage in affected individuals. Screening for HDV antibodies in HBsAg positive patients is recommended, but the diagnostic accuracy of serological tests remains uncertain. This review aimed to assess the diagnostic accuracy of serological tests for HDV. We searched PubMed, Web of Science, Cochrane Central Register of Controlled Trials, Scopus etc. for relevant studies. Studies measuring the sensitivity and specificity of serological HDV tests against PCR as a reference standard were included. Pooled sensitivity and specificity for each test method and sero-marker were calculated. The review included six studies with 11 study arms, evaluating ARCHITECT immunoassay, EIA, ELISA, QMAC, RIA, and Western Blot test methods targeting Anti-HDV IgG, Total anti-HDV and Anti-HDV IgM. Sensitivities for Anti-HDV IgG, Total Anti-HDV and Anti-HDV IgM, tests were 97.4%, 51.9%, and 62.0%, respectively, with specificities of 95.3%, 80.0%, and 85.0%. Our findings, with its limited number of studies, suggest that HDV serological tests, particularly those identifying Anti IgG exhibit high accuracy and can serve as effective screening tools for HDV.

Keywords HDV diagnosis, HDV antibody tests, Hepatitis delta, HDV, HDV serological tests, HDV ELISA

Globally, about 300 million people living with chronic hepatitis B infection are at risk of being infected with the Hepatitis Delta virus (HDV)[1] Hepatitis Delta Virus infects only people with Hepatitis B Virus (HBV) because the HDV virus is a defective virus that requires HBV to complete its replication; its presence aggravates liver damage in patients with HBV[2].

HDV is the cause of one-fifth of cases of liver cirrhosis and one-sixth of hepatocellular cancer(HCC) cases among HBV carriers[3,4] Likewise, patients with HDV/HBV coinfections progress to cirrhosis within five years and HCC within 10 years[5]. Furthermore, HDV infection increases the risk of cirrhosis by twofold, HCC by threefold and mortality by twofold compared to HBV mono-infections[6].

Structurally, the HDV virus is a single-stranded circular RNA virus with a 1.7kb genome that relies on HBV to complete its replication by utilizing the envelope proteins of HBV[5]. HDV has eight genotypes: genotype one is endemic across the world, genotype 2 in Asia, genotype 3 in Latin America, genotype 4 in Japan and China, genotype 5 in West Africa, while genotypes 6–8 are found mostly in central Africa[3,5].

HDV infection presents as either coinfection or superinfection. Coinfection occurs when hepatitis B and D infections happen simultaneously, whereas superinfection occurs when hepatitis D is acquired by a chronically infected hepatitis B patient[7]. Despite clinical similarities, these infections have different prognoses[7,8]. Both coinfection and superinfection can progress through acute and chronic phases, but only about 5% of coinfection cases progress to chronicity[9,10]. Coinfection may lead to more aggressive fulminant disease but is mostly self-limiting and resolves with the clearance of HBV/HDV[4]. In contrast, superinfection almost always results

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in chronicity and is associated with faster progression to liver cirrhosis and hepatocellular carcinoma[10]. Rarely, HDV superinfection may clear during the acute phase along with HBV, even though HBV is chronic[9].

HDV infection triggers various immune responses, producing different markers useful for diagnosis. During the early acute phase of HDV onset (within the first ten days) for both superinfection and coinfection, HDVAg and HDVRNA are the detectable biomarkers in serum. However, HDVAg is transient and may disappear soon after[4]. Because of the transient nature of serum HDAg, it cannot be relied on diagnostically; however, its presents indicate active infection[7]. Anti-HDV IgM appears during the acute phase of the infection from about 2–3 weeks to about two months after acute HDV infection and disappears afterward[10]. Detection of Anti-HDV IgM helps distinguish between acute and chronic infections. However, this is not always reliable because Anti-HDV IgM may be present in chronic patients with disease flare ups[9]. Subsequently, total anti-HDV and Anti-HDV IgG levels increase and persists into chronicity. Detection of Anti-HDV IgG is indicative of infection but cannot distinguish between acute or Chronic infections[4,11].

At the end of the acute phase in coinfection, most HDV biomarkers decline, indicating virus clearance with no progression to chronicity[10]. However, in superinfection, the acute phase reaction often leads to chronicity, characterized by sustained levels of IgG and the presence of HDV RNA[4,9].

As the first line of action, a serological test to detect HDV IgG or HDV IgM or Total antibody (Anti-HD) is recommended in screening for HDV, Then, the positive cases are confirmed for active or past infection with PCR[12]. Rt PCR has been established as the gold standard for HDV RNA detection since it has a better specificity and is more sensitive in detecting HDVRNA[4,13].

High-risk groups for HDV coinfection include men who have sex with men (MSM), hemodialysis recipients, people with risky sexual behaviors, people without immunity against HBV, injection drug users and chronic HBV carriers. The infection route of HDV is like HBV, however mother-to-child transmission is rare[2,14].

Currently, Pegylated interferon alpha is the treatment available for HDV. This is however often inefficacious and prone to a lot of adverse effect. Because of these side effects, patients who show advanced liver damage are not eligible for treatment with this drug. On the contrary by reason of lack of testing most patients with HDV are detected late meaning many patients will miss treatment and suffer bad prognosis of HDV due to lack of testing. With the introduction of more efficacious drugs like the emerging Bulevirtide coupled with improved testing and screening, quality of care for HDV patients will be improved[12,15].

A major challenge of HDV epidemiology is the gaps in the prevalence data in some geographic locations and among certain populations especially low-income settings. These gaps affect the distribution of resources and interventions against the disease in places like Africa, which carries a high HBV burden[16]. Apparently, this epidemiology data deficit is due to inadequate testing and screening for HDV[17]. To bridge this gap, it has been recommended that all HBV patients be reflex tested for HDV[14,16,18].

Presently, in many settings only high-risk chronic HBV patients like hemodialysis patients, people born in high endemic regions, HBsAg-positive individuals with low or undetectable HBV DNA but elevated ALT levels are screened for HDV due to inaccessibility of affordable and accurate screening test[15]. Inevitably this causes a lot of patients to present with more advanced liver damage resulting in bad prognosis.

Scarcity of affordable and accurate standard diagnostic tests to detect HDV has existed as a challenge in HDV management for many years[12]. PCR is the recommended gold standard to diagnosing HDV but until 2013, when the WHO made an international standard for HDV RNA, there were no standards to confirm molecular testing of HDV or compare results from different laboratories. However, this standard faces limitations in confirming all genotypes of HDV as it originated from a HDV genotype 1 strain and might struggle to detect various HDV strains[19]. Furthermore, PCR is inaccessible in low resource setting because they are expensive and require specialized personnel and infrastructure[16].

To solve this issue, serological tests are used as a first line to screen for anti-HDV before the viral RNA is confirmed. However, the diagnostic accuracy of these tests remains uncertain. Thus, this systematic review and meta-analysis identified the various serological test methods available for diagnosing HDV and evaluated their diagnostic accuracy.

Methods

This review followed the Cochrane Diagnostic accuracy reviews guidelines and was reported based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols-Diagnostic Test Accuracy (PRISMA-DTA) guidelines[20]. Its registration ID on PROSPERO is (CRD42023442641). We searched various databases for papers that reported the accuracy of serological tests for diagnosing HDV infection. The target population was people suspected of hepatitis Delta and the Index tests were serological tests that were used to detect hepatitis D antibodies (Anti-HDV IgG, Total Anti-HDV and Anti-HDV IgM). These were compared to HDV RNA detection method Rt PCR as the Reference test.

Information sources

We searched PubMed, Web of Science, Scopus, Cochrane Central Register of Controlled Trials and Global Index Medicus between 16th and 18th June 2024 and retrieved relevant papers published up till 2024. We also found documents through citation tracking of the reference list of eligible papers.

Study selection

Eligibility criteria

The studies included in this review employed comparative study designs and diagnostic cohort designs. These studies analyzed HDV serological tests as the index test, using Rt PCR as the reference standard[21]. All participants underwent the index test, and reference standard and the true negative (TN), false negative (FN), false

positive (FP), and true positive (TP) values could be extracted for analysis. We excluded non-English language and non-human studies as well as case reports, and other review articles. We also excluded studies where both the reference test and index test were not utilized on the target population. Studies where neither the index tests nor the reference standard was utilized on the samples under analysis were also excluded.

Data screening

All studies identified from the searches were imported into Rayyan.ai[22], where they were checked for duplicates and screened by their titles and abstracts. Papers were assessed and included in this review based on the eligibility criteria. GAA did the initial searches, but all screening at the different stages was done by GAA and SO. Any disagreements were referred to a third scientist, KK, disagreements were solved by thorough discussion among the authors. The search strategy is found in the Supplementary Table 1.

Data extraction

Full texts of all included articles were read, and relevant data was extracted. We used a 2×2 table to derive TP, FN, TN and FP values from raw data of included studies for sensitivity and specificity analysis. We designed and used Microsoft Forms to extract information, including the author's details, year of study, type of anti-HDV (IgG, IgM and Total Anti HDV), type of index test used, brand of the tests and reference standard from the identified papers. Papers were identified with the first author's last name and the publication year. For studies that assessed more than one index test an alphabet was assigned for the different tests and each designated as a study arm. Before extraction, a pilot test was conducted to assess the suitability of the data extraction form.

Assessment of methodological quality and publication bias

The studies included were appraised using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS 2) tool. QUADAS 2 employs leading questions grouped under four domains: patient selection, index test, reference standard, and flow and timing. The leading questions answer Yes, No, or Unclear corresponding to Low, High, or Unclear risk, respectively. The highest risk of each domain is adopted as the overall risk of that domain. Risk of bias is assessed using questions under all domains while applicability was assessed with three domains only[23].

Statistical analysis and data synthesis

The meta-analysis was done with Excel version 2021. A univariate fixed effects model using inverse variance method was employed to calculate pooled sensitivity, specificity, and confidence intervals by each type of index test method and sero-markers[24]. The subgroup analysis was done for each index test brand characteristic, whether in-house or commercial.

Results

Study selection

The database search identified 2,380 records. After removing duplicates and applying the eligibility criteria, six studies were included in this systematic review and meta-analysis. These included studies were published between 1998 and 2018. The flowchart for the selection of the studies is shown in Fig. 1.

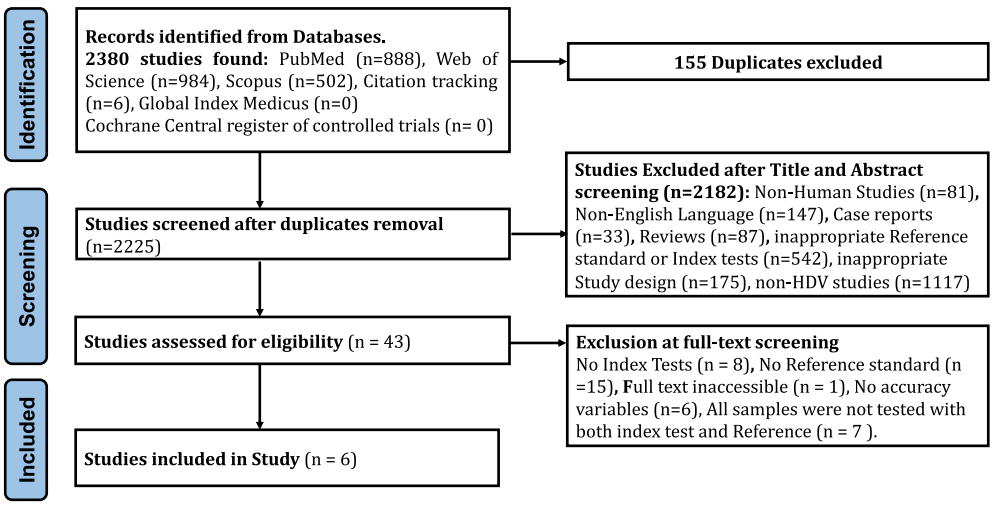

Figure 1. PRISMA flowchart of identification of included literature. Each box represents the number of studies (n) identified in each stage of the study selection process. The blues boxes on the left represents each step of the study selection process. The arrows represent the direction of flow. Excluded studies are shown by the arrows facing right.

Characteristics of included studies

Six studies recruiting 1171 HBsAg + participants were included in this review. The 6 included studies in this review recruited from the general Community 3(50.0%), Blood donation Center 2(33.3%) or Hospital (hepatology clinics) 1(16.7%). While their participants were the General population 2(33.3%), Blood donors 2(33.3%), People who inject drugs (PWID) 1(16.7%) and Chronic HBV carriers 1(16.7%). The ages of the participants ranged from about 29 to 50 years old. And there were more males (50.2%) than females (49.8%).

Four of the six studies analyzed more than one serological test methods on the same set of patients, so each method per study was designated a study arm resulting in 11 arms. The 11 study arms assessed ARCHITECT Immunoassay 1(9.1%), EIA 1(9.1%), ELISA 4(36.4%), QMAC 2(18.2%), RIA 1(9.1%) and Western Blot 2(18.4%) methods. These methods were either Commercial assays 4(36.4%) or In-house assays 7(63.6%) and they detected Anti-HDV IgG 9(81.8%), Total Anti- HDV 1(9.1%) and Anti-HDV IgM 1(9.1%). Table 1 shows the characteristics of the included studies and Table 2 shows the characteristics of the index tests identified from included studies.

Assessment of study quality

The included studies showed a high risk of bias because for about (3/6) 50.0% of the studies, the reference standard was interpreted with knowledge of the index test results. Likewise, there was applicability concerns, due to the reference standard interpretation.

However, the flow and timing domains had No risk concerns (6/6)100.0% similarly the patient selection and index test domains also showed low risk concerns 83.3% (5/6) of included studies for each of the domains. Figure 2 illustrates the results of Study Quality Assessment using QUADAS 2.

Diagnostic accuracy metrics

The pooled sensitivities and specificities for tests based on the targeted immunoglobin were 97.4% (95% CI 94.6–100.0) and 95.3% (95% CI 94.0–96.6) for Anti-HDV IgG detecting tests, 51.9% (95% CI 40.9–62.9) and

Characteristic of participants	**n (%)**
Total participants	N = 1171
Males	50.2%
Females	49.8%
Country of origin	
Mongolia	3 (50.0%)
Cameroon	1 (16.7%)
Taiwan	1 (16.7%)
San Francisco USA	1 (16.7%)
Study settings (origin of participants)	
Community	3 (50.0%)
Blood center	2 (33.3%)
Hospital based	1 (16.7%)
Nature of participants	
General population	2 (33.3%)
Blood donors	2 (33.3%)
PWID	1 (16.7%)
Chronic HBV patients	1 (16.7%)
Characteristics of study arms	**n (%)**
Index tests	
ELISA	4 (36.4%)
Western blot	2 (18.4%)
QMAC	2 (18.2%)
EIA	1 (9.1%)
ARCHITECT immunoassay	1 (9.1%)
RIA	1 (9.1%)
Brand of test	
In-house	7 (63.6%)
Commercial	4(36.4%)
Immunoglobins	
Anti-HDV IgG	9 (81.8%)
Total Anti- HDV	1 (9.1%)
Anti-HDV IgM	1 (9.1%)

Table 1. Characteristics of included studies.

No	References	Year	No. of participants	Cases accessed	Study arm	Index test method	Immunoglobulin tested	Brand of index test	Reference standard method	TP	FP	TN	FN
1	Xiaohua Chen[25]	2017	123	123	Chen 2017a	QMAC	IgG	In house	Rt PCR	70	14	39	0
					Chen 2017b	ELISA	IgG	GenWay Biotech, Inc CA)	Rt PCR	65	18	35	5
					Chen 2017c	Western Blot	IgG	In house	Rt PCR	70	5	48	0
2	Coller[19]	2018	145	145	Coller 2018a	ARCHITECT Immunoassay	IgG	Inhouse	Rt PCR	16	7	122	0
					Coller 2018b	ELISA	IgG	XpressBio (Fredrick, Maryland, USA)	Rt PCR	16	3	126	0
3	Huang[26]	1998	178	119	Huang 1998a	RIA	Total Anti- HDV	Abbot Chicago	Rt PCR	41	8	32	38
					Huang 1998b	EIA	IgM	Sorin biomedica diagnostics, Italy),	Rt PCR	49	6	34	30
4	Jun Inoue[27]	2005	249	194	Inoue 2005	ELISA	IgG	In house	Rt PCR	21	21	152	0
5	Parag Mahale[28]	2018	73	73	Mahale 2018a	QMAC	IgG	In house	Rt PCR	16	0	47	10
					Mahale 2018b	Western Blot	IgG	In house	Rt PCR	26	0	47	0
6	Tsatsralt-Od[29]	2005	403	403	Tsatsralt-Od 2005	ELISA	IgG	In house	Rt PCR	27	14	362	0

Table 2. Characteristics of the index tests identified from included studies.

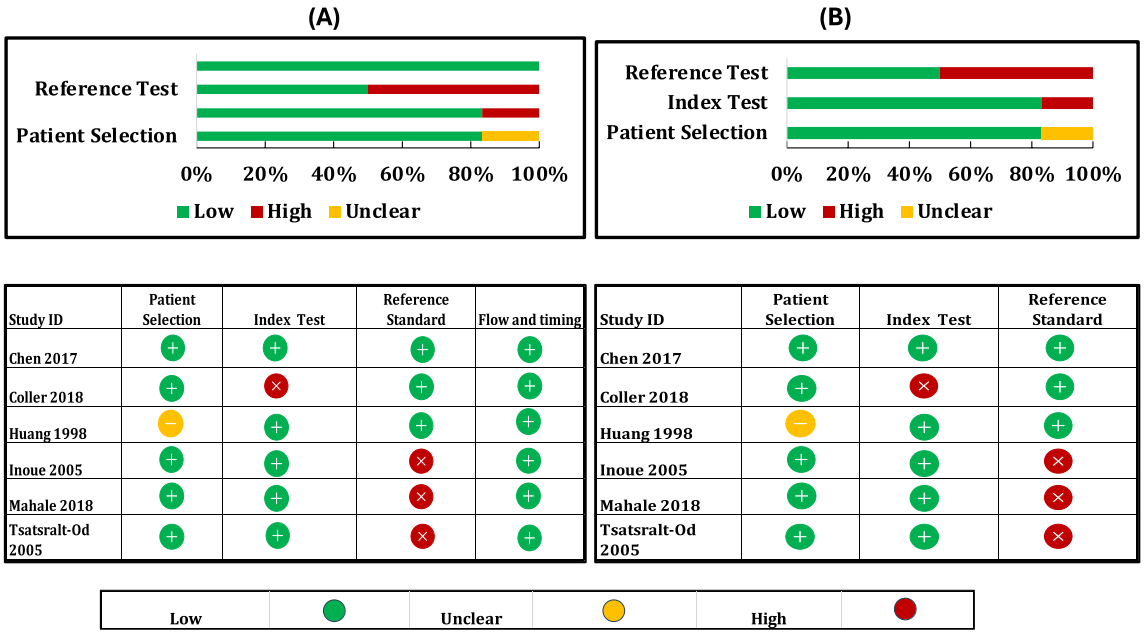

Figure 2. Results of study quality assessment using QUADAS 2 (**A**) is the graphical and traffic light representation of the assessment of risk of Bias of this study. Green color represents low risk, yellow unclear risk whiles Red shows high risk. In answer to leading questions from the QUADAS 2 tool. Each study represented by the study ID was assessed for risk of bias in context of Patient selection, Index test reference standard and flow and timing. The index tests here were the serological tests whiles reference standard was PCR. (**B**) is the graphical and traffic light representation of the assessment of applicability of this study. Green color represents low risk, yellow unclear risk whiles Red shows high risk. In answer to leading questions from the QUADAS 2 tool. Each study represented by the study ID was assessed for applicability in context of Patient selection, Index test and reference standard. The index tests here were the serological tests whiles reference standard was PCR.

80.0% (95% CI 67.6–92.4), for Total Anti HDV tests and 62.0% (95% CI 51.3–72.7) and 85.0% (95% CI 73.9–96.1) for Anti-HDV IgM tests.

Among the test methods identified, ARCHITECT immunoassay demonstrated a pooled sensitivity and specificity of 100.0% (95% CI 76.9–100.0) and 94.6% (95% CI 90.7–98.5) while EIA pooled sensitivity and specificity of 62.0% (95% CI 51.3–72.7) and 85.0% (95% CI 73.9–96.1).

On the other hand, ELISA exhibited a sensitivity and specificity of 94.8% (95% CI 89.7–100.0) and 95.6% (95% CI 94.1–97.0) whereas QMAC demonstrated a sensitivity of 97.2% (95% CI 92.1–100.0) and specificity of

92.0% (95% CI 85.4–98.5). RIA revealed a sensitivity of 51.9% (95% CI 40.9–62.9) and a specificity of 80% (95% CI 67.6–92.4) whilst Western blot also showed a sensitivity and specificity of 100.0% (95% CI: 95.1–100.0) and 95.3% (95% CI 89.7–100.0).

We compared the pooled sensitivity and specificity of the index tests, whether they were commercial or in-house assays. We determined whether the tests being in-house or commercial could impact the performance of the different test methods. Commercial test kits showed a sensitivity of 80.1% (95% CI 75.4–84.7) and specificity of 95.2% (95% CI 92.8–97.7). Compared with In-house test method exhibiting a sensitivity of 98.8% (95% CI 95.5–100.0) and specificity of 94.9(– 93.4–96.6).

Subgroup analysis of diagnostic accuracy metrics

We sub grouped all Anti HDV IgG tests by the Brand of test to assessed whether brand and target immunoglobin affected the tests accuracy. Commercial Anti HDV IgG tests had a sensitivity of 93.3(95% CI 87.5–99.2) and a specificity of 96.4(95% CI 95% CI 93.9–99.0). In- house Anti-HDV IgG noted a sensitivity and specificity of 98.8 (95% CI 95.5–100.0) and 94.9(95% CI 93.4–96.4) respectively.

Table 3 illustrates Pooled sensitivities and specificities of Index tests stratified by Study Characteristics. Supplementary Fig. 1a,b shows forest plots illustrating the index tests' performance.

Discussion

We sought to assess the diagnostic accuracy of serological tests employed for diagnosing hepatitis delta virus. We discovered that Anti-HDV IgG based test performed better than total Anti-HDV and Anti- HDV IgM based tests. Generally, the performance of all the tests methods were similar with overlapping confidence intervals except for RIA and EIA tests which had lower sensitivities.

Furthermore, In-House assays outperformed Commercial assays, whereas among Anti-HDV IgG tests in-house tests performed better.

One key finding of this study was that Anti HDV IgG detecting tests performed better than total Anti HDV and IgM-detection tests, which had a sensitivity and specificity of 51.9% (95% CI 40.9–62.9) and 80.0% (95% CI 67.6–92.4), for Total Anti HDV tests and 62.0% (95% CI 51.3–72.7) and 85.0% (95% CI 73.9–96.1) for IgM tests. Our findings may be due to IgM anti-HDV antibody assays failing to detect low antibody titers during specific phases of the infection[30]. It has been reported that Anti-HDV IgM is detectable from 2 to 3 weeks to about two months after acute HDV infection and disappears afterward[4,9]. Anti HDV IgM is a good marker for differentiating acute infection from chronic infection[9]. However, in chronic patients with flare ups and relapse after therapy Anti-HDV IgM may be elevated[31,32]. Thus, Anti-HDV IgM detection cannot reliably distinguish between acute and chronic HDV infections. Furthermore, Anti-HDV IgM may be absent, in some African HDV genotypes[14]. Hence, relying solely on Anti-HDV IgM for diagnosis may produce false negative results. In contrast, total HDV antibodies appear four weeks after infection while anti-HDV IgG reaches a detectable level after IgM antibodies disappear[33]. Total Anti-HDV was expected to have a better performance because Anti-HDV IgG and total remain in the serum following the resolution of acute HDV infection and in individuals with Chronic coinfection making them better parameters for diagnosing HDV than Anti-HDV IgM[4,34]. However, the performance of Total

Study characteristic	Parameter	Number of study arms	Sensitivity		Specificity	
			TP + FN	(95% CI)	TN + FP	(95% CI)
Immunoglobulins						
	Anti-HDV IgG	9	342	97.4 (94.6–100.0)	1060	95.3 (94.0–96.6)
	Total Anti-HDV	1	79	51.9 (40.9–62.9)	40	80.0 (67.6–92.4)
	Anti-HDV IgM	1	79	62.0 (51.3–72.7)	40	85.0 (73.9–96.1)
Index test						
	Architect immune assay	1	16	100.0 (76.9–100.0)	129	94.6 (90.7–98.5)
	EIA	1	79	62.0 (51.3–72.7)	40	85.0 (73.9–96.1)
	ELISA	4	134	94.8 (89.7–100.0)	731	95.6 (94.1–97.0)
	QMAC	2	96	97.2 (92.1–100.0)	100	92.0 (85.4–98.5)
	RIA	1	79	51.9 (40.9–62.9)	40	80 (67.6–92.4)
	Western blot	2	96	100.0 (95.1–100.0)	100	95.3 (89.7–100.0)
Brand of index test						
	Commercial assays	4	244	80.1 (75.4–84.7)	262	95.2 (92.8–97.7)
	In-house assays	7	256	98.8 (95.5–100.0)	878	94.9 (– 93.4–96.6)
Anti HDV IgG by the brand of test						
	Commercial anti-HDV IgG	2	86	93.3 (87.5–99.2)	182	96.4 (93.9–99.0)
	In-house anti-HDV IgG	7	256	98.8 (95.5–100.0)	878	94.9 (93.4–96.4)

Table 3. Diagnostic accuracy metrics: pooled sensitivities and specificities of index tests stratified by study characteristics.

Anti-HDV in our study may be due to it being assessed by only one study arm and was utilized in an RIA test which have been known to be a less sensitive test method[35].

It is important to mention that there were no studies assessing serum HDVAg. This may be because its use has phased out over the years due to its transient nature. HDVAg is only temporarily detectable in the serum of infected patients at the early acute phase of the infection[36].

This review further highlights a notable finding: among the six evaluated serological tests for HDV antibodies, EIA and RIA performed the least, displaying the lowest sensitivities. In contrast, ELISA, QMAC, Western blot, and ARCHITECT immuno assay showed high sensitivities, ranging between 94% and 100%, with overlapping confidence intervals. This outcome corroborates previous literature, which indicated that EIA and RIA tests had low performance in detecting Anti HDV[35,37].

The lower EIA performance observed in our study may be attributed to the fact that, only one study assessed EIA, and was IgM-based, generally associated with lower sensitivity.

Radioimmunoassays (RIAs) were the first serological techniques used to detect hepatitis viruses, including anti-HDV. However, our results, consistent with existing literature, show that RIAs can produce false-positive results, with RIA having the lowest specificity among all index tests[35]. Despite this, RIA remains widely used in commercial kits for diagnosing various hepatitis viruses[8]. QMAC and Western Blot tests performance in our study aligns with previous literature, demonstrating excellent ability of QMAC to detect high HDV prevalence in a Mongolian cohort and successfully identify HDV in a PWID population[25]. In that same report, Western Blot served as the gold standard to evaluate a novel test and showed similar performance as PCR. This mirrors the performance of Western Blot in our study[28]. It's crucial to note that despite the good performance of the ARCHITECT immunoassay only one study arm evaluated it.

WHO has set an ambitious target of reducing mortality due to viral hepatitis by 65% by 2030[38]. Since HDV is one of the main causes of liver deterioration and mortality among HBV patients, it is imperative that people living with HBV be screened for HDV and positive ones linked to care. Asian Pacific Association for the Study of the Liver (APASL) and the European Association for the Study of the Liver (EASL) recommend HDV testing in all HBV patients with chronic liver disease. This has been reiterated by WHO in its recent update in the Guidelines for prevention diagnosis care and treatment for people living with chronic hepatitis B[39]. These recommendations are supported by reports which suggest that reflex testing improved HDV diagnoses up to five times[18].

Nonetheless due to inaccessibility of cheap and accurate tests most clinicians do not test[14]. It is recommended that for accurate diagnosis of HDV, serological tests be used to screen patients, followed by molecular detection[40]. From our study it is apparent that apart from EIA and RIA's the identified test methods can be used successfully to screen for HDV.

In the context of chronic hepatitis patients, a concerning trend emerges where most cases of hepatitis D virus (HDV) infection are identified at advanced stages, leading to delayed initiation of treatment resulting in low treatment success rates[15]. With the availability and adoption of these accurate and more affordable serological tests, patients can be diagnoses early and linked to essential care services, thereby facilitating early intervention and significantly enhancing prognostic outcomes.

Furthermore, it was revealed that there were no studies assessing the accuracy of RDTs for HDV. Most tests available for Anti-HDV detection cannot be adopted in remote areas where a traditional lab setting is scarce. To achieve the WHO target of eliminating viral Hepatitis infection by 2030, there is an urgent need for more easily applicable testing methods like RDT. HBV RDTs have been a critical tool in screening HBsAg seroprevalence, and it is imperative to develop RDTs targeting anti-HDV. Thus, RDTs for HDV could be the ideal solution to screen HDV in HBV-positive patients widely, thanks to their cost-effectiveness and easy operation.

We expected commercial assays to perform better than In-house in detecting Anti-HDV. However, the reverse was true for our studies. It appears In-house methods work better in detecting Anti- HDV. A study evaluating an In-house ELISA test for hepatitis B confirmed this by recording a 100% sensitivity and specificity for the inhouse test[41]. In house tests are cheaper than Commercial tests however in-house tests may need a more experienced professional to run. Our findings mean that if the in-house test method protocols are followed strictly, they can be used effectively to diagnose HDV in resource-poor settings. Additionally, even though both Commercial Anti-HDV IgG and In-House Anti-HDV IgG tests have comparable performance, In-house Anti-HDV IgG performed better. This further emphasize the good performance of Anti-HDV IgG and In-house tests.

Limitation

A major limitation of this study is the small number of publications retrieved. This highlights the scarcity of HDV studies and the apparent unavailability of HDV testing, as reflected in the low number of identified studies. Owing to this limitation, we could not measure how the type and timing of infection whether coinfection, superinfection, Acute or Chronic will affect the performance of the tests. We also could not assess the influence of HDV genotype on the performance of the tests. Publication Bias was also not assessed due to this limitation. Given the limited number of studies, it is important to interpret the results of this meta-analysis with caution. Results from our study should be interpretated with caution again because, most of the studies analyzed assessed Anti-HDV IgG test with Anti-HDV IgM and Total Anti-HDV being poorly represented. This played a major role in the performance of Anti-HDV IgG against the other target immunoglobulins tests. Although we performed a subgroup analysis of each method stratified by the immunoglobulins, we found that these subgroups could not be compared because of the sparse number of studies.

In conclusion, HDV serological tests, specifically those identifying Anti-HDV IgG demonstrate high accuracy and can be relied upon as effective screening test for HDV in improving access to HDV testing, test methods like ELISA, recognized for their accuracy and adaptability in settings without specialized expertise or infrastructure, can be utilized in low-resource settings. Implementing approaches like reflex testing with serological tests

will enable the efficient screening of a broader population, thereby improving data accuracy and significantly contributing to our comprehension of HDV epidemiology, thus enhancing HDV data consistency. Emphasis should be placed on developing HDV rapid tests (RDTs) to bring crucial testing capabilities to remote settings, where conventional laboratory facilities are scarce. Consequentially, by implementing more effective screening and testing protocols, a greater number of HDV patients can be timely linked to appropriate medical care. This proactive approach to care initiation not only facilitates prompt treatment but also contributes significantly to enhancing treatment outcomes and prognosis for individuals affected by HDV infection.

Data availability

All data generated or analyzed during this study are included in these published articles.

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Competing interests

The authors declare no competing interests.

Additional information

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