Title page

Type of manuscript: Full-Length Text

Title: Diagnostic performance of the HCV core antigen test to identify hepatitis C in HIV-infected patients: a systematic review and meta-analysis

Running head: Diagnostic performance of HCVcAg test in PLWHA

Authors: Daniel SEPÚLVEDA-CRESPO [1,2,¥]; Ana TREVIÑO-NAKOURA [3,4,¥]; José M BELLON [5]; María A. JIMÉNEZ-SOUSA [1,2]; Pablo RYAN [2,6]; Isidoro MARTÍNEZ [1,2,¥]; Amanda FERNÁNDEZ-RODRÍGUEZ [1,2,¥]; Salvador RESINO [1,2,*,¥]

(¥), Both authors contributed equally to this study; (*), Corresponding author

Current affiliations:

(1) Unidad de Infección Viral e Inmunidad. Centro Nacional de Microbiología - Instituto de Salud Carlos III, Majadahonda, Spain.

(2) Centro de Investigación Biomédica en Red en Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain.

(3) Servicio de Medicina Preventiva y Salud Pública, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain.

(4) Universidad Nacional de Educación a Distancia (UNED), Madrid, Spain

(5) Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain.

(6) Servicio de Medicina Interna, Hospital Universitario Infanta Leonor, Madrid, Spain.

Corresponding author: Salvador Resino, Centro Nacional de Microbiología, Instituto de Salud Carlos III (Campus Majadahonda); Carretera Majadahonda-Pozuelo, Km 2.2; 28220 Majadahonda (Madrid), Spain. Tel: +34 918 223 266; Fax: +34 915 097 946; e-mail: sresino@isciii.es

Character count of Title: 139

Character count of Running Head: 46

Word count of Abstract: 308

Word count of Keywords: 5

Words count for the main body: 3148

Count of References: 51

Count of Tables: 1

Count of Figures: 4

Abstract

The standard algorithm for diagnosing hepatitis C virus (HCV) infection has two steps, an HCV antibody test for screening and a nucleic acid amplification test (NAAT) for confirmation. However, the HCV core antigen (HCVcAg) detection assay is an alternative for one-step diagnosis. We aimed to evaluate the diagnostic performance of the Abbott ARCHITECT HCV Ag assay to detect active hepatitis C in serum/plasma in people living with HIV/AIDS (PLWHA) through a systematic review and meta-analysis. PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Library were searched until September 20, 2022 (PROSPERO, CRD42022348351). We included studies evaluating Abbott ARCHITECT HCV Ag assay (index assay) *vs.* NAATs (reference test) in PLWHA coinfected with HCV who did not receive antiviral treatment for HCV. Meta-analysis was performed with the MIDAS module using STATA and random-effects models. QUADAS-2 tool evaluated the risk of bias. The bivariate analysis was conducted on 11 studies with 2,407 samples. Pooled sensitivity was 0.95 (95%CI=0.92-0.97), specificity 0.97 (95%CI=0.93-0.99), positive likelihood ratio 37.76 (95%CI=12.84-111.02), and negative likelihood ratio 0.06 (95%CI=0.04-0.09). The area under the curve was 0.97 (95%CI=0.20-1.00). For low prevalence (≤5%), the post-test probability that an individual with a positive test was a true positive ranged from 4% to 67%, whereas, at high prevalence (≥10%), the post-test probability was between 81% and 87%, indicating that a confirmatory test should be necessary, particularly with prevalence values ≤1%. Regardless of prevalence, the probability that an individual with a negative test was a false negative was close to zero, indicating that the individual was not infected with HCV. In conclusion, the accuracy of the Abbott ARCHITECT HCV Ag assay was very good for HCV screening in serum/plasma samples from PLWHA. The clinical utility to confirm HCV infection was acceptable in high prevalence settings (≥10%) but poor in low prevalence settings (≤1%). Furthermore, it was excellent in excluding active HCV infection.

Keywords: Hepatitis C; people living with HIV; core antigen; diagnostic accuracy; screening

Introduction

Hepatitis C virus (HCV) infection can cause chronic hepatitis C (CHC), which, if not treated in time, can lead to fibrosis, cirrhosis, liver failure, hepatocellular carcinoma, and even death (1). HCV infection is a global health problem since about 58 million people worldwide have CHC, which causes almost 300,000 deaths yearly (2). Developing countries concentrate the majority of cases, with a higher prevalence in high-risk populations such as men who have sex with men (MSM), female sex workers, people who inject drugs (PWID), and prisoners (3). Direct-acting antivirals (DAAs) against HCV have demonstrated high efficacy rates (>90%). However, HCV infection remains a serious social and public health problem because less than 20% of people infected with HCV are aware that they are infected, as CHC remains asymptomatic for a long time, progressively causing liver damage (2, 4). Therefore, the World Health Organization calls for eliminating viral hepatitis by 2030 by detecting 90% of patients with CHC and treating 80% of them (5).

HCV infection is common in people living with HIV/AIDS (PLWHA) since both viruses share transmission routes (6-8). There are around 2.9 million PLWHA coinfected with HCV (4). HCV/HIV-coinfection negatively affects the transmission and natural history of HCV infection. HIV infection reduces the chance of HCV spontaneous clearance, increases chronic HCV infection rates, and accelerates the development of HCV-related liver diseases, such as liver cirrhosis, liver failure, and hepatocellular carcinoma (9, 10). Although combined antiretroviral therapy (cART) against HIV can improve these outcomes and decrease HCV-related mortality (11), the primary cause of morbi-mortality among HIV/HCV-coinfected individuals is related to liver diseases (12). As a result, HCV detection and effective treatment should be prioritized for this population.

Currently, the HCV diagnostic algorithm includes two steps: first, detection of antibodies against HCV (anti-HCV), and second, confirmation of active hepatitis C infection by detection of HCV-RNA (13). HCV-RNA detection in clinical practice is performed by nucleic acid amplification test (NAAT), the gold standard confirmatory assay (14, 15). However, NAATs are time-consuming and involve qualified personnel and advanced equipment, which are expensive (16, 17). Furthermore, RNA is easily degraded, leading to false negative (FN) results (18). The HCV core antigen (HCVcAg) test is an alternative for active HCV infection diagnosis, which is easier, cheaper, and faster than NAATs (17, 19, 20). HCVcAg appears in blood before anti-HCV antibodies, correlates positively with HCV-RNA load, is more stable than HCV-RNA, and is detected within 12-15 days after HCV infection, anticipating the window period for diagnosis.

Previous reports have analyzed the diagnostic performance of the Abbott ARCHITECT HCV Ag assay for screening HCV infection in PLWHA (21-34), which is today's most widely used HCVcAg test for HCV screening (20). Freiman's meta-analysis (35) reported high accuracy of the Abbott ARCHITECT HCV Ag assay in the general population, but they did not report data on clinical application and did not analyze data in PLWHA to diagnose active hepatitis C. To our knowledge, there is no meta-analysis on the diagnostic performance of the HCVcAg test to screen for hepatitis C in PLWHA, a high-risk population with particular characteristics (36).

Objective

This study aimed to evaluate the diagnostic performance of the Abbott ARCHITECT HCV Ag assay for detecting active hepatitis C in serum/plasma in PLWHA through a systematic review and meta-analysis of eligible studies published to date (September 20, 2022).

Material and Methods

The systematic review was completed according to the Cochrane Handbook for Diagnostic Test Accuracy Reviews (37) and the Preferred Reporting Items for Systematic Reviews and Meta-analysis of Diagnostic Test Accuracy (PRISMA-DTA) guidelines (38). A completed PRISMA-DTA checklist is available in **Supplementary File 1**.

Search strategy

Studies were identified using different search commands in Medline/PubMed, EMBASE, SCOPUS, Web of Science, and Cochrane Library (see **Supplementary File 2**) between January 1, 1976, and September 20, 2022. This protocol was designed a priori and registered on the online database PROSPERO (CRD42022348351). The literature search was not restricted by language, publication time, study design, or geographic location. Reference lists of included studies were evaluated for further relevant records. Articles from other languages were translated into English with the help of Google Translate.

Study selection

Studies inclusion was determined according to the following criteria: 1) evaluation of diagnostic accuracy in plasma/serum of PLWHA; 2) comparison between the Abbott ARCHITECT HCV Ag assay and a NAAT (gold standard); and 3) available data to formulate a 2x2 contingency table [true positives (TP), false positives (FP), true negatives (TN), false negatives (FN)]. The exclusion criteria were as follows: 1) no available data to estimate sensitivity or specificity (nor by the corresponding author upon reasonable request); 2) a sample size of less than 10, to avoid bias in the random-effects model; 3) non-human subjects, commercial samples, or off-market assays; 4) data during and after HCV antiviral therapy; and 5) non-original articles, unpublished data or data published in case reports, comments, letters to the editor, conference abstracts, chapter books, and review articles. All studies were independently screened by two investigators (A.T.N. and D.S.C.), who carefully reviewed the full text of the selected papers to extract all data.

Data extraction

Diagnostic accuracy of the HCVcAg test and population characteristics were extracted by two investigators (D.S.C. and A.T.N.), who carefully reviewed the full text of the selected papers to extract all data and judged each study according to the previous criteria. Disagreement was resolved by consensus and/or consultations with the senior author (S.R.). One investigator (D.S.C) contacted authors by e-mail for missing data up to three attempts, excluding those without a response.

Assessment of risk of bias

Study quality was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (39). The risk of bias and concerns over applicability were assessed by two reviewers (A.T.N. and D.S.C.). Discrepancies were resolved by a third reviewer (S.R.). The risk of bias is summarized in a table as 'low', 'unclear', or 'high' for each domain, whereas the degree of applicability is rated as 'low', 'unclear', or 'high' for the first three domains. The 'unclear' category is used only when reported data is insufficient (see **Supplementary File 3**).

Statistical analysis

All statistical analyses were performed with the MIDAS package in STATA 15.0 (STATA Corp., College Station, TX, USA) (40, 41). Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and the area under the curve of the summary receiver operating characteristic curve (AUC-SROC) were calculated using a bivariate model, with the studies that had TP+FN>0 and FP+TN>0. The bivariate analysis considers the size of the study and uses a random-effects approach to obtain heterogeneity beyond the methodological and clinical differences between studies. We also performed a univariate analysis with all studies, including those with TP+FN=0 or FP+TN=0.

The accuracy level was evaluated by plotting the SROC curve and calculating the AUC, considering very good (AUC=0.90-1), good (0.80-0.90), fair (0.70-0.80), poor (0.60-0.70), and failed (0.50-0.60) (42). For clinical utility, a four-quadrant likelihood scatter matrix was used as follows (43): i) left upper quadrant (LUQ; PLR >10, NLR <0.1): confirmation & exclusion; ii) right upper quadrant (RUQ; PLR >10, NLR >0.1): confirmation only; iii) left lower quadrant (LLQ; PLR <10, NLR <0.1): exclusion only, and iv) right lower quadrant (RLQ; PLR <10, NLR >0.1): no confirmation or exclusion. The clinical or patient-relevant utility was also assessed with Fagan's nomogram, which gave the post-test prediction at the population level, taking into account the prevalence or pre-test probability estimation (0.1%, 0.5%, 1%, 5%, 10%, and 15%) and the PLR and NLR values (44).

The Cochran-Q method and inconsistency index (I^2) quantified the heterogeneity between the studies, being significant with $p \leq 0.10$ and $I^2 \geq 50\%$, respectively (45). Galbraith (radial) (46) and bivariate boxplots (bagplot) (47) were also used to analyze the heterogeneity. Furthermore, meta-regression was performed to define the impact of several factors on diagnostic accuracy measures ($p \leq 0.10$): year of publication (Yes: ≤2015; No: >2015), low- or middle-income countries (LMICs; Yes/No), all patients with positive anti-HCV (anti-HCV Ab +) (Yes/No), biological sample type (Yes: only serum; No: plasma or plasma/serum), frozen sample (Yes/No), large sample size (Yes: ≤100; No: >100), and HCV prevalence (≤50; No: >50). We used Deeks' funnel plot asymmetry test to evaluate publication bias, with a symmetric funnel shape when there is no publication bias ($p > 0.10$) (48).

Results

Search results

Figure 1A shows the flowchart summarizing the steps to identify the eligible studies. The initial search of electronic databases reported 9,368 articles covering the literature published between 1976 and 2022. Of these, 30% (n=2,841) were duplicates, and the remaining 6,527 articles were reviewed. Based on the evaluation of titles and abstracts, together with a detailed evaluation, a total of 6,325 studies were filtered out. After evaluating the full texts of 202 studies, 14 were eligible for this meta-analysis because all reported the necessary information and met the inclusion criteria mentioned above (21-34).

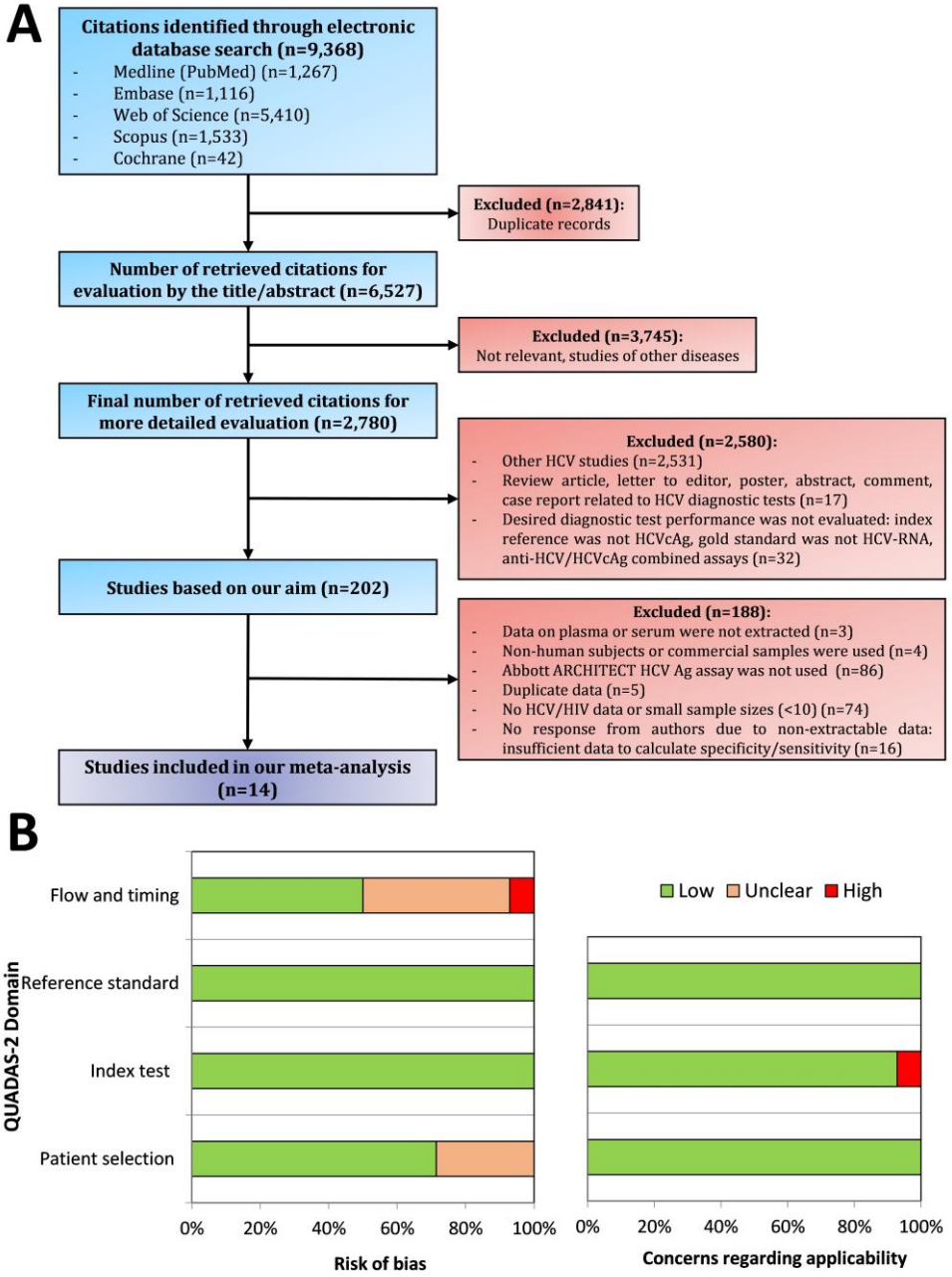


Figure 1. Flow chart of the study searching process **(A);** quality assessment of eligible studies according to the QUADAS-2 tool **(B)**. In figure (B), green indicates a low risk, orange stands for unclear risk, and red indicates a high risk. **Abbreviations**: cAg = core antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IU = international units; QUADAS = quality assessment of diagnostic accuracy study.

Table 1. Summary of studies included in the meta-analysis detecting HCV core antigen with Abbott ARCHITECT HCVcAg assay in serum and/or plasma samples from PLWHA.

Author (year) [reference]	Country	No.	Age (yrs.)	Males (%)	HCV genotype	HBV (%)	Sample type	Sample Condition	GS Cut-off (IU/mL)
Mederacke et al. (2012) (21)	Germany	71	N/D	N/D	1, 3, 4	N/D	Serum/Plasma	Frozen	15 and 600
Garbuglia et al. (2014) (22)	Italy	249	47	69.6	1, 3, 4	3.8	Plasma	Frozen	12
Van Helden et al. (2014) (23)	Germany	97	38.2	84.5	1, 2, 3	9.3	Serum	Frozen	15
Cresswell et al. (2015) (24)	UK	111	45.2	94.6	1, 3, 4	N/D	Serum	Frozen	N/D
Vanhommerig et al. (2015) (25)	Netherlands	91	N/D	100	1, 2, 3, 4	N/D	Serum	Unknown	615
Alados-Arboledas et al. (2017) (26)	Spain	68	49.8	80.5	1, 3, 4	N/D	Plasma	Frozen	15
Duchesne et al. (2017) (27)	Cameroon	78	46.3	43.5	1, 2, 4	N/D	Serum	Frozen	12
Hullegie et al. (2017) (28)	Netherlands	67	41	100	1	N/D	Serum/Plasma	N/D	15 and 12
Mohamed et al. (2017) (29)	Tanzania	65	38	92.2	1, 4	N/D	Serum	Frozen	15
Talal et al. (2017) (30)	USA	19	53.8	59.6	1, 2, 3, 4	N/D	Serum	Frozen	15
Alonso et al. (2018) (31)	Spain	20	N/D	N/D	1, 2, 3	78.3	Serum	Frozen	15
Chayanupatkul et al. (2020) (32)	Thailand	36	41.4	83.3	1	N/D	Serum	Frozen	12
Rossetti et al. (2021) (33)	Italy	20	56	80	1, 2, 3, 4	N/D	Serum/Plasma	Frozen	15 and 12
Sun et al. (2022) (34)	Taiwan	1534	40.5	97.6	1, 2, 6	10.3	Plasma	N/D	15

Abbreviations: GS = gold standard; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IU = international units; No. = sample size; N/D = not available data; PLWHA = people living with HIV/AIDS; UK = United Kingdom; USA = United States of America; yrs = years.

Article characteristics

Table 1 summarizes the main characteristics of the 14 articles included in this meta-analysis. All studies were published between 2012 and 2022, had a cross-sectional design, included adults only, and were published in English, except one published in German (23). Three studies were carried out at LMIC (27, 29, 32). A total of 2,526 individuals were included, with 82.1% male and a mean age of 45. The HCV genotypes ranged from 1 to 6, and only four studies (22, 23, 31, 34) provided information on the HBV status with a prevalence between 3.8 and 78.3%.

HCVcAg quantification was performed using the Abbott ARCHITECT HCV Ag assay, whose lower limit of detection (LLOD) was 3 fmol/L (0.06 pg/mL). The primary gold standard assay to detect HCV-RNA was the 'COBAS Ampliprep/COBAS TaqMan HCV Real-time PCR' (Roche Diagnostics) (n=9; LLOD: 12, 15, and 600 IU/mL) (21, 23, 26, 28-31, 33, 34), followed by the 'Abbott RealTime HCV Assay' (Abbott Diagnostics) (n=4; LLOD: 12 IU/mL) (22, 24, 27, 32) and the 'VERSANT HCV RNA Qualitative Assay' (Siemens Healthcare Diagnostics) (n=1; LLOD: 615 IU/mL) (25).

Assessment of risk of bias

QUADAS-2 (**Figure 1B** and **Supplementary File 3**) showed that the risk of bias in the patient selection domain was unclear in four studies (22, 23, 27, 31) (28.6%) due to the lack of information on whether the study was consecutive, randomized, or not. The patient sample to evaluate the diagnostic test accuracy was also not documented. Both flow bias and timing bias were unclear in six (42.9%) studies (21, 23, 26, 28, 29, 33) and high in one (7.1%) (34) because the delay between the reference test and the index test was not correctly reported.

All studies had a low risk of bias for the index and reference standard domains. Although the analytical sensitivity of the three NAATs used as a reference standard is different, overall, the tests were highly sensitive, and the variability was minimal. Besides, HCV-RNA loads measured by NAATs correlated well with HCVcAg levels, as is shown in most eligible studies (21-24, 27, 29-33). Moreover, it is unlikely to introduce bias even if the reference standard resulted in knowledge of the index test result. The applicability of the included studies was low for all but one study (34), which showed significant concerns about the performance and interpretation of the HCVcAg test.

Diagnostic validity

The bivariate analysis was conducted on 11 studies with 2,407 samples. Pooled sensitivity was 0.95 (95%CI = 0.92-0.97) (**Figure 2A**), specificity was 0.97 (95%CI = 0.93-0.99) (**Figure 2B**), PLR was 37.76 (95%CI = 12.84-111.02) (**Figure 2C**), and NLR was 0.06 (95%CI = 0.04-0.09) (**Figure 2D**). The AUC-SROC was 0.97 (95%CI = 0.20-1.00), suggesting that the overall diagnostic performance of HCVcAg in PLWHA was very good (**Supplementary Figure 1**). The univariate analysis (n=14 articles) showed a pooled sensitivity of 0.96 (95%CI = 0.93-0.98), slightly higher than the bivariate analysis (**Supplementary Figure 2**).

Clinical application

Fagan's nomograms showed that for low prevalence (≤1%), the post-test probability that an individual with a positive test was a TP ranged from 4% to 28%, while, at high prevalence (≥10%), the post-test probability was between 81% and 87%, indicating that a confirmatory test should be necessary, particularly with prevalence values ≤1% (**Figure 3**). However, the probability that an individual with a negative test was an FN was close to zero, regardless of HCV prevalence (**Figure 3**).

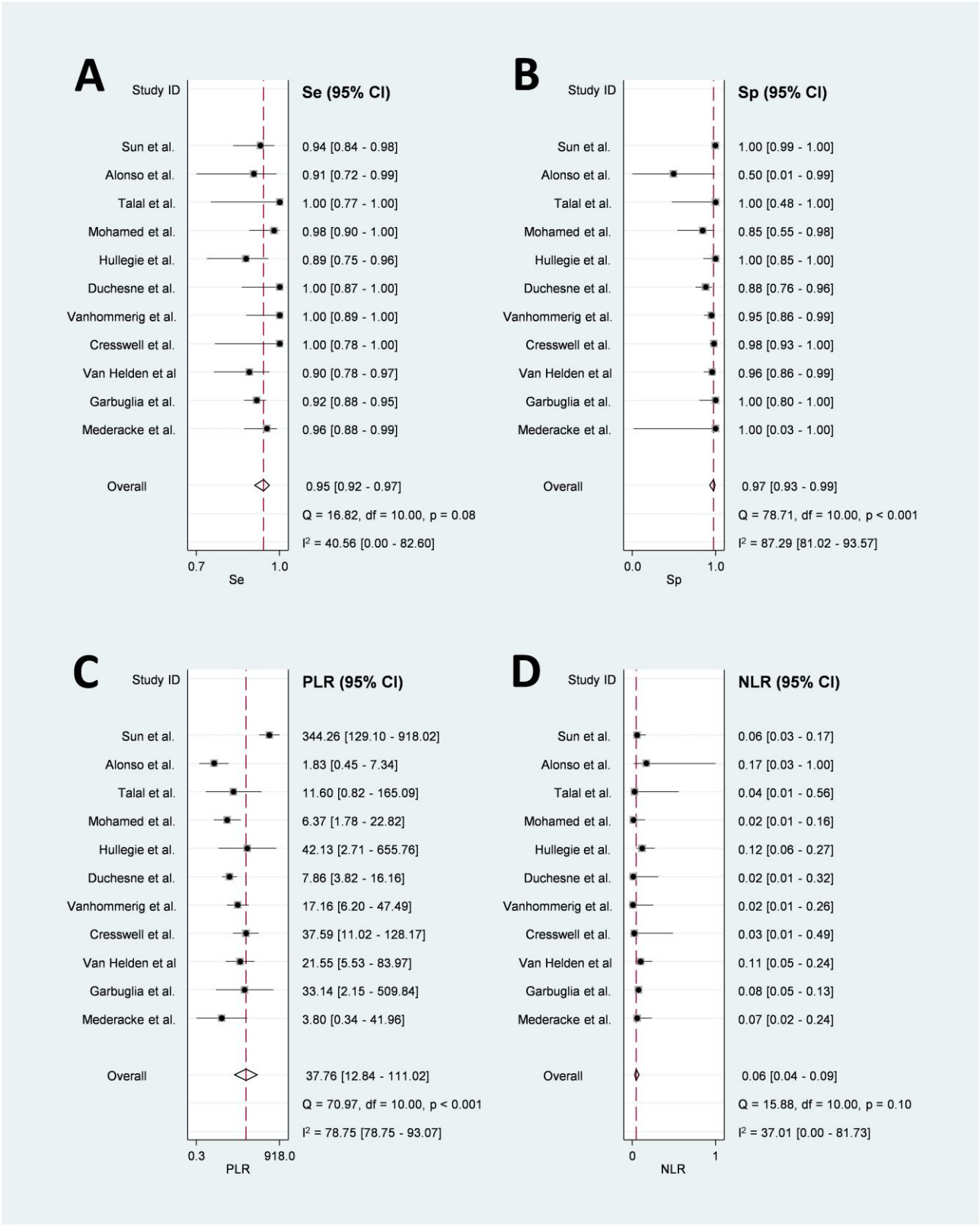


Figure 2. Forest plots of pooled Se **(A)**, Sp **(B),** PLR **(C),** and NLR **(D)** for all studies included in the bivariate analysis for detecting active HCV infection with Abbott ARCHITECT HCV Ag assay in PLWHA compared with a confirmatory nucleic acid test. **Abbreviations**: 95% CI = 95% confidence interval; HCV = hepatitis C virus; I^2 = inconsistency index; NLR = negative likelihood ratio; PLR = positive likelihood ratio; PLWHA = people living with HIV/AIDS; Se = sensitivity; Sp = specificity.

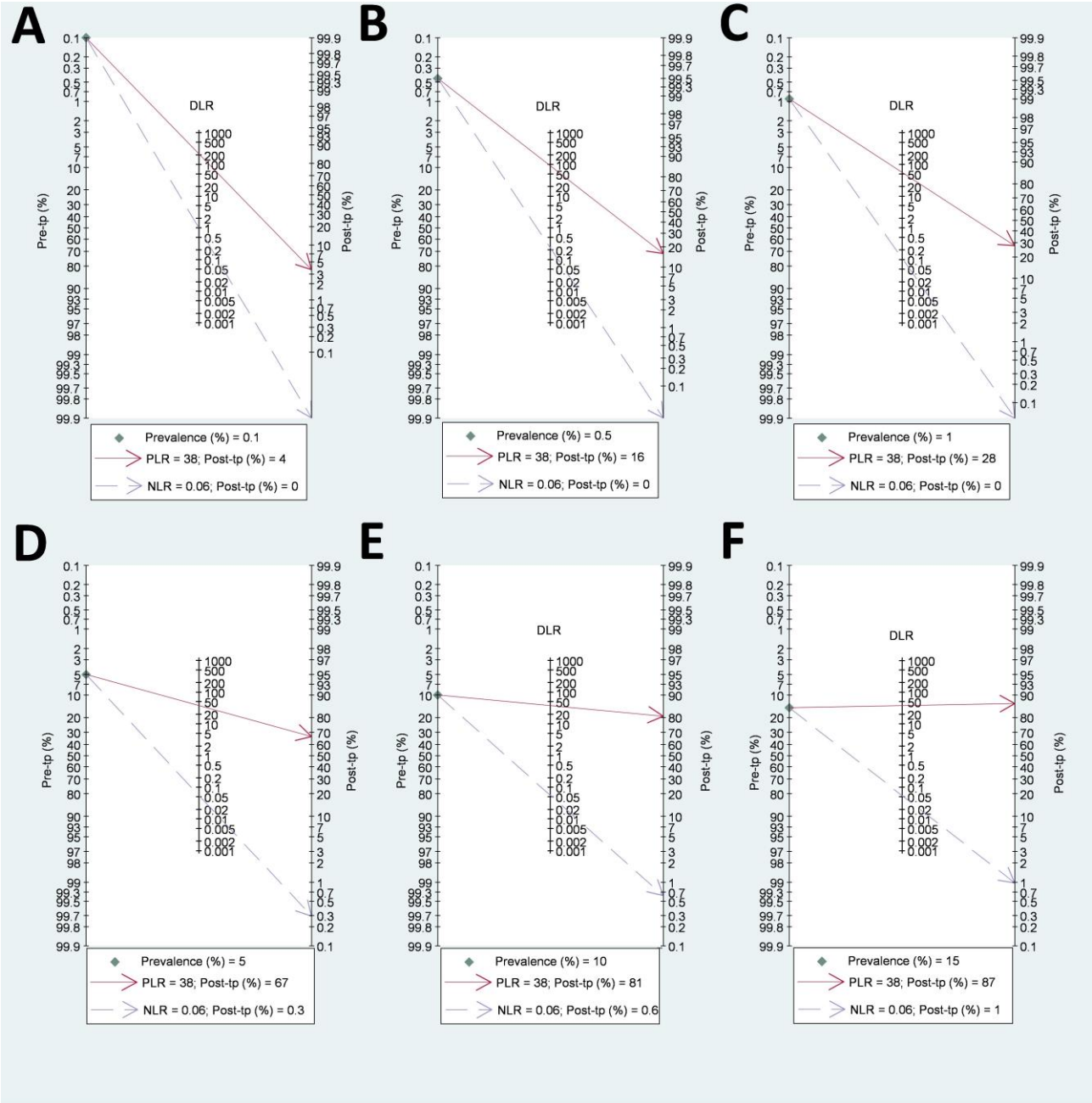


Figure 3. Fagan´s plot of PLR and NLR to evaluate the clinical utility of detecting active HCV infection in PLWHA with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test at different HCV prevalence percentages: 0.1% **(A)**, 0.5% **(B)**, 1% **(C)**, 5% **(D)**, 10% **(E)**, and 15% **(F)**. **Abbreviations**: DLR = diagnostic likelihood ratio; HCV = hepatitis C virus; NLR = negative likelihood ratio; PLR = positive likelihood ratio; PLWHA = people living with HIV/AIDS; Post-tp = post-test probability; Pre-tp = pre-test probability.

Exploration of heterogeneity

The heterogeneity tests showed I^2 = 40.6% (p=0.08) for sensitivity (moderate heterogeneity), I^2 = 87.3% (p<0.001) for specificity (considerable heterogeneity), I^2 = 78.8% (p<0.001) for PLR (substantial heterogeneity), and no significant heterogeneity (I^2 = 37.0% (p=0.10)) for NLR (**Figure 2**). Three studies (23, 30, 31) in the Galbraith plot (**Figure 4A**) and two studies (30, 31) in the bivariate box plot fell outside the 95%CI (**Figure 4B**), suggesting a source of heterogeneity for these studies, especially for one common to both analyses (30). However, the heterogeneity did not change much after removing this article (30) from the analysis.

Meta-regression analysis showed that four factors (LMICs, biological sample type, sample size, and HCV prevalence) had a significant impact on heterogeneity ($p \leq 0.10$) (**Supplementary Table 1**). Moreover, year of publication, LMIC, all patients with anti-HCV Ab +, biological sample type, frozen sample, gold standard cutoff, and sample size had a significant effect on sensitivity ($p \leq 0.10$), but only LMICs, biological sample type, frozen sample, and sample size had a significant impact on specificity ($p \leq 0.10$) (**Supplementary Table 2**). However, these significant differences in sensitivity and specificity were minor, with very close values between the groups, and, in practice, they were not very relevant.

Based on Deeks' funnel plot, publication bias was observed ($p=0.01$), indicating a potential impact on heterogeneity (**Supplementary Figure 3**).

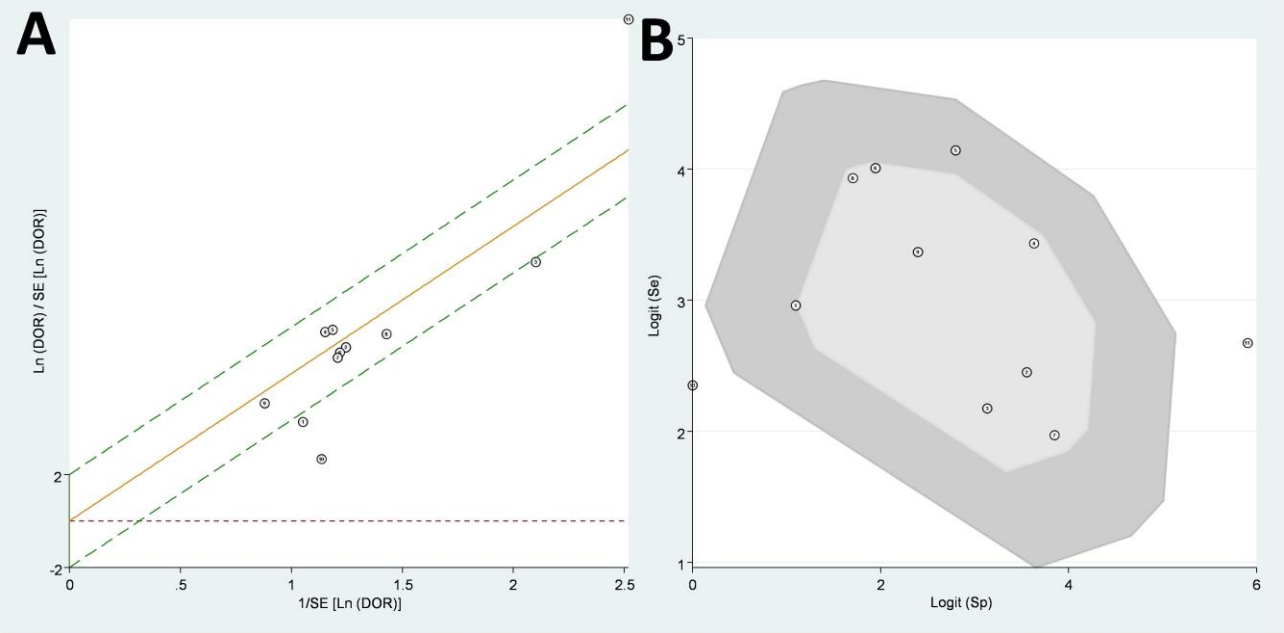


Figure 4. Galbraith plot **(A)** and bagplot **(B)** to assess heterogeneity of the bivariate meta-analysis. Abbreviations: DOR = diagnostic odds ratio; Se = sensitivity; SE = standard error; Sp = specificity.

Discussion

In this bivariate meta-analysis, we found two main findings: 1) the diagnostic validity (accuracy) of the Abbott ARCHITECT HCV Ag assay to diagnose active HCV infection in serum/plasma samples from PLWHA was very high, where the sensitivity, specificity, and AUC-SROC values were very good. 2) The HCVcAg assay showed limited clinical utility to confirm active HCV infection, mainly in low-prevalence settings (≤1%). Still, it was excellent because the HCVcAg assay excluded active HCV infection regardless of prevalence.

The Abbott ARCHITECT HCV Ag assay is an inexpensive, rapid (~40 min), and easy-to-perform assay with high analytical sensitivity for HCV RNA loads above 10,000 IU/mL, although slightly lower for viral values below this cutoff (18, 49). To our knowledge, this meta-analysis is the first to show the diagnostic performance of the Abbott ARCHITECT HCV Ag assay to diagnose active HCV infection in PLWHA. Freiman et al. (35) published an outstanding meta-analysis that evaluated the Abbott ARCHITECT HCV Ag assay to detect active HCV infection. However, they did not perform a meta-analysis on a subgroup of PLWHA due to the lack of necessary studies. Now, we evaluated the diagnostic performance of the Abbott ARCHITECT HCV Ag assay in PLWHA, collecting data from 14 studies (n=2,526 individuals), a sample size large enough to extract conclusive results. Our meta-analysis and that of Freiman et al. (35) achieved very similar results in sensitivity (95.0% *vs.* 93.4%), specificity (97.0% *vs.* 98.8%), NLR (both 0.06), and AUC-SROC (both >97%). However, the overall PLR value from our meta-analysis was lower than that of Freiman et al. (35) (37.76 *vs.* 80.6). Despite the latter, both meta-analyses showed an excellent and similar diagnostic validity (accuracy) of the HCVcAg assay for HCV detection. Moreover, Freiman et al. (35) did not show data on clinical application and only highlighted the possible replacement of NAAT by HCVcAg tests in sceneries with a high HCV prevalence. Our meta-analysis found solid evidence to accept or rule out active HCV infection. Fagan's nomogram showed that the clinical utility of the HCVcAg assay was small in low-prevalence (≤1%) and limited in high-prevalence (≥10%) settings. Thus, NAAT should be necessary to confirm a positive result of the HCVcAg assay. In the best case, the Abbott ARCHITECT HCV Ag test could be an alternative to NAAT in high-prevalence settings (≥10%) where the probability of active HCV infection is greater than 80%. The high prevalence of hepatitis C is usually found in high-risk populations (prisoners, PWID, MSM, or sex workers), where HIV/HCV-coinfection is generally high because HCV and HIV share common transmission routes (6). Besides, these risk populations have a higher chance of HCV reinfection after being cured with DAA treatment because they have high-risk behaviors that lead to HCV transmission (50).

The quality of a meta-analysis depends on the quality of the included studies. In our meta-analysis, the overall quality was medium-high because many elements related to the risk of bias were unclear or missing. Therefore, some studies did not show information on the use of consecutive or random samples, the design of the studies resembled that of case-control studies, and little information was provided on the flow of patients and time in the study.

Heterogeneity is another factor to consider when assessing a meta-analysis. Our meta-analysis showed moderate-substantial heterogeneity, which is common in meta-analyses of diagnostic tests because all potential confounders are difficult to control. The meta-regression showed that LMIC, biological sample type, sample size, and HCV prevalence significantly impacted heterogeneity. It may also be due to other factors not being analyzed due to insufficient raw data from HCV viral load, HCV subtype, HBV-coinfection, or RNA extraction methods. Therefore, a random effects analysis should be used as there is significant heterogeneity between studies, assuming that all studies measure different parameters (51). Furthermore, all analyzed confounders, except HCV prevalence, impacted sensitivity and/or specificity; but their effect was clinically irrelevant.

Limitations

Finally, some limitations must be considered to interpret our data correctly: 1) We found publication bias in favor of a greater tendency to publish studies with favorable results. Probably, some studies with unfavorable data have not been published. 2) There was a lack of essential data in some articles. In several works, plasma and serum samples were used in the same study, and the frozen condition of the sample was unknown. Furthermore, as discussed above, we could not analyze by meta-regression the impact of several relevant factors (HCV viral load, HCV subtype, HBV-coinfection, among others) due to the lack of raw data in many articles. 3) We could not test at what concentration of HCV Ag the RNA is always positive because the Architect HCV Ag assay uses a cutoff point set by the manufacturer. Besides, we have only aggregated data from each study, not data from the individuals included in these studies. 4) The same protocols were not applied to extract and determine HCV-RNA, which could affect the results. Additional studies are needed to improve the evaluation of the diagnostic performance of the Abbott ARCHITECT HCV Ag assay in PLWHA.

Conclusions

In conclusion, the accuracy of the Abbott ARCHITECT HCV Ag assay was very good for HCV screening in serum/plasma samples from PLWHA. The clinical utility to confirm HCV infection was acceptable in high prevalence settings (≥10%), but poor in low prevalence settings (≤1%), and excellent in excluding active HCV infection. This HCVcAg assay could help implement HCV screening programs in PLWHA in high-risk populations with difficult access to the health system (PWID, MSM).

Declarations

Ethics approval and consent to participate

This study was approved by the "Instituto de Salud Carlos III" Ethics Committee (Ref.: CEI PI 13_2021). This study involves clinical-epidemiological data of patients from published articles, so informed consent signed by patients was unnecessary.

Consent for publication

Not applicable.

Availability of data

All relevant data are within the paper and its Supporting Information files.

Competing interests

The authors have no competing interests.

Funding

This study was supported by grants from the Instituto de Salud Carlos III (ISCII; grant # PI20CIII/00004 to SR, and PI19CIII/00009 to IM) and Gilead Science (grant # GLD20_0144 to SR). This research was also supported by CIBER -Consorcio Centro de Investigación Biomédica en Red- (CB 2021), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación and Unión Europea – NextGenerationEU (CB21/13/00044). DS-C is a 'Sara Borrell' researcher from ISCIII (grant nº CD20CIII/00001). AT-N is a Ph.D. student belonging to the Program in Biomedical Sciences and Public Health of the UNED International Doctoral School. No funding bodies had any role in study design, data collection, analysis, decision to publish, or manuscript preparation.

Acknowledgments

We thank the authors of the studies included in this review for providing additional information upon request.

Authors' contributions

Daniel Sepúlveda-Crespo: investigation, resources, writing – original draft.

Ana Treviño-Nakoura: investigation, resources, writing – review, and editing.

José M Bellón: investigation, methodology, formal analysis, writing – review, and editing.

María A Jiménez-Sousa: writing – review, and editing.

Pablo Ryan: writing – review, and editing.

Isidoro Martínez: methodology, writing – reviewing, and editing

Amanda Fernandez-Rodriguez: methodology, writing – reviewing, and editing.

Salvador Resino: funding acquisition, conceptualization, formal analysis, writing – original draft, supervision.

Authors' information (optional)

Not applicable.

References

1. Spearman CW, Dusheiko GM, Hellard M, Sonderup M. 2019. Hepatitis C. Lancet 394:1451-1466.
2. World Health Organization. 2022. Hepatitis C. Avalaible from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c.
3. Sepulveda-Crespo D, Resino S, Martinez I. 2020. Hepatitis C virus vaccine design: focus on the humoral immune response. J Biomed Sci 27:78.
4. World Health Organization. 2022. Global Health Sector Strategies on Viral Hepatitis 2016-2021. Avalaible from: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_32-en.pdf?ua=1.
5. WHO. 2021. The global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections 2022-2030.
6. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, Yanny I, Razavi H, Vickerman P. 2016. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis 16:797-808.
7. Nijmeijer BM, Koopsen J, Schinkel J, Prins M, Geijtenbeek TB. 2019. Sexually transmitted hepatitis C virus infections: current trends, and recent advances in understanding the spread in men who have sex with men. J Int AIDS Soc 22 Suppl 6:e25348.
8. Jin F, Matthews GV, Grulich AE. 2017. Sexual transmission of hepatitis C virus among gay and bisexual men: a systematic review. Sex Health 14:28-41.
9. Aisyah DN, Shallcross L, Hully AJ, O'Brien A, Hayward A. 2018. Assessing hepatitis C spontaneous clearance and understanding associated factors-A systematic review and meta-analysis. J Viral Hepat 25:680-698.
10. Chen JY, Feeney ER, Chung RT. 2014. HCV and HIV co-infection: mechanisms and management. Nat Rev Gastroenterol Hepatol 11:362-71.
11. Gobran ST, Ancuta P, Shoukry NH. 2021. A Tale of Two Viruses: Immunological Insights Into HCV/HIV Coinfection. Front Immunol 12:726419.
12. World Health Organization. 2017. Global hepatitis report 2017, 2017. Avalaible from: https://www.who.int/publications/i/item/9789241565455.
13. Ghany MG, Morgan TR, Panel A-IHCG. 2020. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology 71:686-721.
14. Fevery B, Susser S, Lenz O, Cloherty G, Perner D, Picchio G, Sarrazin C. 2014. HCV RNA quantification with different assays: implications for protease-inhibitor-based response-guided therapy. Antivir Ther 19:559-67.
15. European Association for the Study of the Liver. 2020. EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol 73:1170-1218.
16. Pawlotsky J-M, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, Marra F, Puoti M, Wedemeyer H. 2020. EASL recommendations on treatment of hepatitis C: Final update of the series☆. Journal of Hepatology 73:1170-1218.
17. Galli C, Julicher P, Plebani M. 2018. HCV core antigen comes of age: a new opportunity for the diagnosis of hepatitis C virus infection. Clin Chem Lab Med 56:880-888.
18. Benito R, Arribas J, Algarate S, Cebollada R, Gude MJ. 2018. Hepatitis C virus core antigen for screening organ donors and recipients. Diagn Microbiol Infect Dis 91:126-129.
19. Feld JJ. 2018. Hepatitis C Virus Diagnostics: The Road to Simplification. Clin Liver Dis (Hoboken) 12:125-129.
20. Wang Y, Jie W, Ling J, Yuanshuai H. 2021. HCV core antigen plays an important role in the fight against HCV as an alternative to HCV-RNA detection. J Clin Lab Anal 35:e23755.
21. Mederacke I, Potthoff A, Meyer-Olson D, Meier M, Raupach R, Manns MP, Wedemeyer H, Tillmann HL. 2012. HCV core antigen testing in HIV- and HBV-coinfected patients, and in HCV-infected patients on hemodialysis. J Clin Virol 53:110-5.

22. Garbuglia AR, Monachetti A, Galli C, Sabatini R, Ferreri ML, Capobianchi MR, Bagnarelli P. 2014. HCV core antigen and HCV-RNA in HIV/HCV co-infected patients with different HCV genotypes. BMC Infect Dis 14:222.
23. van Helden J, Weiskirchen R. 2014. [Hepatitis C diagnostics: clinical evaluation of the HCV-core antigen determination]. Z Gastroenterol 52:1164-70.
24. Cresswell FV, Fisher M, Hughes DJ, Shaw SG, Homer G, Hassan-Ibrahim MO. 2015. Hepatitis C core antigen testing: a reliable, quick, and potentially cost-effective alternative to hepatitis C polymerase chain reaction in diagnosing acute hepatitis C virus infection. Clin Infect Dis 60:263-6.
25. Vanhommerig JW, van de Laar TJ, Koot M, van Rooijen MS, Schinkel J, Speksnijder AG, Prins M, de Vries HJ, Bruisten SM. 2015. Evaluation of a hepatitis C virus (HCV) antigen assay for routine HCV screening among men who have sex with men infected with HIV. J Virol Methods 213:147-50.
26. Arboledas JCA, Guerrero IP, Rodriguez MJB, Martos ET, Perez AB, Leon CC, Sierra Sanchez JF, Prieto MDL, Porcuna NC, Mochon MDO, Macias J, de la Iglesia Salgado A, Granger JR, Fernandez MD, Lozano IG, Ramirez ER, Rivero A, Del Carmen Lozano Dominguez M, Viciana I, Montemayor JCG, Garcia FG. 2017. Hepatitis C virus core antigen in the management of patients treated with new direct-acting antivirals. Diagn Microbiol Infect Dis 89:29-34.
27. Duchesne L, Njouom R, Lissock F, Tamko-Mella GF, Rallier S, Poiteau L, Soulier A, Chevaliez S, Vernet G, Rouveau N, Pawlotsky JM, Girard PM, Lacombe K. 2017. HCV Ag quantification as a one-step procedure in diagnosing chronic hepatitis C infection in Cameroon: the ANRS 12336 study. J Int AIDS Soc 20:21446.
28. Hullegie SJ, GeurtsvanKessel CH, van der Eijk AA, Ramakers C, Rijnders BJA. 2017. HCV antigen instead of RNA testing to diagnose acute HCV in patients treated in the Dutch Acute HCV in HIV Study. J Int AIDS Soc 20:21621.
29. Mohamed Z, Mbwambo J, Shimakawa Y, Poiteau L, Chevaliez S, Pawlotsky JM, Rwegasha J, Bhagani S, Taylor-Robinson SD, Makani J, Thursz MR, Lemoine M. 2017. Clinical utility of HCV core antigen detection and quantification using serum samples and dried blood spots in people who inject drugs in Dar-es-Salaam, Tanzania. J Int AIDS Soc 20:21856.
30. Talal AH, Chen Y, Zeremski M, Zavala R, Sylvester C, Kuhns M, Brown LS, Markatou M, Cloherty GA. 2017. Hepatitis C virus core antigen: A potential alternative to HCV RNA testing among persons with substance use disorders. J Subst Abuse Treat 78:37-42.
31. Alonso R, Perez-Garcia F, Lopez-Roa P, Alcala L, Rodeno P, Bouza E. 2018. HCV core-antigen assay as an alternative to HCV RNA quantification: A correlation study for the assessment of HCV viremia. Enferm Infecc Microbiol Clin (Engl Ed) 36:175-178.
32. Chayanupatkul M, Chittmittraprap S, Pratedrat P, Chuaypen N, Avihingsanon A, Tangkijvanich P. 2020. Efficacy of elbasvir/grazoprevir therapy in HCV genotype-1 with or without HIV infection: role of HCV core antigen monitoring and improvement of liver stiffness and steatosis. Antivir Ther 25:305-314.
33. Rossetti B, Loggi E, Raffaelli CS, Mercinelli S, Gandolfo C, Savellini GG, Galli S, Vitale G, Di Donato R, Vukotic R, Grandini E, Margotti M, Guarneri V, Furlini G, Re MC, De Luca A, Andreone P, Galli C, Cusi MG. 2021. Hepatitis C Virus Core Antigen (HCVAg): an affordable assay to monitor the efficacy of treatment in DAAs era. New Microbiol 44:89-94.
34. Sun HY, Liu WD, Wang CW, Wei YJ, Lin KY, Huang YS, Su LH, Chen YT, Liu WC, Su YC, Chen YW, Chuang YC, Lu PL, Hung CC, Yu ML. 2022. Performance of Hepatitis C Virus (HCV) Core Antigen Assay in the Diagnosis of Recently Acquired HCV Infection among High-Risk Populations. Microbiol Spectr doi:10.1128/spectrum.00345-22:e0034522.
35. Freiman JM, Tran TM, Schumacher SG, White LF, Ongarello S, Cohn J, Easterbrook PJ, Linas BP, Denkinger CM. 2016. Hepatitis C Core Antigen Testing for Diagnosis of Hepatitis C Virus Infection: A Systematic Review and Meta-analysis. Ann Intern Med 165:345-55.

36. Martin NK, Boerekamps A, Hill AM, Rijnders BJA. 2018. Is hepatitis C virus elimination possible among people living with HIV and what will it take to achieve it? J Int AIDS Soc 21 Suppl 2:e25062.
37. Anonymous. 2022. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 2. London: Cochrane.
38. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, and the P-DTAG, Clifford T, Cohen JF, Deeks JJ, Gatsonis C, Hooft L, Hunt HA, Hyde CJ, Korevaar DA, Leeflang MMG, Macaskill P, Reitsma JB, Rodin R, Rutjes AWS, Salameh JP, Stevens A, Takwoingi Y, Tonelli M, Weeks L, Whiting P, Willis BH. 2018. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA 319:388-396.
39. Easterbrook PJ, Roberts T, Sands A, Peeling R. 2017. Diagnosis of viral hepatitis. Curr Opin HIV AIDS 12:302-314.
40. Dwamena BJBCDoE. 2009. Midas: Stata module for meta-analytical integration of diagnostic test accuracy studies, statistical software components S456880.
41. Macaskill P, Gatsonis C, Deeks J, Harbord R, Takwoingi Y. 2010. Cochrane handbook for systematic reviews of diagnostic test accuracy. Version 1 0 London: The Cochrane Collaboration.
42. Bradley AP. 1997. The use of the area under the ROC curve in the evaluation of machine learning algorithms. Patt Recog 30:1145–59.
43. Rubinstein ML, Kraft CS, Parrott JS. 2018. Determining qualitative effect size ratings using a likelihood ratio scatter matrix in diagnostic test accuracy systematic reviews. Diagnosis (Berl) 5:205-214.
44. Fagan TJ. 1975. Letter: Nomogram for Bayes theorem. N Engl J Med 293:257.
45. Higgins JP, Thompson SG, Deeks JJ, Altman DG. 2003. Measuring inconsistency in meta-analyses. BMJ 327:557-60.
46. Galbraith RF. 1988. Graphical Display of Estimates Having Differing Standard Errors. Technometrics 30:271-281.
47. Rousseeuw PJ, Ruts I, Tukey JW. 1999. The Bagplot: A Bivariate Boxplot. The American Statistician 53:382-387.
48. Deeks JJ, Macaskill P, Irwig L. 2005. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 58:882-93.
49. Aguilera A, Alados JC, Alonso R, Eiros JM, Garcia F. 2020. Current position of viral load versus hepatitis C core antigen testing. Enferm Infecc Microbiol Clin (Engl Ed) 38 Suppl 1:12-18.
50. Hosseini-Hooshyar S, Hajarizadeh B, Bajis S, Law M, Janjua NZ, Fierer DS, Chromy D, Rockstroh JK, Martin TCS, Ingiliz P, Hung CC, Dore GJ, Martinello M, Matthews GV. 2022. Risk of hepatitis C reinfection following successful therapy among people living with HIV: a global systematic review, meta-analysis, and meta-regression. Lancet HIV 9:e414-e427.
51. Anonymous. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 2.0. The Cochrane Collaboration. 2022. https://training.cochrane.org/handbook-diagnostic-test-accuracy. Accesed on 6 Jun, 2022. Accessed

Supplementary Materials
Supplementary File 1: PRISMA-DTA Checklist and Abstracts Checklist

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	3-4
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	4
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.	5
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
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.	5
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	Suppl. 5-12
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).	Fig. 1
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.	5-6
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	5-6
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	6
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	6-7
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c)	6-7

		handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	
Section/topic	**#**	**PRISMA-DTA Checklist Item**	**Reported on page #**
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	Table 1
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	8-9
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	Fig. 2-4 and Suppl. Fig. 1-3
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	11
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	13
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	14

Section/topic	**#**	**PRISMA-DTA for Abstracts Checklist item**	**Reported on page #**
TITLE and PURPOSE			

Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	2
Objectives	2	Indicate the research question, including components such as participants, index test, and target conditions.	2
METHODS			
Eligibility criteria	3	Include study characteristics used as criteria for eligibility.	2
Information sources	4	List the key databases searched and the search dates.	2
Risk of bias & applicability	5	Indicate the methods of assessing risk of bias and applicability.	2
Synthesis of results	A1	Indicate the methods for the data synthesis.	2
RESULTS			
Included studies	6	Indicate the number and type of included studies and the participants and relevant characteristics of the studies (including the reference standard).	2
Synthesis of results	7	Include the results for the analysis of diagnostic accuracy, preferably indicating the number of studies and participants. Describe test accuracy including variability; if meta-analysis was done, include summary results and confidence intervals.	2
DISCUSSION			
Strengths and limitations	9	Provide a brief summary of the strengths and limitations of the evidence	2
Interpretation	10	Provide a general interpretation of the results and the important implications.	2
OTHER			
Funding	11	Indicate the primary source of funding for the review.	14
Registration	12	Provide the registration number and the registry name	2

Supplementary File 2: Search strategy

Search strategy PubMed

("hepatitis c"[MeSH Terms] OR "hepacivirus"[MeSH Terms] OR ("hepatitis c"[Title/Abstract] OR "hepatitis c virus"[Title/Abstract] OR "hepatitis c viruses"[Title/Abstract] OR "hepatitis c like virus"[Title/Abstract] OR "hepatitis c like viruses"[Title/Abstract] OR "hepatitis virus type c"[Title/Abstract] OR "hcv"[Title/Abstract] OR "h c v"[Title/Abstract] OR "vhc"[Title/Abstract] OR "v h c"[Title/Abstract] OR "hepacivirus"[Title/Abstract] OR "hepaciviruses"[Title/Abstract] OR "hcv viral"[Title/Abstract] OR "hcv infected"[Title/Abstract] OR "hcv infection"[Title/Abstract] OR "hcv rna"[Title/Abstract] OR "hepatitis c virus rna"[Title/Abstract] OR "parenterally transmitted non a non"[Title/Abstract] OR "pt nanbh"[Title/Abstract])) AND ("diagnosis"[MeSH Terms] OR "diagnostic techniques and procedures"[MeSH Terms] OR "clinical laboratory techniques"[MeSH Terms] OR "mass screening"[MeSH Terms] OR "nucleic acid amplification techniques"[MeSH Terms] OR "rna"[MeSH Terms] OR "rna, viral/blood"[MeSH Terms] OR ("clinical laboratory diagnoses"[Title/Abstract] OR "clinical laboratory diagnostic"[Title/Abstract] OR "clinical laboratory techniques"[Title/Abstract] OR "clinical laboratory testing"[Title/Abstract] OR "diagnose"[Title/Abstract] OR "diagnoses"[Title/Abstract] OR "diagnosis of hcv"[Title/Abstract] OR "diagnosis"[Title/Abstract] OR "diagnostic techniques and procedures"[Title/Abstract]OR "diagnostic"[Title/Abstract] OR "hcv infection diagnosis"[Title/Abstract] OR "hcv testing"[Title/Abstract] OR "mass screening"[Title/Abstract] OR "mass screenings"[Title/Abstract] OR "molecular diagnostic techniques"[Title/Abstract] OR "screening approach"[Title/Abstract] OR "screening"[Title/Abstract] OR "testing diagnostic"[Title/Abstract] OR "plasma levels"[Title/Abstract] OR "sera"[Title/Abstract] OR "serum levels"[Title/Abstract] OR "dried blood filter" [Title/Abstract] OR "dried blood spot"[Title/Abstract] OR "dried blood" [Title/Abstract] OR "dried sample" [Title/Abstract] OR "filter paper" [Title/Abstract] OR "Whatman" [Title/Abstract] OR "DBS" [Title/Abstract] OR "assay kits"[Title/Abstract] OR "hcv assays"[Title/Abstract] OR "hcv pcr assay"[Title/Abstract] OR "hcv pcr method"[Title/Abstract] OR "hcv pcr"[Title/Abstract] OR "hcv rna levels"[Title/Abstract] OR "hcv rna quantification assays"[Title/Abstract] OR "hcv rna quantification"[Title/Abstract] OR "hepatitis c markers"[Title/Abstract] OR "hepatitis markers"[Title/Abstract] OR "immunoassay"[Title/Abstract] OR "quantitative assays"[Title/Abstract] OR "quantitative reverse transcription pcr"[Title/Abstract] OR "real time pcr"[Title/Abstract] OR "rna levels"[Title/Abstract] OR "roche cobas taqman assays"[Title/Abstract] OR "roche cobas taqman hcv"[Title/Abstract])) AND ("hepatitis c antigens"[MeSH Terms] OR ("antigens"[Title/Abstract] OR "core antigen assay"[Title/Abstract] OR "core antigen assays"[Title/Abstract] OR "core antigen test"[Title/Abstract] OR "core antigen"[Title/Abstract] OR "hcv ag assay"[Title/Abstract] OR "hcv ag detection"[Title/Abstract]OR "hcv ag"[Title/Abstract] OR "hcv antigen testing"[Title/Abstract] OR "hcv antigen"[Title/Abstract] OR "HCVcAg"[Title/Abstract] OR "hcv core antigen assay"[Title/Abstract] OR "hcv core antigen assays"[Title/Abstract] OR "hcv core antigen detection"[Title/Abstract] OR "hcv core antigen determination"[Title/Abstract] OR "hcv core antigen testing"[Title/Abstract] OR "hcv core antigen"[Title/Abstract] OR "hcv core protein"[Title/Abstract] OR "hcv core region"[Title/Abstract] OR "hcv cp"[Title/Abstract] OR "hcvcoreag"[Title/Abstract] OR "hepatitis c antigens"[Title/Abstract] OR "hepatitis c virus core antigen"[Title/Abstract] OR "hepatitis c virus core"[Title/Abstract] OR "hepatitis non a non b antigen"[Title/Abstract] OR "viral core proteins"[Title/Abstract])) AND ("accuracy"[Title/Abstract] OR "correlation"[Title/Abstract] OR "correlations"[Title/Abstract] OR "negative predictive power"[Title/Abstract] OR "negative predictive value"[Title/Abstract] OR "negative predictive values"[Title/Abstract] OR "NPV"[Title/Abstract] OR "positive predictive power"[Title/Abstract] OR "positive predictive value"[Title/Abstract] OR "positive predictive values"[Title/Abstract] OR "PPV"[Title/Abstract] OR "receiver operating characteristics"[Title/Abstract] OR "regression analysis"[Title/Abstract] OR "ROC"[Title/Abstract] OR "sensitive"[Title/Abstract] OR "sensitivities"[Title/Abstract] OR "sensitivity"[Title/Abstract] OR "specific"[Title/Abstract] OR "specificity"[Title/Abstract] OR "Abbott ARCHITECT HCV Ag assay" OR "Abbott ARCHITECT HCV Ag test" OR "Abbott ARCHITECT i2000SR" OR "Abbott ARCHITECT test" OR "Abbott Diagnostics" OR "Abbott HCV core antigen" OR "Abbott Laboratories" OR "ARCHITECT" OR "ARCHITECT ci8200" OR "Architect core antigen" OR

“Architect HCV Ag” OR “ARCHITECT HCV Core antigen” OR “ARCHITECT i2000SR” OR “ARCHITECT system” OR "cleia method" OR “chemiluminescence immunoassay”) NOT ("review"[Publication Type]) NOT ("meta-analysis"[Publication Type]) NOT ("systematic review"[Publication Type])

Search strategy Embase

#1 'hepatitis c'/exp OR 'hepacivirus'/exp OR 'hepatitis c virus':ti,ab,kw OR 'hepatitis c viruses':ti,ab,kw OR 'hepatitis c like viruses':ti,ab,kw OR 'hepatitis virus type c':ti,ab,kw OR hcv:ti,ab,kw OR 'h c v':ti,ab,kw OR vhc:ti,ab,kw OR 'v h c':ti,ab,kw OR hepacivirus:ti,ab,kw OR hepaciviruses:ti,ab,kw OR 'parenterally transmitted non a non':ti,ab,kw

#2 'diagnosis'/exp OR ('diagnostic techniques'/exp AND 'procedures'/exp) OR 'clinical laboratory techniques'/exp OR 'nucleic acid amplification techniques'/exp OR 'rna'/exp OR 'clinical laboratory diagnostic':ti,ab,kw OR 'clinical laboratory techniques':ti,ab,kw OR 'clinical laboratory testing':ti,ab,kw OR diagnose:ti,ab,kw OR diagnoses:ti,ab,kw OR 'diagnosis of hcv':ti,ab,kw OR diagnosis:ti,ab,kw OR ('diagnostic techniques':ti,ab,kw AND procedures:ti,ab,kw) OR diagnostic:ti,ab,kw OR 'hcv testing':ti,ab,kw OR 'mass screening':ti,ab,kw OR 'mass screenings':ti,ab,kw OR 'screening approach':ti,ab,kw OR screening:ti,ab,kw OR 'plasma levels':ti,ab,kw OR sera:ti,ab,kw OR 'serum levels':ti,ab,kw OR 'dried blood filter':ti,ab,kw OR 'dried blood spot':ti,ab,kw OR 'dried blood':ti,ab,kw OR 'dried sample':ti,ab,kw OR 'filter paper':ti,ab,kw OR whatman:ti,ab,kw OR dbs:ti,ab,kw OR 'assay kits':ti,ab,kw OR 'hcv assays':ti,ab,kw OR 'hcv pcr assay':ti,ab,kw OR 'hcv pcr':ti,ab,kw OR 'hcv rna levels':ti,ab,kw OR 'hcv rna quantification':ti,ab,kw OR 'hepatitis c markers':ti,ab,kw OR 'hepatitis markers':ti,ab,kw OR immunoassay:ti,ab,kw OR 'quantitative assays':ti,ab,kw OR 'quantitative reverse transcription pcr':ti,ab,kw OR 'real time pcr':ti,ab,kw OR 'rna levels':ti,ab,kw OR 'roche cobas taqman':ti,ab,kw

#3 'hepatitis c antigens'/exp OR antigens:ti,ab,kw OR 'cleia method':ti,ab,kw OR 'core antigen assay':ti,ab,kw OR 'core antigen assays':ti,ab,kw OR 'core antigen test':ti,ab,kw OR 'core antigen':ti,ab,kw OR 'hcv ag assay':ti,ab,kw OR 'hcv ag detection':ti,ab,kw OR 'hcv ag':ti,ab,kw OR 'hcv antigen testing':ti,ab,kw OR 'hcv antigen':ti,ab,kw OR hcvcoreag:ti,ab,kw OR hcvcag:ti,ab,kw OR 'hepatitis non a non b antigen':ti,ab,kw OR 'viral core proteins':ti,ab,kw

#4 'accuracy':ti,ab,kw OR 'correlation':ti,ab,kw OR 'correlations':ti,ab,kw OR 'negative predictive power':ti,ab,kw OR 'negative predictive value':ti,ab,kw OR 'negative predictive values':ti,ab,kw OR 'NPV':ti,ab,kw OR 'positive predictive power':ti,ab,kw OR 'positive predictive value':ti,ab,kw OR 'positive predictive values':ti,ab,kw OR 'PPV':ti,ab,kw OR 'receiver operating characteristics':ti,ab,kw OR 'regression analysis':ti,ab,kw OR 'ROC':ti,ab,kw OR 'sensitive':ti,ab,kw OR 'sensitivities':ti,ab,kw OR 'sensitivity':ti,ab,kw OR 'specific':ti,ab,kw OR 'specificity':ti,ab,kw OR 'Abbott ARCHITECT HCV Ag assay' OR ' Abbott ARCHITECT HCV Ag test' OR 'Abbott ARCHITECT i2000SR' OR 'Abbott ARCHITECT test' OR 'Abbott Diagnostics' OR 'Abbott HCV Ag' OR 'Abbott HCV core antigen' OR 'Abbott Laboratories' OR 'ARCHITECT' OR 'Architect core antigen' OR 'ARCHITECT i2000SR'

#5 #1 AND #2 AND #3 AND #4

#6 #5 AND ('Article'/it OR 'Article in Press'/it)

Search strategy Web of Knowledge (WoS)

#1 ((((((((((((((((TS=(hepatitis c)) OR TS=(hepatitis c virus)) OR TS=(hepatitis c viruses)) OR TS=(hepatitis c like virus)) OR TS=(hepatitis c like viruses)) OR TS=(hepatitis virus type c)) OR TS=(hcv)) OR TS=(h c v)) OR TS=(vhc)) OR TS=(v h c)) OR TS=(hepacivirus)) OR TS=(hepaciviruses)) OR TS=(hcv viral)) OR TS=(hcv infected)) OR TS=(hcv infection)) OR TS=(hcv rna)) OR TS=(hepatitis c virus rna)) OR TS=(parenterally transmitted non a non)) OR TS=(pt-nanbh)

#2 ((TS=(clinical laboratory diagnoses)) OR TS=(clinical laboratory diagnostic)) OR TS=(clinical laboratory techniques)) OR TS=(clinical laboratory testing)) OR TS=(diagnose)) OR TS=(diagnoses)) OR TS=(diagnosis of hcv)) OR TS=(diagnosis)) OR TS=(diagnostic techniques and procedures)) OR TS=(diagnostic)) OR TS=(hcv infection diagnosis)) OR TS=(hcv testing)) OR TS=(mass screening)) OR TS=(mass screenings)) OR TS=(molecular diagnostic techniques)) OR TS=(screening approach)) OR TS=(screening)) OR TS=(testing diagnostic)) OR TS=(plasma levels)) OR TS=(sera)) OR TS=(serum levels)) OR TS=(dried blood filter)) OR TS=(dried blood spot)) OR TS=(dried blood)) OR TS=(dried sample)) OR TS=(filter paper)) OR TS=(Whatman)) OR TS=(DBS)) OR TS=(assay kits)) OR TS=(hcv assays)) OR TS=(hcv pcr assay)) OR TS=(hcv pcr method)) OR TS=(hcv pcr)) OR TS=(hcv rna levels)) OR TS=(hcv rna quantification assays)) OR TS=(hcv rna quantification)) OR TS=(hepatitis c markers)) OR TS=(hepatitis markers)) OR TS=(immunoassay)) OR TS=(quantitative assays)) OR TS=(quantitative reverse transcription pcr)) OR TS=(real time pcr)) OR TS=(rna levels)) OR TS=(roche cobas taqman assays)) OR TS=(roche cobas taqman hcv)

#3 ((((((((((((((((((((((((TS=(antigens)) OR TS=(cleia method)) OR TS=(core antigen assay)) OR TS=(core antigen assays)) OR TS=(core antigen test)) OR TS=(core antigen)) OR TS=(hcv ag assay)) OR TS=(hcv ag detection)) OR TS=(hcv ag)) OR TS=(hcv antigen testing)) OR TS=(hcv antigen)) OR TS=(hcv core antigen assay)) OR TS=(hcv core antigen assays)) OR TS=(hcv core antigen detection)) OR TS=(hcv core antigen determination)) OR TS=(hcv core antigen testing)) OR TS=(hcv core antigen)) OR TS=(hcv core protein)) OR TS=(hcv core region)) OR TS=(hcv cp)) OR TS=(hcvcoreag)) OR TS=(hcvcag)) OR TS=(hepatitis c antigens)) OR TS=(hepatitis c virus core antigen)) OR TS=(hepatitis c virus core)) OR TS=(hepatitis non a non b antigen)) OR TS=(viral core proteins)

#4 ((((((((((((((((((((((((((((((((((((((TS=(accuracy)) OR TS=(correlation)) OR TS=(correlations)) OR TS=(negative predictive power)) OR TS=(negative predictive value)) OR TS=(negative predictive values)) OR TS=(NPV)) OR TS=(positive predictive power)) OR TS=(positive predictive value)) OR TS=(positive predictive values)) OR TS=(PPV)) OR TS=(receiver operating characteristics)) OR TS=(regression analysis)) OR TS=(ROC)) OR TS=(sensitive)) OR TS=(sensitivities)) OR TS=(sensitivity)) OR TS=(specific)) OR TS=(specificity)) OR TS=(Abbott ARCHITECT HCV Ag assay)) OR TS=(Abbott ARCHITECT HCV Ag test)) OR TS=(Abbott ARCHITECT HCV Antigen assay)) OR TS=(Abbott ARCHITECT i2000SR)) OR TS=(Abbott ARCHITECT test)) OR TS=(Abbott Diagnostics)) OR TS=(Abbott HCV Ag)) OR TS=(Abbott HCV core antigen)) OR TS=(Abbott Laboratories)) OR TS=(ARCHITECT)) OR TS=(ARCHITECT ci8200)) OR TS=(Architect core antigen)) OR TS=(Architect HCV Ag)) OR TS=(ARCHITECT HCV Core antigen)) OR TS=(ARCHITECT HCVAg)) OR TS=(ARCHITECT i2000SR)) OR TS=(ARCHITECT system)) OR TS=(ARCHITECTHCVAg)) OR TS=(ARCHITECT-i2000R)) OR TS=(cleia method)) OR TS=(chemiluminescence immunoassay)

#5 #1 AND #2 AND #3 AND #4

#6 #5 NOT (DT==("REVIEW" OR "MEETING ABSTRACT" OR "PROCEEDINGS PAPER" OR "NOTE" OR "BOOK CHAPTER" OR "EDITORIAL MATERIAL" OR "LETTER"))

Search strategy SCOPUS

(TITLE-ABS-KEY ("hepatitis c virus") OR TITLE-ABS-KEY ("hepatitis c like virus") OR TITLE-ABS-KEY ({hepatitis virus type c}) OR TITLE-ABS-KEY ({hcv}) OR TITLE-ABS-KEY ({h c v}) OR TITLE-ABS-KEY ({vhc}) OR TITLE-ABS-KEY ({v h c}) OR TITLE-ABS-KEY ("hepacivirus") OR TITLE-ABS-KEY ({hcv viral}) OR TITLE-ABS-KEY ({hcv infected}) OR TITLE-ABS-KEY ({hcv infection}) OR TITLE-ABS-KEY ("hcv rna") OR TITLE-ABS-KEY ({pt nanbh}) OR TITLE-ABS-KEY ({parenterally transmitted non a non})) AND (TITLE-ABS-KEY ({clinical laboratory diagnoses}) OR TITLE-ABS-KEY ({clinical laboratory techniques}) OR TITLE-ABS-KEY ({clinical laboratory testing}) OR TITLE-ABS-KEY ("diagnose") OR TITLE-ABS-KEY ({diagnostic techniques and procedures}) OR TITLE-ABS-KEY ({hcv infection diagnosis}) OR TITLE-ABS-KEY ({hcv testing}) OR TITLE-ABS-KEY ("mass screening") OR TITLE-ABS-KEY ({molecular diagnostic techniques}) OR TITLE-ABS-KEY ("screening*") OR TITLE-ABS-KEY ({testing diagnostic}) OR TITLE-ABS-KEY ({plasma levels}) OR TITLE-ABS-KEY ({sera}) OR TITLE-ABS-KEY ({serum levels}) OR TITLE-ABS-KEY ("dried blood*") OR TITLE-ABS-KEY ("dried sample*") OR TITLE-ABS-KEY ({DBS}) OR TITLE-ABS-KEY ({filter paper}) OR TITLE-ABS-KEY ({Whatman}) OR TITLE-ABS-KEY ({assay kits}) OR TITLE-ABS-KEY ("hcv assay") OR TITLE-ABS-KEY (hcv pcr*) OR TITLE-ABS-KEY ({hcv rna levels}) OR TITLE-ABS-KEY ("hcv rna quantification*") OR TITLE-ABS-KEY ("hepatitis C markers") OR TITLE-ABS-KEY ({immunoassay}) OR TITLE-ABS-KEY ("quantitative assay") OR TITLE-ABS-KEY ({quantitative reverse transcription pcr}) OR TITLE-ABS-KEY ({real time pcr}) OR TITLE-ABS-KEY ({rna levels}) OR TITLE-ABS-KEY ({roche cobas taqman})) AND (TITLE-ABS-KEY ({antigens}) OR TITLE-ABS-KEY ({cleia method}) OR TITLE-ABS-KEY ("core antigen*") OR TITLE-ABS-KEY ("hcv ag*") OR TITLE-ABS-KEY ("hcv antigen*") OR TITLE-ABS-KEY ("hcv core antigen*") OR TITLE-ABS-KEY ("hcv core*") OR TITLE-ABS-KEY ("hcv cp") OR TITLE-ABS-KEY ("hcvcag") OR TITLE-ABS-KEY ("hcvcoreag") OR TITLE-ABS-KEY ("hepatitis c antigen") OR TITLE-ABS-KEY ({viral core proteins})) AND (TITLE-ABS-KEY ({ accuracy }) OR TITLE-ABS-KEY ({ correlation }) OR TITLE-ABS-KEY ({ correlations }) OR TITLE-ABS-KEY ({ negative predictive power }) OR TITLE-ABS-KEY ({ negative predictive value }) OR TITLE-ABS-KEY ({ negative predictive values }) OR TITLE-ABS-KEY ({ NPV}) OR TITLE-ABS-KEY ({ positive predictive power }) OR TITLE-ABS-KEY ({ positive predictive value }) OR TITLE-ABS-KEY ({ positive predictive values }) OR TITLE-ABS-KEY ({ PPV}) OR TITLE-ABS-KEY ({ receiver operating characteristics }) OR TITLE-ABS-KEY ({ regression analysis }) OR TITLE-ABS-KEY ({ ROC }) OR TITLE-ABS-KEY ({ sensitive }) OR TITLE-ABS-KEY ({ sensitivities }) OR TITLE-ABS-KEY ({ sensitivity }) OR TITLE-ABS-KEY ({ specific }) OR TITLE-ABS-KEY ({ specificity }) OR ALL ({ Abbott ARCHITECT HCV Ag assay }) OR ALL ({ Abbott ARCHITECT HCV Ag test }) OR ALL ({ Abbott ARCHITECT HCV Antigen assay }) OR ALL ({ Abbott ARCHITECT i2000SR }) OR ALL ({ Abbott ARCHITECT test }) OR ALL ({ Abbott Diagnostics }) OR ALL ({ Abbott HCV Ag }) OR ALL ({ Abbott HCV core antigen }) OR ALL ({ Abbott Laboratories }) OR ALL ({ ARCHITECT }) OR ALL ({ ARCHITECT ci8200}) OR ALL ({ Architect core antigen }) OR ALL ({ Architect HCV Ag }) OR ALL ({ ARCHITECT HCV Core antigen }) OR ALL ({ ARCHITECT HCVAg }) OR ALL ({ ARCHITECT i2000SR }) OR ALL ({ ARCHITECT system }) OR ALL ({ ARCHITECTHCVAg }) OR ALL ({ ARCHITECT-i2000R })) AND (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "cp") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "sh")) AND (EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "ed") OR EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "dp"))

Search strategy Cochrane

#1 MeSH descriptor: [Hepatitis C] explode all trees
#2 MeSH descriptor: [Hepacivirus] explode all trees
#3 ("hepatitis c"):ti,ab,kw
#4 ("hepatitis c virus"):ti,ab,kw
#5 ("hepatitis c viruses"):ti,ab,kw
#6 ("hcv"):ti,ab,kw
#7 ("h c v"):ti,ab,kw
#8 ("vhc"):ti,ab,kw
#9 ("hepacivirus"):ti,ab,kw
#10 ("hcv viral"):ti,ab,kw
#11 ("hcv infected"):ti,ab,kw
#12 ("hcv infection"):ti,ab,kw
#13 ("hcv rna"):ti,ab,kw
#14 ("hepatitis c virus rna"):ti,ab,kw
#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 MeSH descriptor: [Diagnosis] explode all trees
#17 MeSH descriptor: [Diagnostic Techniques and Procedures] explode all trees
#18 MeSH descriptor: [Clinical Laboratory Techniques] explode all trees
#19 MeSH descriptor: [Mass Screening] explode all trees
#20 MeSH descriptor: [Nucleic Acid Amplification Techniques] explode all trees
#21 MeSH descriptor: [RNA] explode all trees
#22 ("clinical laboratory diagnoses"):ti,ab,kw
#23 ("clinical laboratory diagnostic"):ti,ab,kw
#24 ("clinical laboratory techniques"):ti,ab,kw
#25 ("clinical laboratory testing"):ti,ab,kw
#26 ("diagnose"):ti,ab,kw
#27 ("diagnoses"):ti,ab,kw
#28 ("diagnosis of hcv"):ti,ab,kw
#29 ("diagnosis"):ti,ab,kw
#30 ("diagnostic techniques and procedures"):ti,ab,kw
#31 ("diagnostic"):ti,ab,kw
#32 ("hcv infection diagnosis"):ti,ab,kw
#33 ("hcv testing"):ti,ab,kw
#34 ("mass screening"):ti,ab,kw
#35 ("mass screenings"):ti,ab,kw
#36 ("molecular diagnostic techniques"):ti,ab,kw
#37 ("screening approach"):ti,ab,kw
#38 ("screening"):ti,ab,kw
#39 ("testing diagnostic"):ti,ab,kw
#40 ("plasma levels"):ti,ab,kw
#41 ("sera"):ti,ab,kw
#42 ("serum levels"):ti,ab,kw
#43 ("dried blood"):ti,ab,kw
#44 ("dried sample"):ti,ab,kw
#45 ("filter paper"):ti,ab,kw
#46 ("Whatman"):ti,ab,kw
#47 ("DBS"):ti,ab,kw
#48 ("assay kits"):ti,ab,kw
#49 ("hcv assays"):ti,ab,kw
#50 ("hcv pcr"):ti,ab,kw

#51 ("hcv rna levels"):ti,ab,kw
#52 ("hcv rna quantification"):ti,ab,kw
#53 ("hepatitis markers"):ti,ab,kw
#54 ("immunoassay"):ti,ab,kw
#55 ("quantitative assays"):ti,ab,kw
#56 ("quantitative reverse transcription pcr"):ti,ab,kw
#57 ("real time pcr"):ti,ab,kw
#58 ("rna levels"):ti,ab,kw
#59 ("roche cobas taqman"):ti,ab,kw
#60 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59
#61 MeSH descriptor: [Hepatitis C Antigens] explode all trees
#62 ("antigens"):ti,ab,kw
#63 ("cleia method"):ti,ab,kw
#64 ("core antigen assays"):ti,ab,kw
#65 ("core antigen"):ti,ab,kw
#66 ("hcv ag"):ti,ab,kw
#67 ("hcvcAg"):ti,ab,kw
#68 ("hcv antigen"):ti,ab,kw
#69 ("hcv core antigen"):ti,ab,kw
#70 ("hcv core protein"):ti,ab,kw
#71 ("hcv core region"):ti,ab,kw
#72 ("hepatitis c antigens"):ti,ab,kw
#73 ("hepatitis c virus core antigen"):ti,ab,kw
#74 ("hepatitis c virus core"):ti,ab,kw
#75 ("viral core proteins"):ti,ab,kw
#76 #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75
#77 ("accuracy"):ti,ab,kw
#78 ("correlation"):ti,ab,kw
#79 ("correlations"):ti,ab,kw
#80 ("negative predictive power"):ti,ab,kw
#81 ("negative predictive value"):ti,ab,kw
#82 ("negative predictive values"):ti,ab,kw
#83 ("NPV"):ti,ab,kw
#84 ("positive predictive power"):ti,ab,kw
#85 ("positive predictive value"):ti,ab,kw
#86 ("positive predictive values"):ti,ab,kw
#87 ("PPV"):ti,ab,kw
#88 ("receiver operating characteristics"):ti,ab,kw
#89 ("regression analysis"):ti,ab,kw
#90 ("ROC"):ti,ab,kw
#91 ("sensitive"):ti,ab,kw
#92 ("sensitivities"):ti,ab,kw
#93 ("sensitivity"):ti,ab,kw
#94 ("specific"):ti,ab,kw
#95 ("specificity"):ti,ab,kw
#96 "Abbott ARCHITECT i2000SR"
#97 "Abbott Diagnostics"

#98 "Abbott Laboratories"
#99 "ARCHITECT"
#100 "ARCHITECT ci8200"
#101 "ARCHITECT i2000SR"
#102 "ARCHITECT system"
#103 "cleia method"
#104 "chemiluminescence immunoassay"
#105 #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104
#106 #15 and #60 and #76 and #105

Supplementary File 3: Risk of bias assessment adapted from QUADAS-2

Domain 1: Patient Selection

1.1 Risk of Bias: Could the selection of patients have introduced bias?

Signaling questions and answer guidelines

Signaling question 1: Was a consecutive or random sample of patients or specimens enrolled?

- Yes: the study enrolled a consecutive or random sample of eligible patients
- No: the study selected patients by selection or convenience
- Unclear: the study did not report how the patient selection was

Signaling question 2: Was a case-control design avoided?

- Yes: the study is not a case-control design
- No: the study is a case-control design
- Unclear: the study design was not reported, or we were unable to identify from the text

Signaling question 3: Did the study avoid inappropriate exclusions?

- Yes: the study enrolled consecutive or random samples of eligible patients
- No: the study excluded samples based on their prior testing, as these exclusions significantly reduce the generalizability of a study's findings
- Unclear: the study did not report exclusion criteria, or we were unable to identify from the text

Risk of Bias was evaluated as 'low risk' if studies scored 'yes' on all the questions or two questions were answered with 'yes' and one with 'unclear'; 'high risk' if two or more questions were answered with 'no' or one question was answered with 'no' and two with 'unclear'; and 'unclear risk' if studies scored 'unclear' on all the questions, two questions are answered with 'unclear' and one with 'yes', two questions were answered with 'yes' and one with 'no', or each question was answered with 'yes', 'no' and 'unclear'

1.2 Applicability: Are there concerns that the included patients and setting do not match the review question?

- Low concern: the study enrolled a broad study population in any setting
- High concern: the study inappropriately included healthy or blood donors only
- Unclear concern: the population was not well characterized, or we could not identify if a study's patients did not match our review question.

Domain 2: Index Test

2.1 Risk of Bias: Could the conduct or interpretation of the index test have introduced bias?

Signaling question 1: Were the index test results interpreted without knowing the reference standard results?

- Yes: results of the reference standard (HCV-RNA) test were blinded. Studies where the HCVcAg test was reported blinded to the HCV-RNA test or if it was clear that the HCVcAg test was reported before the results of the HCV-RNA test were available
- No: results of reference standard were unblended. The results of the HCVcAg test were reported on previous knowledge of the HCV-RNA test
- Unclear: we were unable to identify whether stored samples were tested or the HCVcAg test results were interpreted without knowledge of the HCV-RNA test results

Signaling question 2: If a threshold was used, was it pre-specified?

- Yes: the limit of detection for commercially available HCVcAg tests was pre-specified by the manufacturer
- No: the threshold of the HCVcAg test was personally selected to optimize sensitivity and specificity, leading to over-optimistic estimates of test performance

- Unclear: we could not determine whether the threshold of the HCVcAg test was pre-specified or not

Risk of Bias was evaluated as 'low risk' if studies scored 'yes' on all the questions, or one question was answered with 'yes' and the other one with 'unclear'; 'high risk' if studies scored 'no' on all the questions, or one question was answered with 'no' and another one with 'unclear'; and 'unclear risk' if studies scored 'unclear' on all the questions; or questions were answered with 'yes' and 'no'

2.2 Applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question?

- Low concern: the HCVcAg test was performed according to the manufacturer's recommendations
- High concern: the HCVcAg test procedure was inconsistent with the manufacturer recommendations (i.e., additional processing steps were added), or there was a delayed assessment of samples to perform the HCVcAg test
- Unclear concern: the HCVcAg test was not discussed in the study, or we were unable to determine how the HCVcAg test was conducted or interpreted

Domain 3: Reference standard

3.1 Risk of Bias: Could the reference standard, its conduct, or its interpretation have introduced bias?

Signaling question 1: Is the reference standard likely to classify the target condition correctly?

- Yes: the reference standard for HCV-RNA testing was a nucleic acid amplification test
- No: the reference standard for HCV-RNA testing was not a nucleic acid amplification test, or a combination of different nucleic acid amplification tests was used
- Unclear: there is insufficient information about which was reference standard for HCV-RNA testing used, or we were unable to identify from the text

Signaling question 2: Were the reference standard results interpreted without knowing the index test results?

- Yes: studies where the HCV-RNA test was interpreted blindly to the results of the HCVcAg test
- No: studies where the HCV-RNA test was not interpreted blindly to the results of the HCVcAg test
- Unclear: we were unable to identify whether stored samples were tested or if the HCV-RNA test results were interpreted without knowledge of the HCVcAg test results

3.2 Applicability: Are there concerns that the target condition as defined by the reference standard does not match the question?

- Low concern: the HCV-RNA test was performed according to the manufacturer's recommendations
- High concern: the HCV-RNA test procedure was inconsistent with the manufacturer recommendations, or there was a delayed assessment of samples to perform the HCV-RNA test
- Unclear concern: the HCV-RNA test was not discussed in the study, or we were unable to determine how the HCV-RNA test was conducted or interpreted

Domain 4: Flow and timing

4.1 Risk of Bias: Could the patient flow have introduced bias?

Signaling question 1: Was there an appropriate interval between the index test and reference standard?

- Yes: samples for HCVcAg and reference standards tests did obtain at the same time
- No: samples for HCVcAg and reference standards tests did not obtain at the same time

- Unclear: it was not discussed in the study, or we were unable to determine when HCVcAg and reference standards tests test were conducted or interpreted

Signaling question 2: Did all patients in the study receive the same reference standard?

- Yes: the study used the same rt-PCR for all samples
- No: the study used different types of rt-PCR to analyze all samples
- Unclear: it was not defined in the study, or we were unable to interpret the used rt-PCR

Signaling question 3: Were all patients included in the analysis?

- Yes: the whole population recruited into the study was included in the analysis, or any exclusion was adequately described
- No: participants were missing, or the study excluded samples without a given reason
- Unclear: not enough information was given to assess why participants were excluded from the analysis, or we were unable to find an explanation for the exclusion of samples

Risk of Bias was evaluated as 'low risk' if studies scored 'yes' on all the questions or two questions were answered with 'yes' and one with 'unclear'; 'high risk' if two or more questions were answered with 'no' or one question was answered with 'no' and two with 'unclear'; and 'unclear risk' if studies scored 'unclear' on all the questions, two questions are answered with 'unclear' and one with 'yes', two questions were answered with 'yes' and one with 'no', or each question was answered with 'yes', 'no' and 'unclear'

Summary of the quality assessment by using QUADAS-2

	Risk of bias				Concerns regarding applicability		
Author (year)	**Patient selection**	**Index test**	**Ref. standard**	**Flow and timing**	**Patient selection**	**Index test**	**Ref. standard**
Mederacke et al. (2012)	L	L	L	UC	L	L	L
Garbuglia et al. (2014)	UC	L	L	L	L	L	L
Van Helden et al. (2014)	UC	L	L	UC	L	L	L
Cresswell et al. (2015)	L	L	L	L	L	L	L
Vanhommerig et al. (2015)	L	L	L	L	L	L	L
Alados-Arboledas et al. (2017)	L	L	L	UC	L	L	L
Duchesne et al. (2017)	UC	L	L	L	L	L	L
Hullegie et al. (2017)	L	L	L	UC	L	L	L
Mohamed et al. (2017)	L	L	L	UC	L	L	L
Talal et al. (2017)	L	L	L	L	L	L	L
Alonso et al. (2018)	UC	L	L	L	L	L	L
Chayanupatkul et al. (2020)	L	L	L	L	L	L	L
Rossetti et al. (2021)	L	L	L	UC	L	L	L
Sun et al. (2022)	L	L	L	H	L	H	L

H= high; L= low; Ref = reference; UC = unclear

Supplementary Tables

Supplementary Table 1. Results of bivariate meta-regression (inconsistency index) in subgroup analysis for detecting active HCV infection in PLWHA with Abbott ARCHITECT HCVcAg assay compared with a confirmatory nucleic acid test.

Parameter	Category	I^2 [95%CI]	X^2	*p*-value
Year of publication	Yes: ≤2015 No: >2015	0 [0-100]	0.27	0.87
LMIC	Yes No	73 [39-100]	7.31	**0.03**
All patients with anti-HCV Ab +	Yes No	0 [0-100]	1.87	0.39
Biological sample type	Yes: only serum No: plasma or plasma/serum	84 [67-100]	12.63	**0.001**
Frozen sample	Yes No	53 [0-100]	4.22	0.12
Gold standard cutoff	≤15 IU/mL >15 IU/mL	31 [0-100]	2.90	0.23
Sample size	Yes: ≤100 No: >100	75 [44-100]	7.85	**0.02**
HCV prevalence	≤50% >50%	62 [15-100]	5.27	**0.07**

95%CI = 95% confidence interval; Anti-HCV Ab + = positive anti-HCV; cAg = core antigen; HCV = hepatitis C virus; IU = international units; I^2 = inconsistency index; IU = international units; LMIC = low- or middle-income country; PLWHA = people living with HIV/AIDS; X^2 = Pearson's chi-squared test.

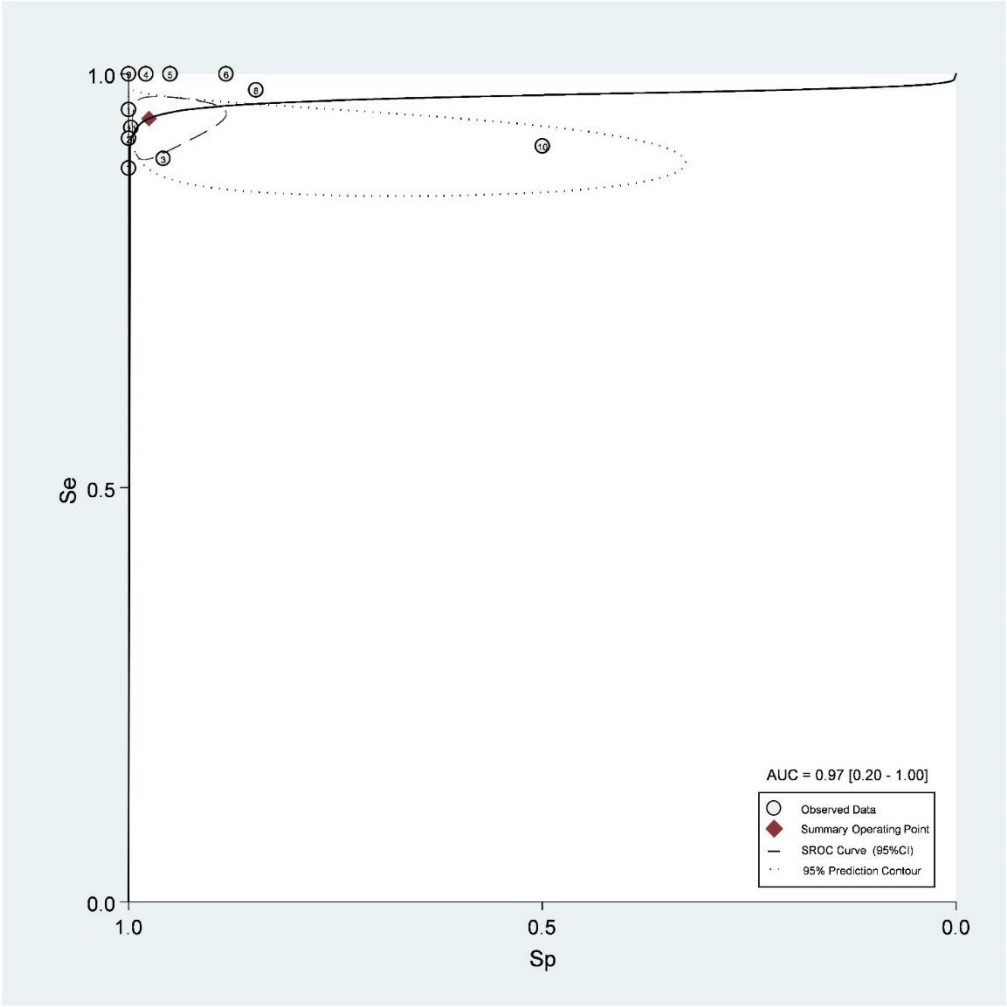
Supplementary Table 2. Results of bivariate meta-regression (sensitivity and specificity) and subgroup analysis in detecting active HCV infection in PLWHA with Abbott ARCHITECT HCVcAg assay compared with a confirmatory nucleic acid test.

Parameter	**Category**	**No.**	**Se [95%CI]**	***p*-value**	**Sp [95%CI]**	***p*-value**
Year of publication	Yes: ≤2015	5	0.94 [0.91-0.97]	**<0.001**	0.98 [0.94-1.00]	0.55
	No: >2015	6	0.95 [0.92-0.98]		0.97 [0.93-1.00]	
LMIC	Yes	2	0.99 [0.96-1.00]	**0.07**	0.88 [0.72-1.00]	**0.01**
	No	9	0.93 [0.91-0.95]		0.98 [0.97-1.00]	
All patients with anti-HCV Ab +	Yes	4	0.95 [0.92-0.98]	**<0.001**	0.92 [0.77-1.00]	0.29
	No	7	0.95 [0.92-0.98]		0.98 [0.96-1.00]	
Biological sample type	Yes: only serum	7	0.96 [0.94-0.99]	**<0.001**	0.94 [0.91-0.97]	**<0.001**
	No: plasma or plasma/serum	4	0.93 [0.90-0.95]		1.00 [0.99-1.00]	
Frozen sample	Yes	8	0.95 [0.92-0.98]	**0.03**	0.95 [0.90-1.00]	**0.01**
	No	3	0.94 [0.90-0.99]		0.99 [0.98-1.00]	
Gold standard cutoff	≤15 IU/mL	8	0.94 [0.91-0.96]	**<0.001**	0.97 [0.94-1.00]	0.49
	>15 IU/mL	3	0.97 [0.95-1.00]		0.98 [0.93-1.00]	
Sample size	Yes: ≤100	8	0.95 [0.92-0.98]	**0.03**	0.94 [0.89-0.98]	**<0.001**
	No: >100	3	0.94 [0.89-0.99]		1.00 [0.99-1.00]	
HCV prevalence	≤50%	4	0.98 [0.95-1.00]	0.81	0.98 [0.95-1.00]	0.55
	>50%	7	0.94 [0.91-0.97]		0.96 [0.90-1.00]	

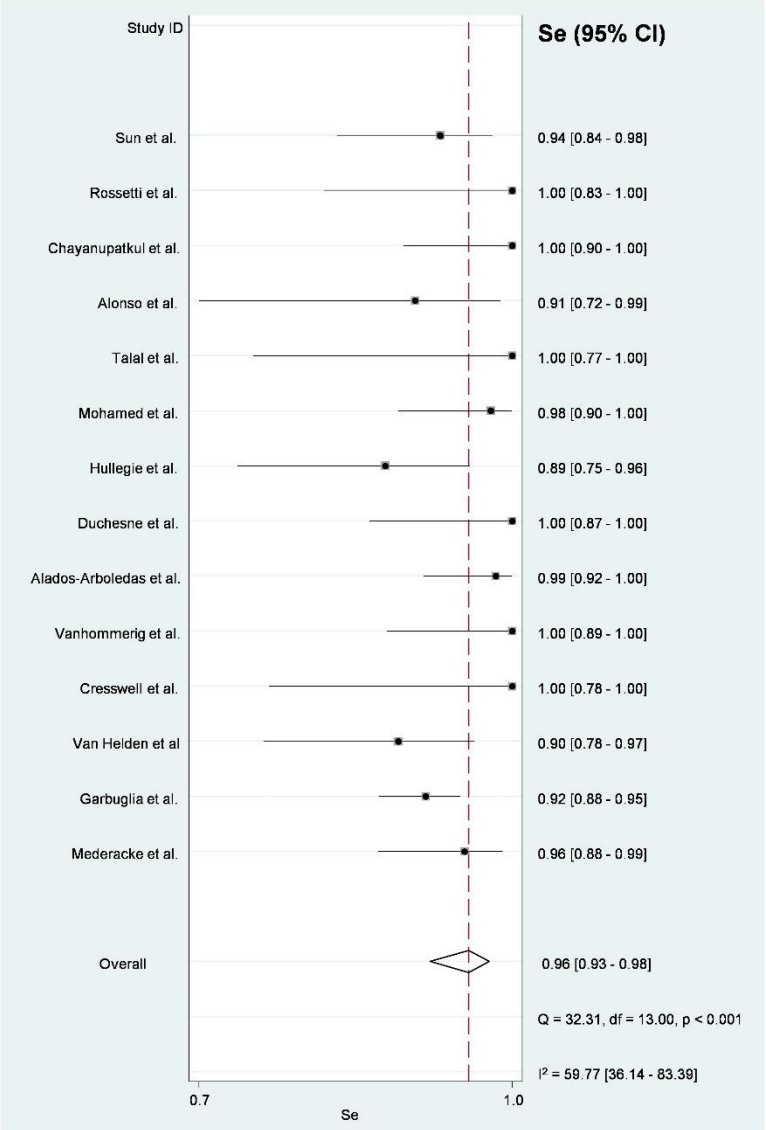
95%CI = 95% confidence interval; Anti-HCV Ab + = positive anti-HCV; cAg = core antigen; HCV= hepatitis C virus; IU= international units; LMIC= low- or middle-income country; No.= number of articles; PLWHA = people living with HIV/AIDS; Se= sensitivity; Sp= specificity.

Supplementary Figures

Supplementary Figure 1. Hierarchical SROC curve plot in detecting active HCV infection in PLWHA with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test. **Abbreviations**: 95%CI = 95% confidence interval; AUC = area under the curve; HCV = hepatitis C virus; PLWHA = people living with HIV/AIDS; Se = sensitivity; Sp = specificity; SROC = summary receiver operating characteristic.



Supplementary Figure 2. Forest plots of pooled sensitivity for all studies included in the univariate analysis in detecting active HCV infection in PLWHA with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test. **Abbreviations**: 95% CI = 95% confidence interval; HCV = hepatitis C virus; I^2 = inconsistency index; PLWHA = people living with HIV/AIDS; Q = Cochran's Q test; Se = sensitivity



Supplementary Figure 3. Deeks's funnel plot asymmetry test for publication bias in detecting active HCV infection in PLWHA with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test. **Abbreviations**: DOR = diagnostic odds ratio; ESS = single effective size; HCV = hepatitis C virus; PLWHA = people living with HIV/AIDS.