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Authors: Daniel Sepúlveda Crespo[1,2,¥] | Ana Treviño-Nakoura[3,4,¥] | José M. Bellón[5] | Amanda Fernández-Rodríguez[1,2] | Pablo Ryan[2,6] | Isidoro Martínez[1,2,¥] | M. A. Jiménez-Sousa[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

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Abstract

Objectives: Hepatitis C virus (HCV) core antigen (HCVcAg) assay is an alternative for diagnosing HCV infection in a single step. This meta-analysis aimed to evaluate the Abbott ARCHITECT HCV Ag assay's diagnostic performance (validity and utility) for diagnosing active hepatitis C.

Methods: PubMed, EMBASE, Scopus, Web of Science, and Cochrane Library were searched until Jan 10, 2023. The protocol was registered at the prospective international register of systematic reviews (PROSPERO: CRD42022337191). Abbott ARCHITECT HCV Ag assay was the test for evaluation, and nucleic acid amplification tests with a cut-off ≤50 IU/mL were the gold standard. Statistical analysis was performed using STATA with the MIDAS module and random-effects models.

Results: The bivariate analysis was conducted on 46 studies (18,116 samples). The pooled sensitivity was 0.96 (95%CI=0.94-0.97), specificity 0.99 (95%CI=0.99-1.00), positive likelihood ratio 141.81 (95%CI=72.39-277.79), and negative likelihood ratio 0.04 (95%CI=0.03-0.06). The area under the SROC curve was 1.00 (95%CI= 0.34-1.00). For active hepatitis C prevalence values of 0.1-15%, the probability that a positive test was a true positive was 12-96%, respectively, indicating that a confirmatory test should be necessary, particularly with a prevalence ≤5%. However, the probability that a negative test was a false negative was close to zero, indicating the absence of HCV infection.

Conclusions: The validity (accuracy) of the Abbott ARCHITECT HCV Ag assay for screening active HCV infection in serum/plasma samples was excellent. Although the HCVcAg assay showed limited diagnostic utility in low prevalence settings (≤1%), it might help diagnose hepatitis C in high prevalence scenarios (≥5%).

1 | INTRODUCTION

Hepatitis C virus (HCV) infection is a global health problem that can cause fibrosis, cirrhosis, liver failure, hepatocellular carcinoma, and cancer-related death.[1] The World Health Organization (WHO) has estimated that 58 million people lived with chronic HCV infection worldwide in 2019, causing almost 300,000 deaths yearly from HCV-related liver diseases [2]. Although currently there is no vaccine against HCV,[3] direct-acting antivirals (DAAs) agents cure more than 95% of HCV-infected patients.[4] In this framework, the WHO aims to eliminate hepatitis C as a significant health problem by 2030 by diagnosing 90% of HCV-infected patients and decreasing hepatitis C incidence by 80%.[5] However, since acute hepatitis C is asymptomatic or with non-specific symptoms, >80% of HCV-infected people are unaware that they are infected.[2,6] The majority of this burden of hepatitis C is concentrated in developing countries and key populations, including people who inject drugs (PWID), men who have sex with men (MSM), female sex workers (FSW), and prisoners.[2,6] To this must be added the recent worldwide concern about the impact of the mysterious acute hepatitis in young children and its unknown etiology.[7]

The standard algorithm for detecting HCV in plasma, serum, or blood currently includes a two-step scheme. First, the detection of anti-HCV antibodies (anti-HCV) by immunoassay to detect patients exposed to HCV. Second, HCV-RNA testing by nucleic acid amplification test (NAAT) to identify active hepatitis C.[8] Commercial NAATs are the gold standard and are widely used in routine clinical practice,[9] but this methodology is expensive, time-consuming, and involves trained personnel and complex laboratory equipment. Furthermore, RNA is easily degraded, leading to false negatives (FN).[10]

A cheaper and faster alternative to identify active hepatitis C is the detection of the HCV core antigen (HCVcAg).[10,11] HCVcAg is a highly conserved protein among all HCV genotypes detected in peripheral blood within 12-15 days after HCV infection, and its presence is associated with active hepatitis C. In comparison, HCV-RNA can be detected in serum/plasma 1-2 weeks after HCV exposure, while HCVcAg appears 1-2 days after HCV-RNA detection.[10] Remarkably, there is a positive correlation between HCVcAg levels and HCV-RNA load, but HCVcAg is a more stable protein than HCV-RNA[10] and appears around 4-6 weeks before anti-HCV. There are different platforms to perform HCVcAg assays, with the Abbott ARCHITECT HCV Ag test (Abbott Diagnostics) currently the most used worldwide and is now the highest quality.[10] It is an inexpensive, rapid (~40 min), and easy-to-perform assay with high analytical sensitivity for HCV-RNA loads >10,000 IU/mL.[12,13]

Three previous meta-analyses assessed the diagnostic performance of the HCVcAg test for diagnosing active HCV infection.[14-16] The first was that of Gu *et al.*[14], where most studies were performed with HCVcAg ELISA kits, a type of assay rarely used in current clinical practice. Furthermore, all the data were analyzed without separating by type of HCVcAg assay. The second was that of Freiman *et al.*[15], where the meta-analysis was stratified by the type of HCVcAg assay, with the Abbott ARCHITECT HCV Ag assay being the most numerous. Freiman *et al.* performed a very informative meta-analysis about the diagnostic validity (accuracy) of the HCVcAg assay, but it did not show data on clinical application. Finally, the third was carried out by Flores *et al.* [16], where the Abbott ARCHITECT HCV Ag assay was also the most frequent. Studies performed by Flores *et al.*[16] and Gu *et al.*[14] analyzed all data together without stratification by HCVcAg assay type and did not show diagnostic utility data. In these three previous meta-analyses,[14-16] another limitation was that data were mixed from people without a diagnosis of HCV or untreated HCV patients, along with data from patients on HCV treatment. Besides, no attention was paid to the cut-off point of the NAAT assays (gold standard).

1.1 │ Objective

This systematic review and meta-analysis aimed to assess the Abbott ARCHITECT HCV Ag assay's diagnostic performance (validity and utility) for diagnosing active hepatitis C, examining published and selected studies to date (January 10, 2023).

2 │ MATERIAL & METHODS

Our study was carried out following the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy guidelines[17] and the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA)[18] (see **Supplementary File 1**).

2.1 │ Search strategy

We systematically reviewed all studies reporting diagnostic accuracy data of the Abbott ARCHITECT HCV Ag assay in plasma/serum to diagnose active HCV infection. Searches in the scientific literature were conducted in the following databases: PubMed, EMBASE, Web of Science (WoS), SCOPUS, and Cochrane Library from January 1, 1976, to January 10, 2023. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022337191) (**Supplementary File 2)**. Other relevant publications were identified by checking reference lists of retrieved publications, systematic reviews, and meta-analyses. The search was not restricted by language or geography.

2.2 │ Study selection

Studies meeting the following inclusion criteria were selected: 1) evaluate the diagnostic accuracy in plasma/serum of the Abbott ARCHITECT HCV Ag assay, compared to NAATs (gold standard) with a threshold HCV-RNA level ≤50 IU/mL; 2) have data on diagnostic accuracy to calculate diagnostic performance [true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN)]; 3) participants who were unaware of their HCV infection or who, if they knew, did not receive antiviral treatment against HCV. Studies meeting the following exclusion criteria were rejected: 1) did not report or contained sufficient data to analyze diagnostic performance or data were not available from the corresponding author on reasonable request; 2) data still unpublished or published in meeting abstracts, proceeding papers, letters to the editor, editorial materials, books, case reports, and review articles; 3) articles with small sample sizes (n≤10); 4) data related to non-human subjects or commercial samples; 5) data from HCV treatment monitoring after initiation of anti-HCV therapy; 6) duplicated data. In this case, the article that studied the largest cohort was selected, excluding the remaining studies or merging data.

Two researchers (DS-C and AT-N) conducted the literature search, screened titles and abstracts, and selected suitable studies following predefined inclusion and exclusion criteria for full-text review. Discrepancies regarding study eligibility were resolved by discussion between reviewers (DS-C and AT-N) and the senior author (SR). Google Translate and DeepL Translator were used to translate the abstracts before selection for studies that were not in Spanish or English.

2.3 │ Data extraction

Two researchers (AT-N and SR) independently extracted and collated data on epidemiological characteristics and HCVcAg test accuracy from each study. If the data needed to be clarified or the two reviewers could not reach a consensus, a third reviewer (JMB) was consulted. When data were not explicit or missing, an investigator (DS-C) contacted the authors to obtain data. The study was excluded when no response was received (at least three attempts).

2.4 │ Quality assessment

Two reviewers (DS-C and AT-N) independently evaluated the risk of bias and concerns regarding the applicability of all included studies following the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) guidelines.[19] Any disagreement in the score was discussed until a consensus was reached or checked by a third researcher (SR). The QUADAS-2 tool assesses four key domains: patient selection, index test, reference standard, and patient flow and timing. Each domain was scored considering items as ‘yes’, ‘no’, or ‘unclear’, resulting in a global rating of

'low', 'unclear', or 'high' for each study according to the criteria established in **Supplementary File 3**.

2.5 | Statistical analysis

The diagnostic performance was assessed using STATA v15 (STATA Corp., College Station, TX, USA) with the MIDAS module and random-effects models.[20,21]

We conducted a bivariate meta-analysis (studies with TP+FN>0 and FP+TN>0) to produce pooled estimates of sensitivity (Se), specificity (Sp), positive and negative likelihood ratios (PLR and NLR), and the area under the curve of the summary receiver operating characteristic curve (AUC-SROC). Besides, a univariate meta-analysis was carried out, including those studies with TP+FN=0 or FP+TN=0. Diagnostic utility was evaluated using a four-quadrant likelihood ratio scatter matrix[22] and Fagan´s nomogram considering PLR, NLR, and pre-and post-test probabilities.[23]

The forest plot displays the heterogeneity of each included study. An inconsistency index (I^2) ≥50% or a $p \leq 0.10$ (Cochran's Q test)[21] indicates substantial heterogeneity.[24,25] Heterogeneity was analyzed using the Galbraith plot.[26] A bivariate box plot or bagplot evaluated the interdependence between sensitivity and specificity. A sequential sensitivity analysis removing individual studies was conducted to perform robust research and investigate its influence on heterogeneity and diagnostic performance measurements.

Besides, a meta-regression analysis for the HCVcAg detection was performed to define the impact on diagnostic accuracy measures ($p \leq 0.10$)[21] of diverse factors: year of publication (Yes: ≤2015; No: > 2015), Low- and Middle-income Countries (LMICs) (Yes/No), patients with positive anti-HCV antibodies (anti-HCV Ab +) (Yes/No), biological sample type (Yes: only serum; No: plasma or plasma/serum), frozen sample (Yes: frozen; No: unknown), large sample size (Yes: ≤200; No:>200), overall QUADAS-2 risk (Yes: low; No: unclear/high), risk of bias in QUADAS-2 (Yes: low; No: unclear/high), applicability concerns in QUADAS-2 (Yes: low; No: unclear/high), COBAS Ampliprep/COBAS TaqMan HCV Real-time PCR (Yes/No), Abbott RealTime HCV Assay (Yes/No), and other non-Abbott and non-COBAS real-time PCR assays (Yes/No). A low overall QUADAS-2 risk refers to a selected article with a low risk of bias in the four domains and a low applicability concern in the three domains; if a domain is classified as unclear or high, that item is listed as 'No'. The same criteria are followed for the risk of bias in QUADAS-2 and applicability concerns in QUADAS-2 factors, but considering only the risk of bias and applicability concerns domains, respectively. With the 'gold standard-NAATs' subgroup analysis, we checked if the data could be biased due to the different NAATs technologies used concerning the moment in which the study is carried out, knowing that we have already established a first filter (lower limit of detection; LLoD < 50 IU/mL). The publication bias was evaluated using a Deeks' funnel plot asymmetric test[27], with a $p \leq 0.10$ indicating publication bias.[21]

3 | RESULTS

3.1 | Search results

The initial search of the databases retrieved a total of 9,458 articles. After deleting duplications, a total of 6,593 studies were retained. By screening titles and abstracts, 6,389 articles were excluded. After evaluating the full text of 204 papers, 75 studies met the inclusion criteria (**Figure 1A**).[28-102]

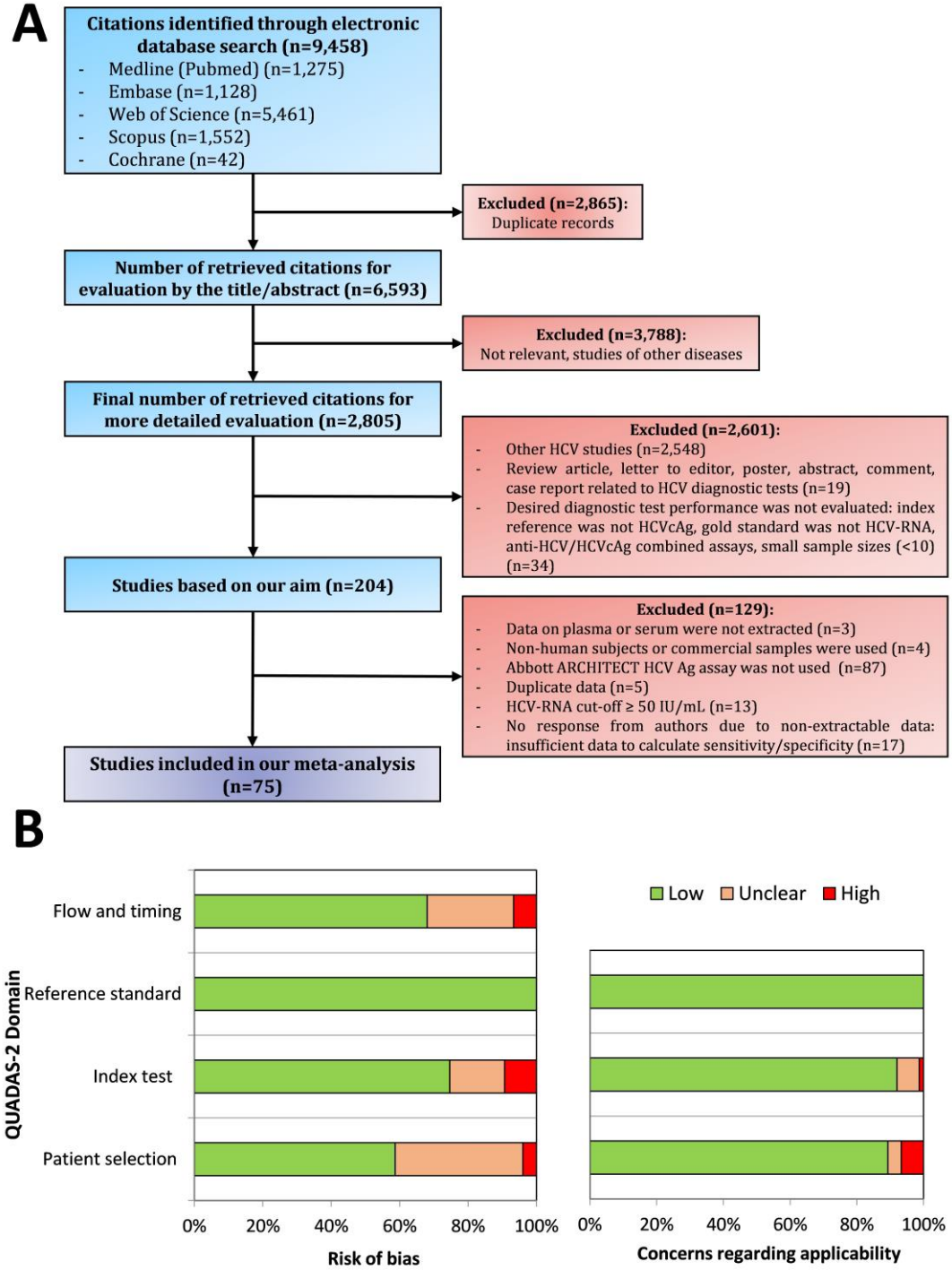

FIGURE 1 Flow diagram of search strategy **(A)** and quality of included studies according to QUADAS-2 guidelines **(B)**. In figure (B), green stands for low risk, orange indicates unclear risk, and red indicates high risk. **Abbreviations**: cAg = core antigen; HCV = hepatitis C virus; IU = international units; QUADAS = quality assessment of diagnostic accuracy study.

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

Author (year) [reference]	Country	No.	Age (yrs.)	Males (%)	HCV genotype	HIV (%)	HBV (%)	Sample type	Sample Condition	GS Cut-off (IU/mL)
Miedouge et al. (2010) [59]	France	2913	N/D	N/D	1, 2, 3, 4, 5, 6	N/D	N/D	Serum	Frozen	15
Park et al. (2010) [61]	South Korea	282	N/D	50.7	1, 2, 3	N/D	N/D	Serum	N/D	15
Ergunay et al. (2011) [42]	Turkey	272	N/D	N/D	1, 3, 4	N/D	N/D	Serum	Frozen	15
Kesli et al. (2011) [52]	Turkey	212	59	42.5	1	N/D	N/D	Serum	N/D	20
Kuo et al. (2012) [55]	Taiwan	405	N/D	47.2	N/D	N/D	N/D	Serum	N/D	15
Alados-Arboledas et al. (2013) [30]	Spain	127	N/D	N/D	N/D	N/D	N/D	Serum	Frozen	15
Hadziyannis et al. (2013) [45]	Greece	105	N/D	N/D	1, 2, 3, 4	N/D	N/D	Serum	Frozen	15
Buket et al. (2014) [33]	Turkey	115	57.9	43.5	N/D	N/D	N/D	Serum	N/D	10
Chevaliez (2014) [38]	France	514	51.3	61.9	1, 2, 3, 4, 5, 6	N/D	N/D	Serum	N/D	15 and 12
Florea et al. (2014) [43]	Romania	76	N/D	25	N/D	0	0	Serum	Frozen	15
Garbuglia et al. (2014) [44]	Italy	249	47	69.6	1, 3, 4	100	3.8	Plasma	Frozen	12
Heidrich et al. (2014) [46]	Germany	596	52	57	1, 2, 3,	N/D	N/D	Serum	N/D	15
Kadkhoda et al. (2014) [48]	Canada	154	N/D	50	1, 2, 3, 4	1.3	0	Serum/plasma	Frozen	15
Reyes-Mendez et al. (2014) [65]	Mexico	211	N/D	N/D	N/D	N/D	N/D	Serum	Frozen	12
Van Helden et al. (2014) [71]	Germany	3558	N/D	N/D	1, 2, 3	4.4	6.6	Serum	Frozen	15
Kamal et al. (2015) [50]	Egypt	460	38.5	59.6	4	0	2.2	Serum	Frozen	12
Demircili et al. (2016) [40]	Turkey	189	51.4	42.3	1, 2, 3, 4	N/D	N/D	Serum	Frozen	15
Medici et al. (2016) [58]	Italy	188	N/D	N/D	N/D	N/D	N/D	Serum/plasma	Frozen	15
Çetiner et al. (2017) [35]	Turkey	132	49.9	54.5	1, 2, 3, 4	N/D	N/D	Serum	N/D	15
Duchesne et al. (2017) [41]	Cameroon	1009	50.4	43	1, 2, 4	7.7	10.6	Serum	Frozen	12
Hullegie et al. (2017) [47]	Netherlands	67	41	100	1	100	N/D	Serum/plasma	N/D	15 and 12
Mohamed et al. (2017) [60]	Tanzania	153	38	92.2	1, 4	43.9	9.8	Serum	Frozen	15
Rockstroh et al. (2017) [66]	Germany	411	50.1	53	1	N/D	N/D	Plasma	Frozen	25
Talal et al. (2017) [69]	USA	109	53.8	59.6	1, 2, 3, 4	17.4	N/D	Serum	Frozen	15
Wasitthankasem et al. (2017) [72]	Thailand	290	50.1	83.5	1, 3, 6	0.3	4.5	Plasma	N/D	12
Adland et al. (2018) [29]	UK	195	37	84	1, 3	N/D	N/D	N/D	N/D	12
Alonso et al. (2018) [31]	Spain	204	N/D	N/D	1, 2, 3, 4	12.3	27.9	Serum	Frozen	15
Benito et al. (2018) [32]	Spain	72	57	75.8	N/D	N/D	N/D	Serum	Frozen	15
Chang et al. (2018) [36]	Taiwan	221	N/D	N/D	1, 2, others	N/D	N/D	Serum	Frozen	15
Lamoury et al. (2018) [57]	Australia	119	N/D	N/D	1, 2, 3, 6	N/D	N/D	Plasma	Frozen	15
Catlett et al. (2019) [34]	Australia	186	46	84	N/D	N/D	N/D	Plasma	Frozen	12
Kyuregyan et al. (2019) [56]	Russia	31	42.2	41.9	1, 3	N/D	N/D	Serum	Frozen	12 and 10
Pérez-García et al. (2019) [62]	Spain	40	51.9	60	1, 2, 3	2.5	N/D	Serum/plasma	N/D	15

Suttichaimongkol et al. (2019) [68]	Thailand	165	54	70.9	1, 3, 6	1.8	1.8	Serum/plasma	Frozen	15
Pollock et al. (2020) [63]	UK	744	43	63.8	1, 2, 3, 4	5	0.5	Serum	N/D	12
Wong et al. (2020) [73]	Malaysia	112	54.0	59.8	N/D	N/D	N/D	Serum/plasma	N/D	21
Abid et al. (2021) [28]	Pakistan	200	46.4	28.5	N/D	N/D	N/D	Plasma	Frozen	12
Chen et al. (2021) [37]	Taiwan	412	N/D	N/D	N/D	N/D	N/D	Serum	N/D	15
Kallala et al. (2021) [49]	Tunisia	109	N/D	44	1, 2, 3	N/D	N/D	Serum/plasma	N/D	15
Kannan et al. (2021) [51]	India	156	N/D	N/D	N/D	N/D	N/D	Serum	N/D	34
Kumar et al. (2021) [53]	Singapore	89	53.5	47.3	1	N/D	N/D	Serum/plasma	N/D	15
Kumbhar et al. (2021) [54]	India	208	46	66.8	N/D	N/D	N/D	Plasma	Frozen	12
Ponnuvel et al. (2021) [64]	India	140	36	75.7	1, 3, 4	1.42	5.7	Plasma	Frozen	12
Chuaypen et al. (2022) [39]	Thailand	93	54	67.7	1, 3	0	0	Serum	N/D	12
Torrecillas et al. (2022) [70]	Spain	208	N/D	N/D	N/D	N/D	N/D	Serum/plasma	N/D	15
Sun et al. (2022) [67]	Taiwan	1615	39.8	97.7	1, 2, 6	100	9,9	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 = no available data; UK = United Kingdom; USA = United States of America; yrs = years.

3.2 | Article characteristics

Forty-six studies[28-73] were in the bivariate meta-analysis (**Table 1)**. The remaining 29 articles[74-102] were added to the 46 studies from the bivariate analysis to make the univariate analysis (see **Supplementary Table 1**). Overall, all studies ranged from 2009 to 2022 and were published in English, except three that were available in Spanish,[30] German,[71] and Korean.[98] All studies had a cross-sectional design except for two longitudinal reports,[46,64] including subjects with hepatitis C and those susceptible to HCV infection. A total of 23,648 samples were included for HCVcAg testing of active hepatitis C. Fifty-nine reports provided information on HCV genotypes 1 to 6. When registered, 61.6% of study participants were male (ranging from 21.6% to 100%) with an average age of 50 (between 30 and 69), and the prevalence rate of HCV/HIV coinfection was 16.1% (0-100%), while it was 4.8% (0-36%) for HCV/HBV coinfection.

The 'ARCHITECT HCV Ag' test (Abbott Diagnostics), a chemiluminescent microparticle immunoassay, was used to quantify HCVcAg. Samples were considered negative when the HCVcAg was ≤3 fmol/L (≤0.06 pg/mL). The main gold standard tests for detecting HCV viremia were the COBAS Ampliprep/COBAS TaqMan HCV Real-time PCR (Roche Diagnostics) (n=51) and the Abbott RealTime HCV Assay (Abbott Diagnostics) (n=22) with a LLoD of 15 and 12 IU/mL, respectively.

3.3 | Risk of bias assessment

Figure 1B summarizes the quality assessment results (full description in **Supplementary File 3**). Twenty-one studies (28%) were found to have an overall low risk of bias. The risk of bias was high in three articles (4%) for the patient selection domain,[40,86,99] seven studies (9.3%) for the index test domain,[30,66,68,75,82,83,96] and five studies (6.7%) for the flow and timing.[56,66,67,79,88] A similar trend was reported for concern regarding the applicability, where most studies (n=61, 81.3%) reported low concerns. Moreover, all studies had low concerns regarding the applicability of the reference standard domain.

3.4 | Diagnostic accuracy

When appropriate, a bivariate meta-analysis was conducted (46 studies and 18,116 total samples) to derive pooled estimates. The pooled diagnostic performance values were Se=0.96 (95%CI = 0.94-0.97) (**Figure 2A**), Sp=0.99 (95%CI = 0.99-1.00) (**Figure 2B**), PLR=141.81 (95%CI = 72.39-277.79) (**Figure 3A**), and NLR=0.04 (95%CI = 0.03-0.06) (**Figure 3B**). The AUC-SROC was 1.00 (95%CI = 0.34-1.00), demonstrating excellent diagnostic accuracy (**Supplementary Figure 1**).

Univariate analysis was done to use all available data. While the pooled specificity value was unchanged, the pooled sensitivity value (Se=0.97; 95%CI = 0.96-0.98) was slightly higher than that of the bivariate analysis (**Supplementary Figure 2**)

3.5 | Clinical application

The four-quadrant likelihood ratio scatters matrix shows that PLR and NLR were in the LUQ, showing confirmation & exclusion of active HCV infection (**Figure 4**). Besides, we performed a simulation for several prevalence values of active hepatitis C (0.1%, 0.5%, 1%, 5%, 10%, and 15%) using Fagan's plots (**Supplementary Figure 3**). We found that the probability that a person with a positive test was a TP was 12%, 42%, 59%, 88%, 94%, and 96%, respectively, indicating that a confirmatory test should be necessary, particularly with a prevalence ≤5%. However, the probability that a person with a negative test was an FN was close to zero in all cases (**Supplementary Figure 3**).

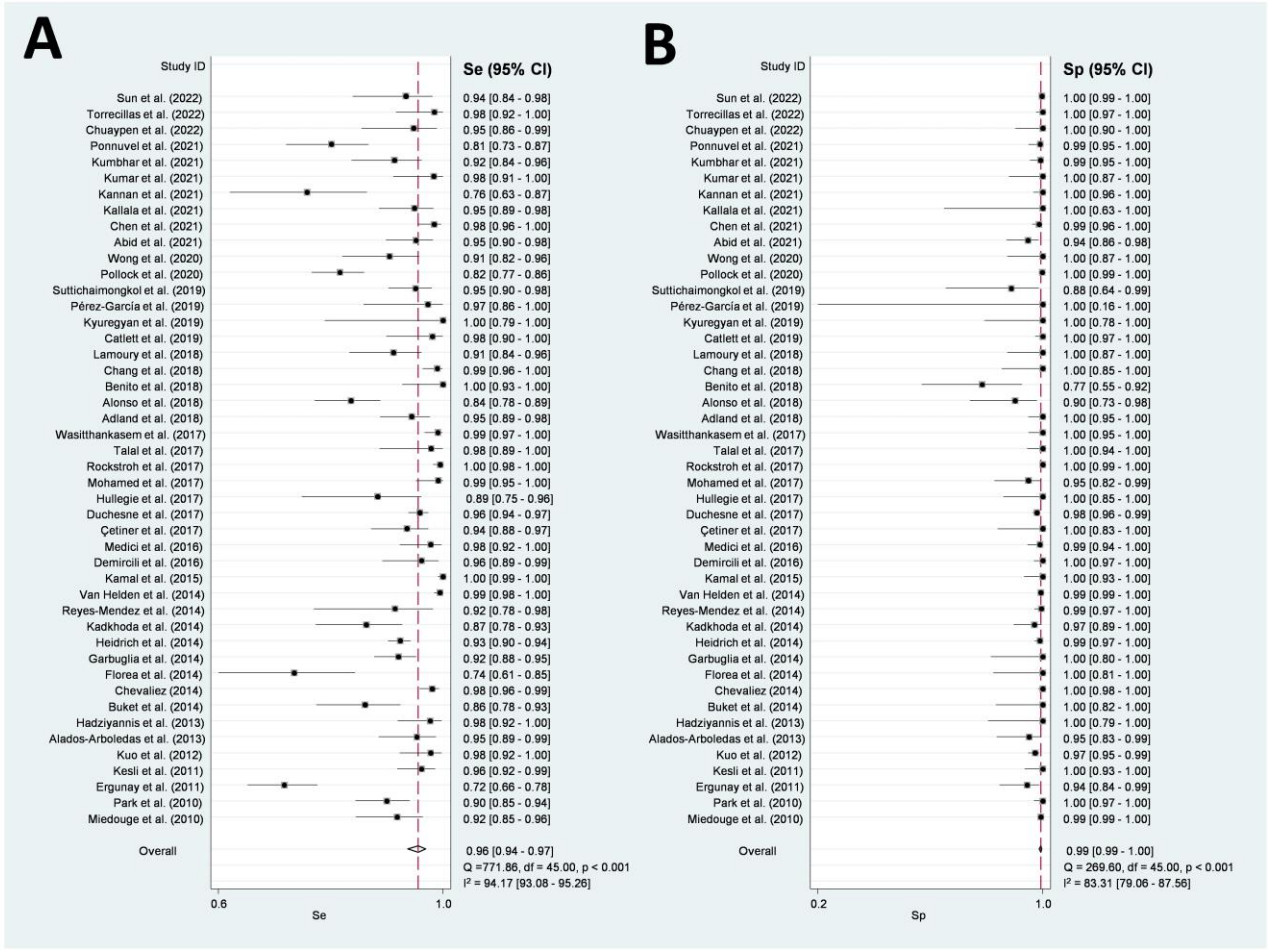

FIGURE 2 Bivariate analysis of sensitivity **(A)** and specificity **(B)** in detecting active hepatitis C infection with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test. **Abbreviations**: 95% CI = 95% confidence interval; df = degrees of freedom; I^2 = inconsistency index; Q= Cochran's Q test; Se = sensitivity; Sp = specificity.

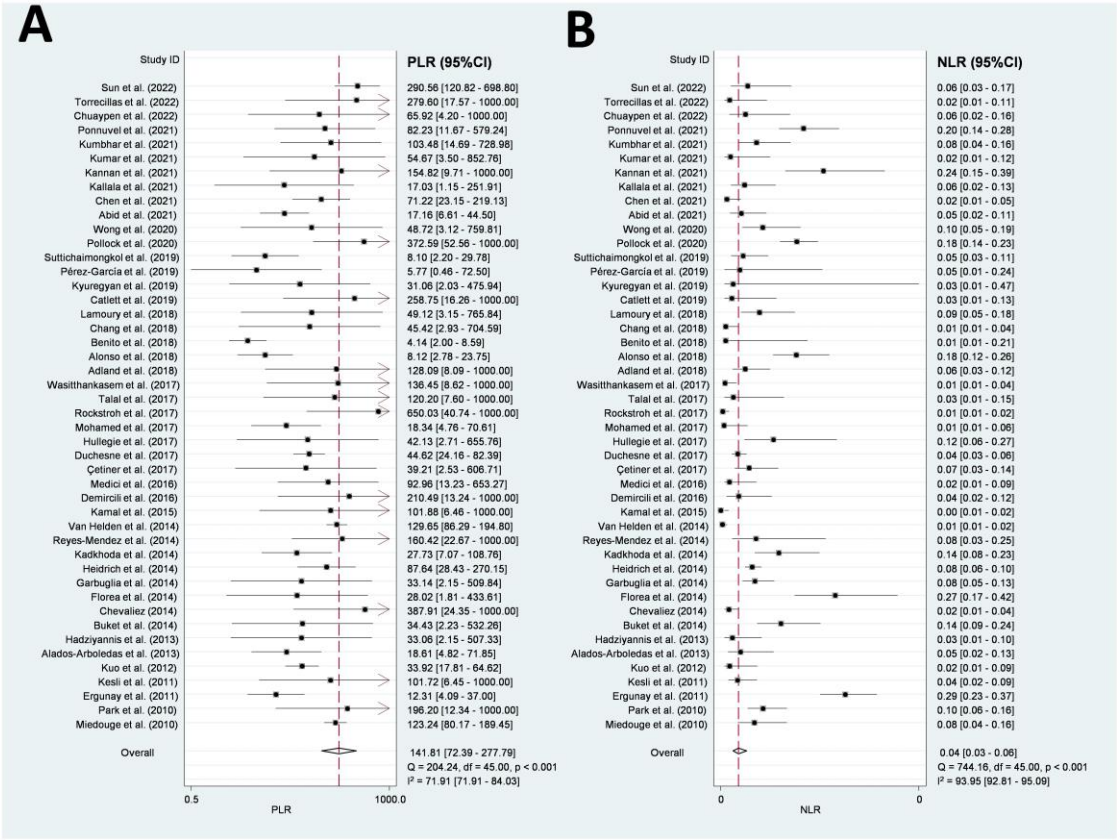

FIGURE 3 Bivariate analysis of positive **(A)** and negative **(B)** likelihood ratio in detecting active hepatitis C infection with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test. **Abbreviations**: 95% CI = 95% confidence interval; df = degrees of freedom; I^2 = inconsistency index; Q= Cochran's Q test; NLR = negative likelihood ratio; PLR = positive likelihood ratio.

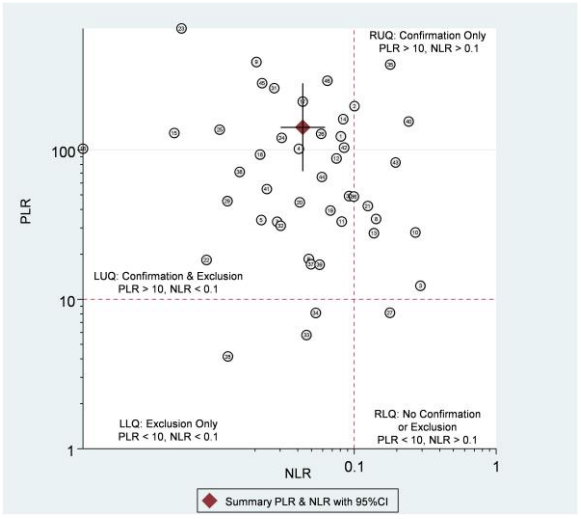

FIGURE 4 Likelihood ratio scattergram to detect active HCV infection with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test. **Abbreviations**: 95% CI = 95% confidence interval; LLQ = left lower quadrant (Only exclusion: PLR <10, NLR <0.1); LUQ = left upper quadrant (Confirmation and exclusion: PLR >10, NLR <0.1); NLR = negative likelihood ratio; PLR = positive likelihood ratio; RLQ = right lower quadrant (Absence of confirmation or exclusion: PLR <10, NLR >0.1); RUQ = right upper quadrant (Only confirmation: PLR >10, NLR >0.1).

3.6 | Exploration of heterogeneity

Heterogeneity is estimated in **Figures 2** & **3,** where sensitivity, specificity, PLR, and NLR showed substantial heterogeneity (p<0.10 and I^2>50%). The Galbraith plot (**Figure 5A**) also shows a significant heterogeneity, where 15 articles stand out for their remarkable impact.[30,33,36,38,40,41,60,61,71,76,79,89,96,100,102] However, no article with a relevant impact on heterogeneity was found using sensitivity analysis (**Supplementary Table 2**). Moreover, meta-regression analysis showed that the frozen sample (Yes/No) and applicability concerns in QUADAS-2 (Low *vs*. Unclear/High) significantly impacted heterogeneity (p=0.02) (**Supplementary Table 3**).

The interdependence analysis between sensitivity and specificity shows a slight skewness toward higher specificity than sensitivity values (**Figure 5B**), suggesting an inevitable threshold variability, even though the articles included were relatively homogeneous in the cut-off points of NAATs. The bagplot shows that studies were not clustered together, with nine outliers.[30,35,38,40,47,61,69,71,84] However, the sensitivity analysis did not find any articles with a relevant impact on diagnostic performance measures. It only showed that the pooled PLR ranged from 126.5 to 154.4 when one study was omitted (**Supplementary Table 4**). Meta-regression analysis showed that all factors included had a significant effect on sensitivity and specificity (p<0.10), except the overall QUADAS-2 risk, applicability concerns in QUADAS-2, COBAS Ampliprep/COBAS TaqMan HCV Real-time PCR, and other non-Abbott and non-COBAS real-time PCR assays on specificity (**Supplementary Table 5**). Nevertheless, although significant, these differences in sensitivity and specificity values were minor and, thus, clinically irrelevant.

Finally, publication bias was not discarded by Deeks' funnel plot asymmetry test (p<0.001) (**Supplementary Figure 4**).

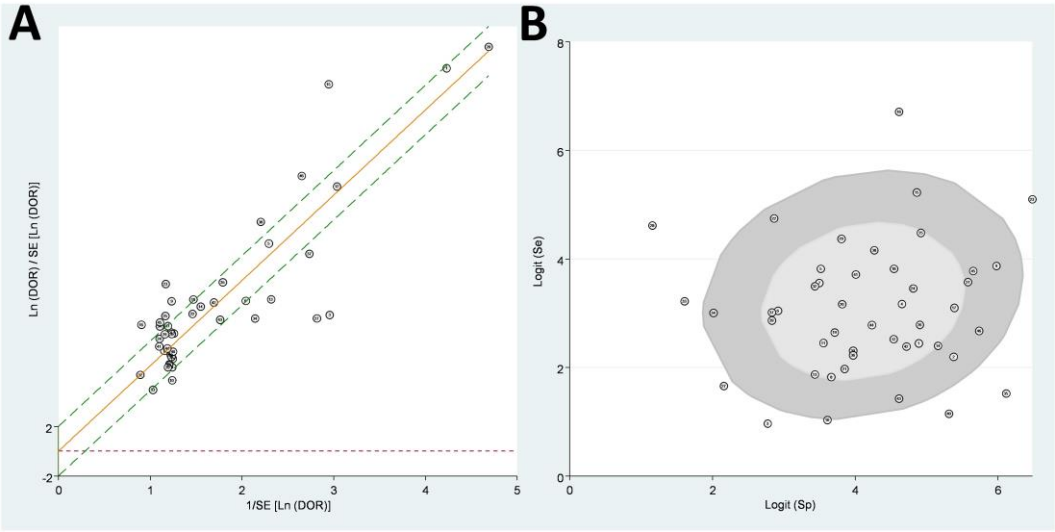

FIGURE 5 Galbraith plot (radial) **(A)** and bagplot **(B)** to assess heterogeneity of the bivariate meta-analysis. Abbreviations: DOR = diagnostic odds ratio; Ln = natural logarithm; Se = sensitivity; SE = standard error; Sp = specificity

4 | DISCUSSION

In this Abbott ARCHITECT HCV Ag assay bivariate analysis, we found that the validity (accuracy) to detect active HCV infection in serum/plasma samples was excellent, with very high sensitivity, specificity, and AUC. However, although this HCVcAg assay showed diagnostic utility for confirming and excluding active HCV infection, diagnostic performance was only acceptable for high-prevalence settings (≥5%) and limited in low-prevalence locations (≤1%).

This meta-analysis has differential characteristics concerning the three previous meta-analyses about the HCVcAg assay diagnostic performance,[14-16] providing various assets that give it added value. First, the previous meta-analysis included other assays and primarily relied on the Abbott ARCHITECT HCV Ag assay with limited bias, even though it is the highest quality and most widely used assay currently;[10] we looked in detail at data from 75 studies (n=23,648 samples) specific to the Abbott ARCHITECT HCV Ag test. Second, the cut-off point of the NAATs (gold standard) was considered for selecting those studies with a low cut-off point (≤50 IU/mL) and, therefore, more precise for diagnosing active hepatitis C. Third, we analyzed the diagnostic performance of people who did not know of their infection or who, if they knew, were not receiving HCV treatment against HCV. In other words, it is a scenario resembling screening for active hepatitis C because data from patients under HCV treatment were discarded. Fourth, we showed the diagnostic utility of the Abbott ARCHITECT HCV Ag test by evaluating various settings of active hepatitis C prevalence that could be extrapolated to real life in different risk populations and countries.

The strength of our work is that it was conducted in a standardized way according to a predefined protocol. The systematic review was performed without language restrictions, according to a priori protocol in several international biomedical databases, including PubMed, EMBASE, WoS, SCOPUS, and Cochrane Library. Besides, two independent investigators conducted article selection, data extraction, and quality assessment, and any disagreement was discussed until a consensus was reached or checked by a third researcher. Another point of interest in our study is the selection of the interval of publication dates to carry out the search strategy (1976-2023). Thanks to this and an optimized search strategy, we provided a complete and improved flowchart in which we got all the eligible papers and established specific and not general exclusion criteria (see red boxes in Figure 1). Moreover, we set a database with all the HCVcAg detection techniques, from its origins to the present, to verify that the Abbott ARCHITECT HCV Ag test was the most used and provided the best sensitivity and specificity values, finding that from the 90s, the publications associated with the detection of HCVcAg began to have relevance, growing exponentially until the present day the interest in this topic.

The diagnostic validity (accuracy) of the HCVcAg assay is an intrinsic property. In the bivariate meta-analysis, the accuracy for HCV detection was excellent because pooled sensitivity and specificity were close to 100% and AUC near 1. The univariate meta-analysis showed a value of sensitivity similar to the bivariate analysis. Besides, the pooled PLR≥100 and NLR≤0.1 showed strong evidence to accept and exclude active HCV infection. However, the disease prevalence may affect diagnostic effectiveness (accuracy) since the percentage of correctly classified subjects varies as prevalence varies. In our study, if HCV prevalence increases, the post-test probability of finding a TP increases, while if HCV prevalence decreases, the post-test probability of finding a TP decreases. Fagan's nomogram showed that the diagnostic utility of the Abbott ARCHITECT HCV Ag test for diagnosing active HCV infection was limited in low-prevalence settings (≤1%) because a confirmatory NAAT will be required to validate positive HCVcAg assay results. Otherwise, this HCVcAg test can be an exciting alternative to NAATs for high-prevalence settings (≥5%) because the probability of having an active HCV infection is close to 90% or higher. On the other hand, HCV prevalence has almost no impact on the post-test probability of finding a TN. Thus, an individual with a negative test has <1% chance of having active HCV infection, regardless of HCV prevalence, indicating that a negative result should be sufficient to rule out the presence of active

HCV infection. Therefore, the Abbott ARCHITECT HCV Ag test could improve the current two-step HCV detection algorithm for high-prevalence settings (≥5%) since it is cheaper, faster, and easier to perform.[103] This HCVcAg assay could be used in high-risk populations,[104] where early detection and management of HCV infection are essential to minimize virus transmission. Moreover, it could be helpful in countries with high HCV prevalence and significant iatrogenic transmission, especially in populations with limited health personnel, facilities, or rapid diagnostic tests (Egypt, Nigeria, Iran, or Pakistan, among others).[105,106]

The cut-off point of both the NAAT and HCVcAg tests impacts diagnostic performance. In this work, the LLoD was <50 IU/mL, increasing the accuracy of HCV diagnosis. Plasma HCV-RNA and HCVcAg levels can fluctuate, affecting the proportion of subjects with FP or FN. The Abbott ARCHITECT HCV Ag test has an LLoD <3 fmol/L (~3,000 IU/mL), and although the frequency of people with very low HCV-RNA load (≤3,000 IU/mL) is about 5%, the benefit of HCVcAg assay for HCV screening may be limited among these individuals.[107]

The quality of the included studies affects the accuracy of the systematic review. It should be noted that all studies had a low risk of bias for the reference standard domain since it is unlikely to introduce bias even if index test results are known in advance. Although the accuracy of the NAAT as a reference standard is not 100%, NAATs are highly sensitive, and inter-test variability is minimal. Moreover, viral loads measured in this technique correlate well with HCVcAg. In our meta-analysis, the risk of bias was medium-low because only 21 studies had a low risk, seven were a high risk, and many elements were unclear or missing. Some of the main drawbacks were that it needed to be known whether the studies included consecutive or random samples, whether the design of the studies was case-control, or provided little information about blinding of the HCVcAg test and the flow of patients and time in the study. It should also be noted that all studies had low concerns regarding applicability for the reference standard domain because circulating HCV is associated with active HCV infection, and the specificity of NAATs is high. However, the applicability concerns from this meta-analysis were medium-high because 61 studies had a low QUADAS-2 risk of applicability concerns, and the other 14 had a medium risk.

This meta-analysis had a significant heterogeneity, evaluated by Cochran's Q test and I^2. Q test is recognized to have excessive power to detect heterogeneity when many studies and patients are included,[24] as in our work. In this case, the I^2 test is more suitable for assessing heterogeneity because it does not depend on the number of included studies and is easier to interpret.[24] The heterogeneity found in this meta-analysis is very common in meta-analyses of diagnostic tests because it is difficult to control for all potential confounders, such as sample size, different objectives, the prevalence of disease, study design, reference tests, screening tests, and sample type and condition, among others. Therefore, we performed a random-effects analysis, assuming that the studies are heterogeneous.[17] A meta-regression was also conducted to determine potential confounders, finding significant values for frozen samples (Yes/No) and applicability concerns in QUADAS-2 (Yes: low; No: unclear/high). Besides, we found that all analyzed confounders impacted sensitivity and/or specificity, possibly due to the large sample size studied; however, their effect was clinically insignificant.

4.1 | Limitations

This meta-analysis has some limitations that must be considered. First, our analysis revealed a publication bias, suggesting a greater tendency to publish positive results than studies with adverse effects. Second, we could not analyze by meta-regression the impact of HCV viral load, HCV genotype, and HIV/HCV and HBV/HCV coinfections due to the lack of information in many included articles. Thirdly, plasma and serum samples were comprised in several studies, being classified as ‘not only serum’ for meta-regression analysis. In the same way, the sample condition (fresh *vs*. frozen) was unknown in many studies and was classified as unfrozen.

5 | CONCLUSION

In conclusion, the results of the bivariate meta-analysis suggest that the validity (accuracy) of the Abbott ARCHITECT HCV Ag test for detecting active HCV in serum/plasma samples was excellent. Although the HCVcAg assay showed limited diagnostic utility in low prevalence settings (≤1%), it might help diagnose hepatitis C in high prevalence settings (≥5%).

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 the patients from the published articles, so the informed consent signed by the patients was unnecessary.

Consent for publication

Not applicable.

Data Availability statement

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

Conflict of interest statement

Authors have no competing interests to declare.

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Author contributions:

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

Ana Treviño: investigation, resources, writing – reviewing, and editing

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

Amanda Fernandez-Rodriguez: writing – reviewing, and editing

Pablo Ryan: writing – reviewing, and editing

Isidoro Martínez: funding acquisition, writing – reviewing, and editing

María A Jiménez-Sousa: methodology, writing – reviewing, and editing

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

Authors' information (optional)

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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 at the end.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
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
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	3 and 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.	PROSPERO CRD42022337191
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
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 and 6
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. 6-13
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.	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).	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 and 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) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	6 and 7

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	6 and 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.	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.	Figs 2, 3 and Suppl. Fig 1 and 2
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).	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).	13
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.	1, 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 Science (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
#105 #15 and #60 and #76 and #105

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

Adapted from *Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155(8):529-536*.

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: the reference standard (HCV-RNA) test results 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; 'high risk' if one or two questions were answered with 'no'; and 'unclear risk' if questions were answered with 'yes' and 'unclear'.

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

<u>Domain 3: Reference standard</u>

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? We will score "yes" for all studies

- 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 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

<u>Domain 4: Flow and timing</u>

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. (2009)	UC	L	L	L	L	L	L
Miedouge et al. (2010)	L	UC	L	UC	L	L	L
Park et al. (2010)	L	L	L	L	L	L	L
Ergunay et al. (2011)	L	UC	L	L	L	L	L
Kesli et al. (2011)	UC	L	L	L	H	L	L
Song et al. (2011)	L	L	L	L	L	L	L
Kuo et al. (2012)	L	L	L	L	L	L	L
Murayama et al. (2012)	L	UC	L	L	H	L	L
Vermehren et al. (2012)	UC	L	L	L	L	L	L
Alados-Arboledas et al. (2013)	UC	H	L	UC	L	L	L
Durante-Mangoni et al. (2013)	L	L	L	L	L	L	L
Hadziyannis et al. (2013)	L	UC	L	L	L	L	L
Ottiger et al. (2013)	L	H	L	L	L	L	L
Tedder et al. (2013)	H	UC	L	UC	L	L	L
Buket et al. (2014)	L	L	L	L	L	L	L
Chevaliez (2014)	UC	UC	L	UC	L	L	L
Florea et al. (2014)	L	L	L	L	L	L	L
Garbuglia et al. (2014)	UC	L	L	L	L	L	L
Heidrich et al. (2014)	UC	L	L	L	L	L	L
Kadkhoda et al. (2014)	UC	UC	L	UC	L	L	L
Karabay et al. (2014)	L	H	L	L	L	UC	L
Reyes-Mendez et al. (2014)	L	L	L	L	L	L	L
Van Helden et al. (2014)	UC	L	L	UC	L	L	L
Kamal et al. (2015)	L	L	L	L	L	L	L
Thong et al. (2015)	L	L	L	L	L	L	L
Aghemo et al. (2016)	L	UC	L	L	L	L	L
Demircili et al. (2016)	H	L	L	L	H	L	L
Kim et al. (2016)	UC	L	L	L	L	L	L
Medici et al. (2016)	L	L	L	L	L	L	L

Nguyen et al. (2016)	UC	L	L	L	L	L	L
Alados-Arboledas et al. (2017)	L	L	L	UC	L	L	L
Alonso et al. (2017)	L	H	L	L	L	L	L
Çetiner et al. (2017)	L	L	L	L	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
Lamoury et al. (2017)	L	L	L	UC	L	L	L
Loggi et al. (2017)	L	L	L	UC	L	L	L
Mohamed et al. (2017)	L	L	L	UC	L	L	L
Rockstroh et al. (2017)	L	H	L	H	L	UC	L
Talal et al. (2017)	L	L	L	L	L	L	L
Wasitthankasem et al. (2017)	L	L	L	UC	L	L	L
Adland et al. (2018)	L	L	L	L	L	L	L
Alonso et al. (2018)	UC	L	L	L	L	L	L
Benito et al. (2018)	UC	L	L	L	L	L	L
Chang et al. (2018)	L	L	L	L	L	L	L
Chevaliez et al. (2018)	L	L	L	H	L	L	L
Lamoury et al. (2018)	UC	L	L	L	L	L	L
Lucejko et al. (2018)	L	L	L	L	L	L	L
van Tilborg et al. (2018)	L	L	L	UC	L	L	L
Biondi et al. (2019)	UC	L	L	UC	L	UC	L
Catlett et al. (2019)	L	L	L	L	L	L	L
Feng et al. (2019)	L	L	L	L	L	L	L
Kyuregyan et al. (2019)	UC	UC	L	H	H	L	L
Lucejko et al. (2019)	UC	L	L	L	L	L	L
Pérez-García et al. (2019)	L	L	L	L	L	L	L
Suttichaimongkol et al. (2019)	L	H	L	UC	L	L	L
Chayanupatkul et al. (2020)	L	L	L	L	L	L	L
Gras et al. (2020)	UC	H	L	UC	L	UC	L
Lin et al. (2020)	L	L	L	H	L	L	L
Pollock et al. (2020)	L	L	L	L	L	UC	L
Wong et al. (2020)	UC	L	L	L	L	L	L
Abid et al. (2021)	L	UC	L	L	L	L	L
Chen et al. (2021)	UC	L	L	L	L	L	L
Kallala et al. (2021)	UC	L	L	L	UC	L	L
Kannan et al. (2021)	UC	L	L	L	UC	L	L
Konstantinidou et al. (2021)	H	L	L	L	H	L	L
Kumar et al. (2021)	L	UC	L	UC	L	L	L
Kumbhar et al. (2021)	UC	UC	L	L	UC	L	L
Mancebo et al. (2021)	UC	L	L	UC	L	L	L
Ponnuvel et al. (2021)	UC	L	L	L	L	L	L
Rossetti et al. (2021)	L	L	L	UC	L	L	L
Ko et al. (2022)	L	L	L	L	L	L	L
Chuaypen et al. (2022)	UC	L	L	L	L	L	L
Torrecillas et al. (2022)	UC	L	L	L	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. Summary of studies included in the univariate meta-analysis detecting HCV core antigen with Abbott ARCHITECT HCV Ag assay in serum and/or plasma samples

Author (year) [reference]	Country	No.	Age (yrs.)	Males (%)	HCV genotype	HIV (%)	HBV (%)	Sample type	Sample Condition	GS Cut-off (IU/mL)
Mederacke et al. (2009) [93]	Germany	109	N/D	N/D	1, 2, 3	0	0	Plasma	Frozen	15
Song et al. (2011) [98]	South Korea	109	N/D	N/D	1, 2, 3	N/D	N/D	Serum	Frozen	15
Murayama et al. (2012) [94]	Japan	80	N/D	N/D	1, 2	N/D	N/D	Plasma	Frozen	15 and 12
Vermehren et al. (2012) [102]	Germany	160	44	46	1	0	0	Serum	Frozen	12
Durante-Mangoni et al. (2013) [80]	Italy	114	50.8	57	1, 2, 3	0	0	Serum	Frozen	15
Ottiger et al. (2013) [96]	Switzerland	97	N/D	61.9	1, 2, 3	6	0	Plasma	Frozen	15
Tedder et al. (2013) [99]	UK	54	N/D	N/D	1, 2, 3	0	0	Plasma	Frozen	31
Karabay et al. (2014) [83]	Turkey	60	54.9	68.3	1	0	0	Serum	N/D	12
Thong et al. (2015) [100]	Thailand	189	45	71.4	1, 3, 6	45.0	N/D	Serum	Frozen	12
Aghemo et al. (2016) [74]	Italy	58	59	64	1, 2, 3, 4, 5	0	0	Serum	N/D	12
Kim et al. (2016) [84]	South Korea	92	51.4	44.6	1, 2	N/D	N/D	Serum	Frozen	15
Nguyen et al. (2016) [95]	Ireland	139	47	73	1	N/D	N/D	Serum/plasma	N/D	12
Alados-Arboledas et al. (2017) [76]	Spain	236	53	80.5	1, 2, 3, 4	31.3	N/D	Plasma	Frozen	15
Alonso et al. (2017) [75]	Spain	28	53.1	67.9	1, 2, 3, 4	35.7	28.6	Serum	N/D	15
Lamoury et al. (2017) [87]	Australia, Belgium, Canada, Germany, Norway, Switzerland, and UK	92	41	83	1, 2, 3	0	0	Plasma	Frozen	15
Loggi et al. (2017) [89]	Italy	96	60.5	64	1, 2, 3, 4	N/D	36	Serum	N/D	15
Chevaliez et al. (2018) [79]	France	631	49.8	54.5	1	0	0	Plasma	Frozen	15
Lucejko et al. (2018) [90]	Poland	33	49.4	59	1, 3, 4	0	0	Serum/plasma	Frozen	15
van Tilborg et al. (2018) [101]	Canada, Germany, and USA	202	54.8	61	1, 2, 3, 4, 5, 6	0	1.4	Serum	Frozen	15
Biondi et al. (2019) [77]	Canada	68	55.8	59	1, 2, 3, 4, 6	N/D	1.7	Serum	Frozen	15
Feng et al. (2019) [81]	China	782	47.8	50.1	1, 2, 3	N/D	N/D	Serum	N/D	15
Lucejko et al. (2019) [91]	Poland	265	N/D	53	N/D	0	0	Plasma	Frozen	15
Chayanupatkul et al. (2020) [78]	Thailand	101	47.1	78.2	1	35.6	0	Serum	Frozen	12
Gras et al. (2020) [82]	France	13	30.3	100	1, 3, 4	0	N/D	Plasma	Frozen	15
Lin et al. (2020) [88]	Taiwan	110	63.6	57.3	1	N/D	7	Serum	N/D	15 and 12

Konstantinidou et al. (2021) [86]	Greece	233	65.9	59.7	N/D	N/D	N/D	Serum	Frozen	15
Mancebo et al. (2021) [92]	Spain	262	54.8	61.3	1, 2, 3, 4, 5	N/D	N/D	Plasma	N/D	15
Rossetti et al. (2021) [97]	Italy	178	59	60	1, 2, 3, 4	11	0	Serum/plasma	Frozen	15 and 12
Ko et al. (2022) [85]	Taiwan	98	61.7	36.7	1, 2, 6	N/D	0	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 = no available data; UK = United Kingdom; USA = United States of America; yrs = years.

Supplementary Table 2. Sensitivity analysis for heterogeneity

Deleted study	**Q, p-value**	**I^2 [95%CI]**
Miedouge et al. (2010)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Park et al. (2010)	Q = 70.013, p < 0.001	I^2 = 97.95 [95-99]
Ergunay et al. (2011)	Q = 68.058, p < 0.001	I^2 = 97.95 [95-99]
Kesli et al. (2011)	Q = 72.806, p < 0.001	I^2 = 97.95 [95-99]
Kuo et al. (2012)	Q = 70.429, p < 0.001	I^2 = 97.95 [95-99]
Alados-Arboledas et al. (2013)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Hadziyannis et al. (2013)	Q = 64.296, p < 0.001	I^2 = 97.95 [95-99]
Buket et al. (2014)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Chevaliez (2014)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Florea et al. (2014)	Q = 69.512, p < 0.001	I^2 = 97.95 [95-99]
Garbuglia et al. (2014)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Heidrich et al. (2014)	Q = 70.267, p < 0.001	I^2 = 97.95 [95-99]
Kadkhoda et al. (2014)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Reyes-Mendez et al. (2014)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Van Helden et al. (2014)	Q = 69.729, p < 0.001	I^2 = 97.95 [95-99]
Kamal et al. (2015)	Q = 70.558, p < 0.001	I^2 = 97.95 [95-99]
Demircili et al. (2016)	Q = 68.431, p < 0.001	I^2 = 97.95 [95-99]
Medici et al. (2016)	Q = 70.264, p < 0.001	I^2 = 97.95 [95-99]
Çetiner et al. (2017)	Q = 71.882, p < 0.001	I^2 = 97.95 [95-99]
Duchesne et al. (2017)	Q = 72.059, p < 0.001	I^2 = 97.95 [95-99]
Hullegie et al. (2017)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Mohamed et al. (2017)	Q = 70.362, p < 0.001	I^2 = 97.95 [95-99]
Rockstroh et al. (2017)	Q = 55.738, p < 0.001	I^2 = 96.95 [94-99]
Talal et al. (2017)	Q = 69.033, p < 0.001	I^2 = 97.95 [95-99]
Wasitthankasem et al. (2017)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Adland et al. (2018)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Alonso et al. (2018)	Q = 70.184, p < 0.001	I^2 = 97.95 [95-99]
Benito et al. (2018)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Chang et al. (2018)	Q = 70.580, p < 0.001	I^2 = 97.95 [95-99]
Lamoury et al. (2018)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Catlett et al. (2019)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Kyuregyan et al. (2019)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Pérez-García et al. (2019)	Q = 70.339, p < 0.001	I^2 = 97.95 [95-99]
Suttichaimongkol et al. (2019)	Q = 66.882, p < 0.001	I^2 = 97.95 [95-99]
Pollock et al. (2020)	Q = 69.949, p < 0.001	I^2 = 97.95 [95-99]
Wong et al. (2020)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Abid et al. (2021)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]
Chen et al. (2021)	Q = 66.135, p < 0.001	I^2 = 97.95 [95-99]
Kallala et al. (2021)	Q = 70.741, p < 0.001	I^2 = 97.95 [95-99]
Kannan et al. (2021)	Q = 70.355, p < 0.001	I^2 = 97.95 [95-99]
Kumar et al. (2021)	Q = 70.288, p < 0.001	I^2 = 97.95 [95-99]
Kumbhar et al. (2021)	Q = 70.116, p < 0.001	I^2 = 97.95 [95-99]

Ponnuvel et al. (2021)	Q = 71.659, p < 0.001	I^2 = 97.95 [95-99]
Chuaypen et al. (2022)	Q = 54.201, p < 0.001	I^2 = 96.95 [94-99]
Torrecillas et al. (2022)	Q = 70.026, p < 0.001	I^2 = 97.95 [95-99]
Sun et al. (2022)	Q = 70.056, p < 0.001	I^2 = 97.95 [95-99]

95%CI = 95% confidence interval; I^2 = inconsistency index; Q = Cochran's Q test

Supplementary Table 3. Results of bivariate meta-regression (inconsistency index) and subgroup analysis in detecting active HCV infection with Abbott ARCHITECT HCV Ag 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]	0.65	0.72
LMIC	Yes No	0 [0-100]	1.16	0.56
All patients with anti-HCV Ab +	Yes No	0 [0-100]	0.01	1.00
Biological sample type	Yes: only serum No: not only serum	0 [0-100]	1.06	0.59
Frozen	Yes No	75 [44-100]	7.88	**0.02**
Sample size	Yes: ≤200 No: >200	0 [0-100]	0.77	0.68
QUADAS-2 risk	Yes: low No: unclear/high	0 [0-100]	2.82	0.24
Risk of bias - QUADAS-2	Yes: low No: unclear/high	0 [0-100]	3.54	0.17
Applicability concerns - QUADAS-2	Yes: low No: unclear/high	74 [42-100]	7.64	**0.02**
COBAS Ampliprep/COBAS TaqMan HCV Real-time PCR	Yes No	26 [0-100]	2.82	0.26
Abbott RealTime HCV Assay	Yes No	49 [0-100]	2.82	0.14
Other non-Abbott and non-COBAS real-time PCR assays	Yes No	20 [0-100]	2.82	0.28

95%CI = 95% confidence interval; Anti-HCV Ab = anti-HCV antibodies; cAg = core antigen; HCV = hepatitis C virus; I^2 = inconsistency index; IU = international units; LMIC = low- or middle-income country; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; PCR = Polymerase chain reaction; X^2 = Pearson's chi-squared test.

Supplementary Table 4. Sensitivity analysis for diagnostic performance measures

Deleted study	Se [95%CI]	Sp [95%CI]	PLR [95%CI]	NLR [95%CI]
Miedouge et al. (2010)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Park et al. (2010)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	148.4 [72.0-305.9]	0.04 [0.03-0.06]
Ergunay et al. (2011)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	134.4 [69.4-260.2]	0.04 [0.03-0.06]
Kesli et al. (2011)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	152.7 [76.6-304.2]	0.04 [0.03-0.06]
Kuo et al. (2012)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	137.2 [70.5-267.0]	0.04 [0.03-0.06]
Alados-Arboledas et al. (2013)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Hadziyannis et al. (2013)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	154.4 [75.9-314.3]	0.04 [0.03-0.06]
Buket et al. (2014)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Chevaliez (2014)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Florea et al. (2014)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	152.6 [75.6-307.9]	0.04 [0.03-0.06]
Garbuglia et al. (2014)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Heidrich et al. (2014)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	139.8 [71.5-273.2]	0.04 [0.03-0.06]
Kadkhoda et al. (2014)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Reyes-Mendez et al. (2014)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Van Helden et al. (2014)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	140.5 [71.7-275.5]	0.04 [0.03-0.06]
Kamal et al. (2015)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	130.5 [68.2-249.6]	0.04 [0.03-0.06]
Demircili et al. (2016)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.1 [71.9-277.1]	0.04 [0.03-0.06]
Medici et al. (2016)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	140.4 [71.7-275.0]	0.04 [0.03-0.06]
Çetiner et al. (2017)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	149.1 [72.7-305.5]	0.04 [0.03-0.06]
Duchesne et al. (2017)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	152.1 [75.0-308.7]	0.04 [0.03-0.06]
Hullegie et al. (2017)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Mohamed et al. (2017)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	142.7 [70.8-287.3]	0.04 [0.03-0.06]
Rockstroh et al. (2017)	0.95 [0.94-0.97]	0.99 [0.99-1.00]	150.8 [72.5-313.7]	0.05 [0.03-0.06]
Talal et al. (2017)	0.95 [0.94-0.97]	0.99 [0.99-1.00]	136.2 [70.2-264.4]	0.05 [0.03-0.07]
Wasitthankasem et al. (2017)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Adland et al. (2018)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Alonso et al. (2018)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	134.0 [69.4-259.0]	0.04 [0.03-0.06]
Benito et al. (2018)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Chang et al. (2018)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	146.4 [72.2-296.8]	0.04 [0.03-0.06]
Lamoury et al. (2018)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Catlett et al. (2019)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Kyuregyan et al. (2019)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Pérez-García et al. (2019)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	139.9 [71.5-273.8]	0.04 [0.03-0.06]
Suttichaimongkol et al. (2019)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	154.0 [75.3-315.1]	0.04 [0.03-0.06]
Pollock et al. (2020)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	140.0 [71.5-274.0]	0.04 [0.03-0.06]
Wong et al. (2020)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Abid et al. (2021)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]
Chen et al. (2021)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	152.7 [75.5-309.1]	0.04 [0.03-0.06]
Kallala et al. (2021)	0.95 [0.94-0.97]	0.99 [0.99-1.00]	126.5 [66.9-239.0]	0.05 [0.03-0.06]
Kannan et al. (2021)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	136.4 [70.2-265.0]	0.04 [0.03-0.06]
Kumar et al. (2021)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	135.7 [70.0-263.1]	0.05 [0.03-0.06]
Kumbhar et al. (2021)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	136.4 [70.2-265.1]	0.04 [0.03-0.06]

Ponnuvel et al. (2021)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	150.8 [77.1-295.0]	0.04 [0.03-0.06]
Chuaypen et al. (2022)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	139.7 [76.5-255.1]	0.04 [0.03-0.06]
Torrecillas et al. (2022)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	138.8 [71.1-271.0]	0.04 [0.03-0.06]
Sun et al. (2022)	0.96 [0.94-0.97]	0.99 [0.99-1.00]	141.8 [72.4-277.8]	0.04 [0.03-0.06]

95%CI = 95% confidence interval; NLR = negative likehood ratio; PLR = positive likehood ratio; Se = sensitivity; Sp = specificity.

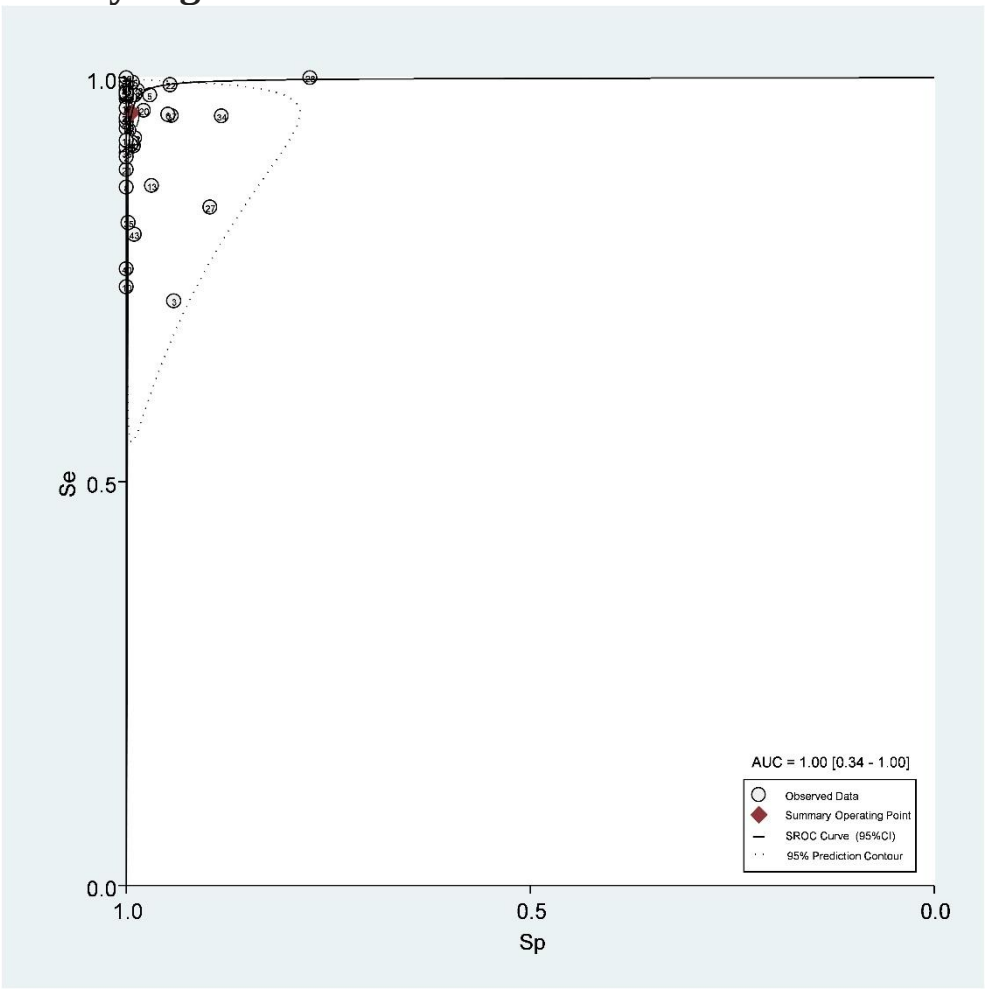
Supplementary Table 5. Results of bivariate meta-regression (sensitivity and specificity) and subgroup analysis in detecting active HCV infection with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test.

Parameter	Category	No.	Se [95%CI]	*p*-value	Sp [95%CI]	*p*-value
Year of publication	Yes: ≤2015	16	0.95 [0.92-0.98]	**<0.001**	0.99 [0.99-1.00]	**0.010**
	No: >2015	30	0.96 [0.95-0.98]		0.99 [0.99-1.00]	
LMIC	Yes	18	0.95 [0.92-0.98]	**<0.001**	0.99 [0.98-1.00]	**<0.001**
	No	28	0.96 [0.95-0.98]		0.99 [0.99-1.00]	
All patients with anti-HCV Ab +	Yes	21	0.96 [0.94-0.98]	**<0.001**	0.99 [0.99-1.00]	**0.020**
	No	25	0.96 [0.94-0.98]		0.99 [0.99-1.00]	
Biological sample type	Yes: only serum	27	0.96 [0.94-0.98]	**<0.001**	0.99 [0.99-1.00]	**<0.001**
	No: not only serum	19	0.96 [0.93-0.98]		1.00 [0.99-1.00]	
Frozen	Yes	26	0.96 [0.94-0.98]	**<0.001**	0.99 [0.98-1.00]	**<0.001**
	No	20	0.95 [0.93-0.98]		1.00 [0.99-1.00]	
Sample size	Yes: ≤200	24	0.95 [0.93-0.98]	**<0.001**	0.99 [0.98-1.00]	**<0.001**
	No: >200	22	0.96 [0.94-0.98]		0.99 [0.99-1.00]	
QUADAS-2 risk	Yes:low	13	0.96 [0.94-0.99]	**<0.001**	1.00 [0.99-1.00]	0.800
	No: unclear/high	33	0.95 [0.94-0.97]		0.99 [0.99-1.00]	
Risk of bias - QUADAS-2	Yes: low	14	0.96 [0.93-0.98]	**<0.001**	1.00 [0.99-1.00]	0.940
	No: unclear/high	32	0.96 [0.94-0.97]		0.99 [0.98-1.00]	
Applicability concerns - QUADAS-2	Yes: low	37	0.96 [0.94-0.97]	**<0.001**	0.99 [0.98-1.00]	**<0.001**
	No: unclear/high	9	0.95 [0.91-0.99]		1.00 [1.00-1.00]	
COBAS Ampliprep/COBAS TaqMan HCV Real-time PCR	Yes	12	0.96 [0.93-0.99]	**<0.001**	1.00 [0.99-1.00]	0.660
	No	34	0.96 [0.94-0.97]		0.99 [0.98-1.00]	
Abbott RealTime HCV Assay	Yes	29	0.96 [0.95-0.98]	**<0.001**	0.99 [0.98-1.00]	**<0.001**
	No	17	0.95 [0.92-0.98]		1.00 [0.99-1.00]	
Other non-Abbott and non-COBAS real-time PCR assays	Yes	5	0.91 [0.83-0.99]	**<0.001**	0.99 [0.98-1.00]	0.420
	No	41	0.96 [0.95-0.98]		0.99 [0.99-1.00]	

95%CI = 95% confidence interval; Anti-HCV Ab = anti-HCV antibodies; cAg = core antigen; HCV = hepatitis C virus; IU = international units; LMIC = low- or middle-income country; No.= number of articles; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; PCR = Polymerase chain reaction; Se = sensitivity; Sp = specificity.

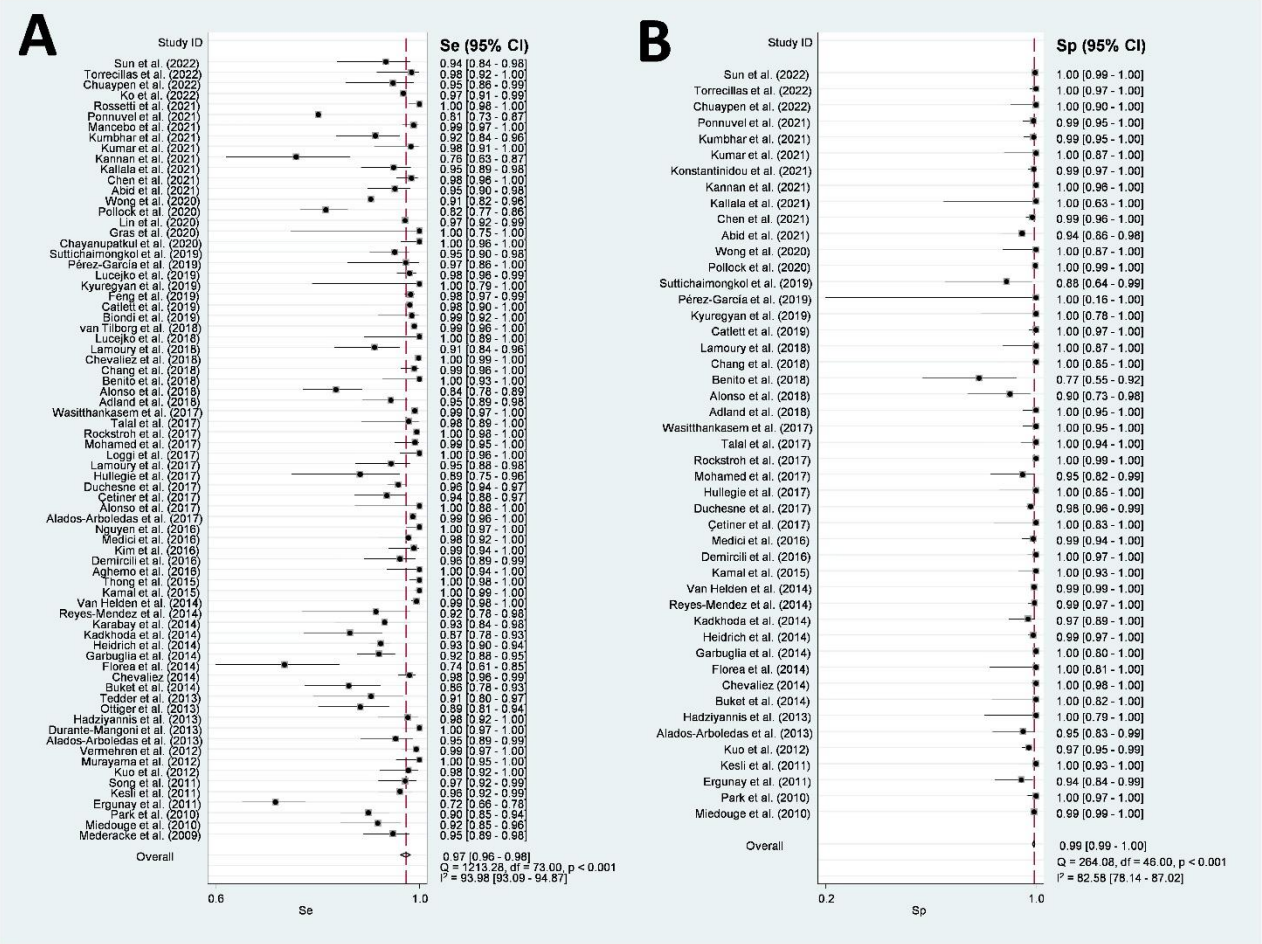
Supplementary Figures

Supplementary Figure 1



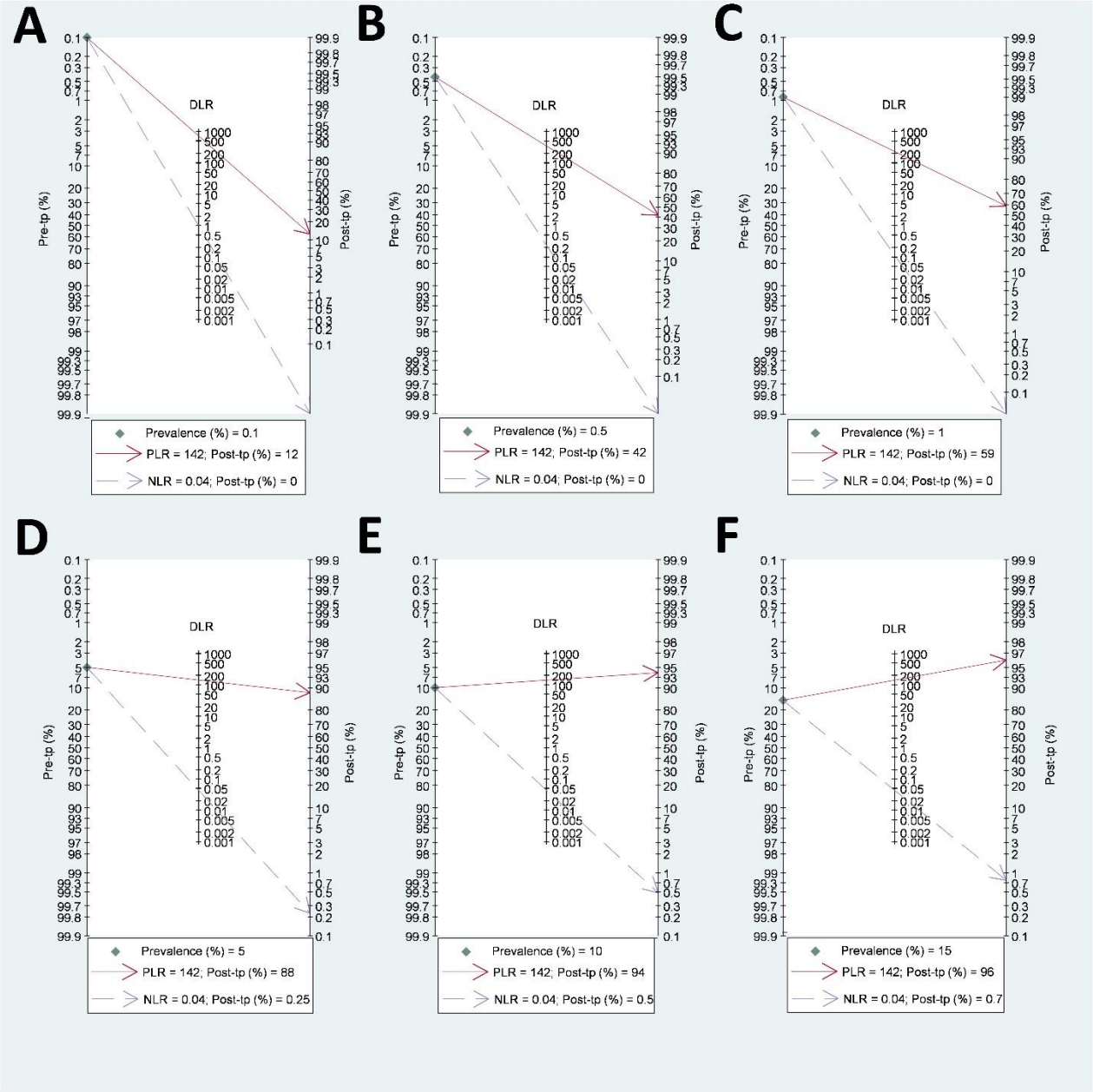
Supplementary Figure 1. SROC curve plot in detecting active HCV infection with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test. **Abbreviations**: 95%CI = 95% confidence interval; AUC = area under the curve; HCV = hepatitis C virus; Se = sensitivity; Sp = specificity; SROC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

Supplementary Figure 2



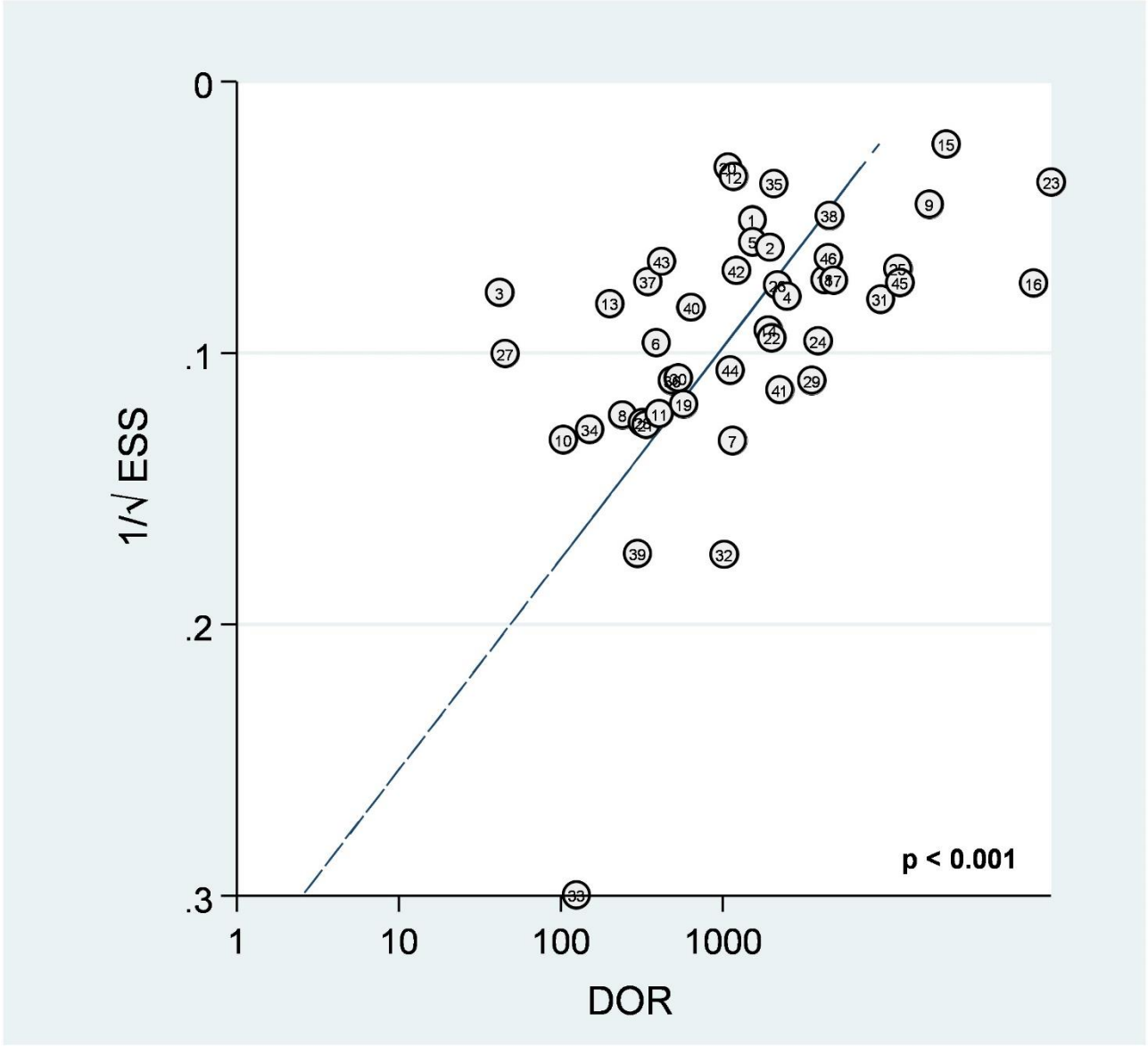
Supplementary Figure 2. Univariate analysis of sensitivity **(A)** and specificity **(B)** in detecting active HCV infection with Abbott ARCHITECT HCV Ag assay compared with a confirmatory nucleic acid test. **Abbreviations**: 95% CI = 95% confidence interval; df = degrees of freedom; HCV = hepatitis C virus; I^2 = inconsistency index; Q = Cochran's Q test; Se = sensitivity; Sp = specificity.

Supplementary Figure 3



Supplementary Figure 3. Fagan´s plot in detecting active HCV infection 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; Post-tp = post-test probability; Pre-tp = pre-test probability.

Supplementary Figure 4



Supplementary Figure 4. Deeks's funnel plot asymmetry test for publication bias in detecting active HCV infection 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.