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RESEARCH ARTICLE

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Accuracy of reverse-transcription polymerase chain reaction and loop-mediated isothermal amplification in diagnosing severe fever with thrombocytopenia syndrome: A systematic review and meta-analysis

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Abstract

Nucleic acid molecular diagnostic technology plays an important role in the detection of severe fever with thrombocytopenia syndrome (SFTS). However, no relevant reports have been published on the accuracy of reverse-transcription polymerase chain reaction (RT-PCR) and reverse-transcription loop-mediated isothermal amplification (RT-LAMP) in the diagnosis of SFTS. Thus, we conducted a meta-analysis and systematic review to evaluate the accuracy of the two methods. On June 19, 2022, we comprehensively searched the PubMed, Embase, Cochrane Library, Web of Science, Scoups, Ovid, Proquest, China National Knowledge Infrastructure Database, Wan Fang Data, Traditional Chinese Medicine Database (Sinomed), VIP Database, and Reading Showing Database for articles on nucleic acid diagnostic techniques, such as RT-PCR and RT-LAMP, used to diagnose SFTS. Statistical analysis was performed using STATA 14.0 and Meta-Disc 1.4. Sixteen articles involving 2942 clinical blood samples were included in the analysis. RT-PCR and RT-LAMP were used as index tests, whereas RT-PCR or other detection methods were used as reference standards. The pooled values for the sensitivity, specificity, positive and negative likelihood ratios of the RT-PCR test were 0.97 (95% confidence interval [CI]: 0.92–0.99), 1.00 (95% CI: 0.98–1.00), 483.87 (95% CI: 58.04–4033.76), and 0.03 (95% CI:0.01–0.08), respectively. Those for the RT-LAMP test were 0.95 (95% CI: 0.91–0.97), 0.99 (95% CI: 0.93–1.00), 111.18 (95% CI: 13.96–885.27), and 0.05 (95% CI: 0.03–0.09), respectively. Both RT-PCR and RT-LAMP have high diagnostic value in SFTS and can be applied in different scenarios for laboratory confirmation or on-site screening.

KEYWORDS

diagnose, meta-analysis, RT-LAMP, RT-PCR, sever fever with thrombocytopenia syndrome

1 | INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is an infectious disease that was first reported in 2007[1] and diagnosed in 2009[2] in Henan Province, China. It is caused by Dabie bandavirus, a type of tick-borne *Bunyavirales*,[3,4] and has a mortality rate[2,4-6] of 6%–30%. More than 20 provinces and cities in Chinese mailand have reported cases before 2018,[6] as well as human-to-human transmission cases.[7] Thus far, cases in Chinese taiwan, Japan,[9] South Korea,[10] Vietnam,[11] the United States,[12] and other regions have been reported. Vaccines and therapeutic drugs[13,14] that specifically treat this disease are lacking; thus, early diagnosis plays an important role in preventing the spread of the disease and implementing early as early intervention as possible.

Diagnostic techniques used to identify SFTS include traditional pathogen detection, such as virus isolation and serum antigen testing, as well as antibody detection techniques, such as enzyme-linked immunosorbent assay (ELISA), and neutralization test.[2] With the progress of technology, significant developments have been likewise made in nucleic acid molecular diagnosis testing, expanding its applications to various scenarios and detection targets[15–17] and turning it into the gold standard of many virological diseases, such as coronavirus disease 2019, an acute infectious disease that is spreading globally.[18] Meanwhile, ELISA and other traditional virus detection techniques have some disadvantages; they are time-consuming, expensive, and complicated to perform.[4,19] Nevertheless, nucleic acid detection diagnostic methods are rapid, quantitative, and highly sensitive.[4]

Reverse-transcription polymerase chain reaction (RT-PCR) can detect low-copy viral RNA quantitatively and is used for the early diagnosis of SFTS when viral immunoglobulin M/G cannot be detected.[20] Alternatively, reverse-transcription loop-mediated isothermal amplification (RT-LAMP) can be completed in 15–60 min,[21,22] making it suitable for rapid on-site screening in facilities lacking expensive instruments and equipment. These two methods have been widely applied in the diagnosis of SFTS. However, a comprehensive evaluation of the diagnostic performance of these two methods is needed.

This study evaluates the accuracy of the two nucleic acid diagnostic technologies for the diagnosis of SFTS, including the analysis of sensitivity, specificity and heterogeneity.

2 | METHODS

2.1 | Database search strategy

A comprehensive database search was conducted by two authors. Any discrepancies were resolved by a third person. We searched 12 scientific databases including the PubMed, Embase, Cochrane Library, Web of Science, Proquest, Scoups, Ovid, China National Knowledge Infrastructure Database, Wan Fang Data, Traditional Chinese Medicine Database (SinoMed), VIP Database, and Reading Showing databases on June 19, 2022. The keywords used were "severe fever with thrombocytopenia syndrome," "severe fever with thrombocytopenia syndrome bunyavirus," "SFTS," "polymerase chain reaction," "loop-mediated isothermal amplification," "real-time polymerase chain reaction," and "nucleic acids." The results of the screening of the studies are shown in Figure 1. This study was registered in the PROSPERO database (CRD42022307270).

2.2 | Study selection

The inclusion criteria in our meta-analysis were as follows: (1) The diagnostic study is focused on nucleic acid testing and the index test methods used were RT-PCR or RT-LAMP; (2) the reference standard must be mentioned; and (3) information, such as a number of samples, sensitivity, and specificity, are mentioned.

The exclusion criteria were as follows: (1) The study investigated another disease or the samples analyzed were not obtained from the patients; (2) non-Chinese or non-English studies; (3) case reports, reviews, and theses; and (4) duplicate publications or articles with incomplete data.

2.3 | Data extraction

Two independent authors (Tian and Ren) reviewed all the titles/abstracts of the articles and if their views varied, another reviewer decided whether the article would be included. All the articles

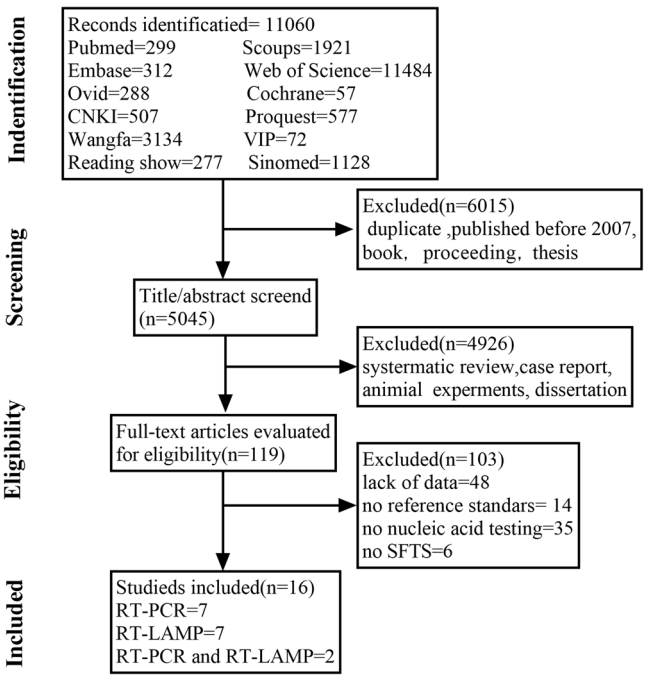

FIGURE 1 Flow chart of the research process as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

selected in the meta were read separately and independently and were then discussed until a consensus was reached. The extracted data included sample size, sample type, publication information, index and reference data, reference standards, and target genes. The results of the comparison of the two methods, including true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) results, were also extracted.

2.4 | Quality assessment

The risk of bias in these articles was evaluated by using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2)[23] tool.

2.5 | Meta-analysis

STATA 14.0 software, Meta-Disc 1.4, and Review Manager 5.3 (RevMan 5.3) were used to perform the meta-analysis. RevMan 5.3 was used to analyze the QUADAS-2 results. If the p value of the Spearman correlation coefficient >0.05 and the shape of the summary receiver operating characteristic (SROC) was not determined as "shoulder-arm," no heterogeneity was caused by the threshold effect. We used Cochran's Q test and the I^2 test for the diagnostic odds ratio (DOR) to calculate the heterogeneity caused by the nonthreshold effect. If the I^2 of the DOR < 50% and p-value > 0.1, no heterogeneity exists, and the fixed-effects model was then used. Otherwise, we used the random-effects model. Next, we calculated the pooled sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR). And the area under the SROC curve (AUC) was used to evaluate the accuracy of the results. The publication bias was also determined using Deeks' funnel plot.

3 | RESULTS

3.1 | Literature search

A total of 11060 articles were retrieved from the different databases, of which 6015 were excluded due to publication before 2007, duplicates, and theses and proceedings article types. Non-molecular diagnostic studies, animal experiments, and other irrelevant studies were excluded by reading the title/abstract of the articles. After reading the full text of the articles, 103 were discarded, including 48 that did not use clinical patient samples or lacked data, 35 that were not on nucleic acid-related diagnostic techniques, 14 that lacked reference standards, and 6 that were not on or related to SFTS. A final total of 16 articles were included, seven on RT-PCR[19,20,24–28] and seven on RT-LAMP,[16,21,29–33] and two that were on both RT-PCR and RT-LAMP.[15,34] A flowchart of the research process is shown in Figure 1.

3.2 | Character information

All 16 articles were published between 2012 and 2022 and are presented in Table 1. These studies were conducted in East Asia, including China, Korea, and Japan, which have high prevalence rates of SFTS. Two studies were prospective, whereas the others were retrospective and only one used plasma samples. The rest of the studies used serum samples. Five studies assessed different index tests. To accurately present all the data obtained, these studies were thus included in the meta-analysis.

3.3 | Quality assessment

The risk of bias was assessed with the QUADAS-2 tool on the RevMan 5.3 program, and a mild to moderate risk bias was determined in all the studies (Figure 2). Regarding patient selection, seven articles recruited patients from case–control studies, including patients with confirmed SFTS, SFTS contacts, and other patients with febrile illnesses, as well as healthy donors, which resulted in a high risk of bias. Regarding index tests, the risk of bias could not be clarified because some of the included studies only described the kits used but did not specify the specific thresholds for the positivity of samples. Regarding flow and timing, more than half of the articles used a combination of methods to validate clinical samples, indicating a moderate risk of bias, which may have affected the evaluation of the results. Regarding reference standards, we found that all studies met the criteria and found no risk of bias.

Regarding applicability concerns, we did not focus on any particular patient demographics, and all the studies recruited patients suspected of or diagnosed with SFTS, which is suitable for evaluating the accuracy of the diagnostic methods used. All the included studies investigated RT-PCR or RT-LAMP; thus, concerns regarding index tests were low. Finally, all the studies used common or classic reference standards, which have higher reliability.

3.4 | Threshold effects of RT-PCR and RT-LAMP

In the diagnostic tests, heterogeneity caused by threshold effects were determined using Spearman's correlation coefficients between the sensitivity (Se) and specificity (Sp) and the shape of the SROC curve. The Spearman's correlation coefficient of RT-PCR was −0.601 ($p = 0.03$), which indicates heterogeneity in RT-PCR studies, whereas that of RT-LAMP was 0.213 ($p = 0.56$), indicating no heterogeneity. The shapes of the SROC curves for RT-PCR and RT-LAMP are shown in Figure 3.

3.5 | Nonthreshold effects of RT-PCR and RT-LAMP

Cochran's Q test and the I^2 test were used to determine the heterogeneity of non-threshold effects by calculating DOR (Figure S1). For RT-PCR, $I^2 = 74.2\% > 50\%$ and $p < 0.1$, indicating heterogeneity

TABLE 1 Basic information and characteristics of the included studies

Author	Year	Location	Sample size	Sample type	Index test	Index test target gene	Reference method	Reference method target gene	TP	FP	FN	TN
Zhang	2017	China	873	Serum	RT-RDT	S	real-time RT-PCR	S	266	43	26	538
Yoo	2020	Korea	117	Serum	real-time RT-PCR	S	RT-PCR and sequencing	SM	14	0	0	103
	2020	Korea	117	Serum	real-time RT-PCR	SM	RT-PCR and sequencing	SM	14	2	0	101
Jalal	2021	Korea	121	Serum	Single round RT-PCR	M	RT-PCR, seroconversion and virus isolation	-	23	0	13	85
	2021	Korea	121	Serum	Nested RT-PCR	M	RT-PCR, seroconversion and virus isolation	-	36	0	0	85
	2021	Korea	121	Serum	Nested RT-PCR	S	RT-PCR, seroconversion and virus isolation	-	34	0	2	85
	2021	Korea	121	Serum	RT-qPCR	S	RT-PCR, seroconversion and virus isolation	-	34	0	2	85
Huang	2014	China	138	Serum	RT-LAMP	S	real-time RT-PCR	_	112	0	1	25
	2014	China	138	Serum	RT-PCR	S	real-time RT-PCR	_	110	0	3	25
Cui	2012	China	89	Serum	RT-CPA	M	viral culture and real-time RT-PCR	S	48	0	3	38
Zhou	2020	China	120	Serum	RT-RPA	L	RT-qPCR	L	24	1	1	94
Yang	2012	China	37	Serum	RT-LAMP	L	RT-qPCR, virus isolation	SLM	18	0	2	63
Sano	2021	Japan	72	Serum	RT-LAMP (Standard)	L	RT-qPCR	S	49	2	4	17
	2021	Japan	72	Serum	RT-LAMP (Simplified)	L	RT-qPCR	S	45	2	8	17
Xu	2013	China	32	Serum	RT-LAMP	L	RT-qPCR	-	17	0	1	14
Sun	2012	China	584	Serum	real-time RT-PCR	SLM	seroconversion, IgG, virus isolation	-	69	1	1	513
Lv	2013	China	58	Serum	RT-PCR	_	RT-qPCR		37	0	1	20
Jang	2022	Korea	133	Serum	RT-LAMP	L	real-time RT-PCR	SLM	21	0	2	112
Kim	2018	Korea	41	Plasma	real-time RT-PCR	SM	real-time RT-PCR, IFA	-	15	1	5	20
	2018	Korea	41	Plasma	iNAD	-	real-time RT-PCR, IFA	-	20	3	0	18
Li(1)	2013	China	293	Serum	real-time RT-PCR	S	virus isolation, IgG, seroconversion	-	61	0	0	232
Huang	2022	China	46	Serum	RT-RPA	L	real-time RT-PCR	L	34	0	0	12
Li(2)	2013	China	188	Serum	real-time RT-PCR	S	diagnosed clinically	-	40	0	0	98

Abbreviations: CPA, RPA, iNAD, a novel isothermal amplification technique; IFA, immunofluorescence assays; IgG, immunoglobulin G; RDT, on-site rapid diagnostic test of RT-qPCR; RT-qPCR, quantitative reverse-transcription polymerase chain reaction.

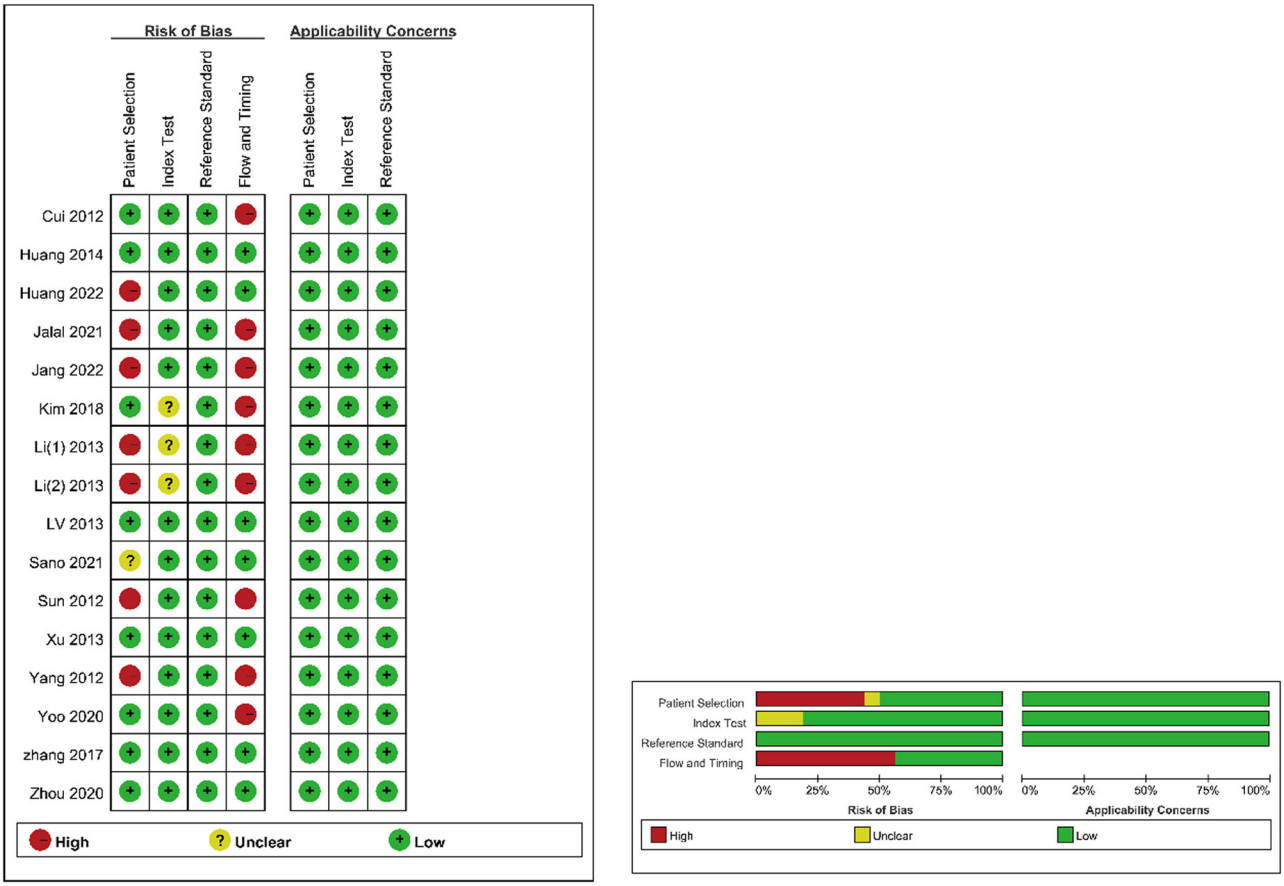

FIGURE 2 Quality assessment of the included studies.

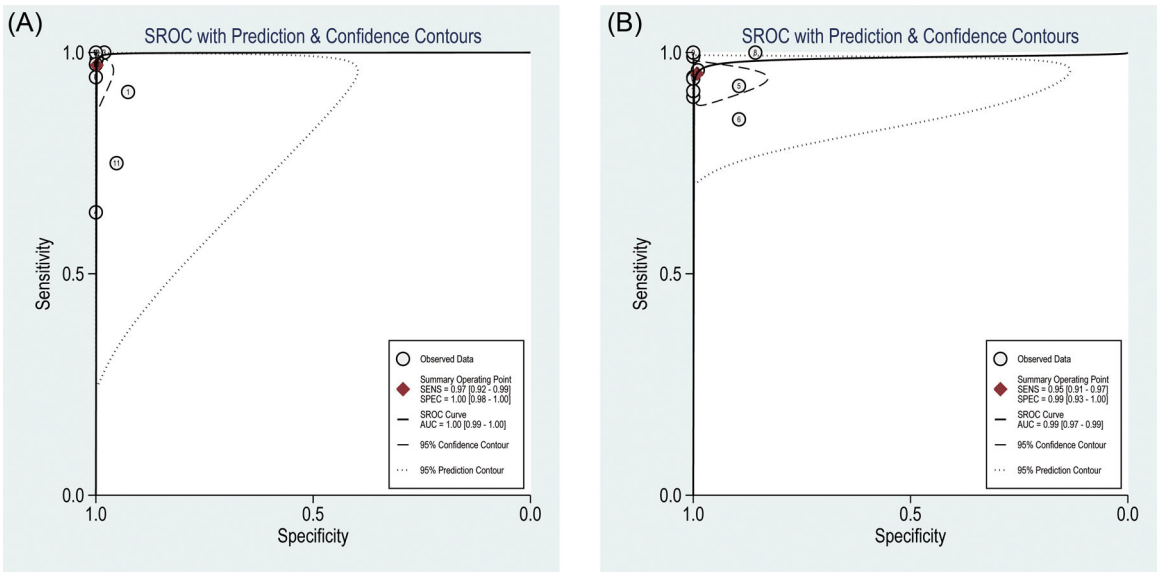

FIGURE 3 Summary receiver operating characteristic curves for reverse-transcription polymerase chain reaction (RT-PCR) (A) and reverse-transcription loop-mediated isothermal amplification (RT-LAMP) (B) in the diagnosis of severe fever with thrombocytopenia syndrome.

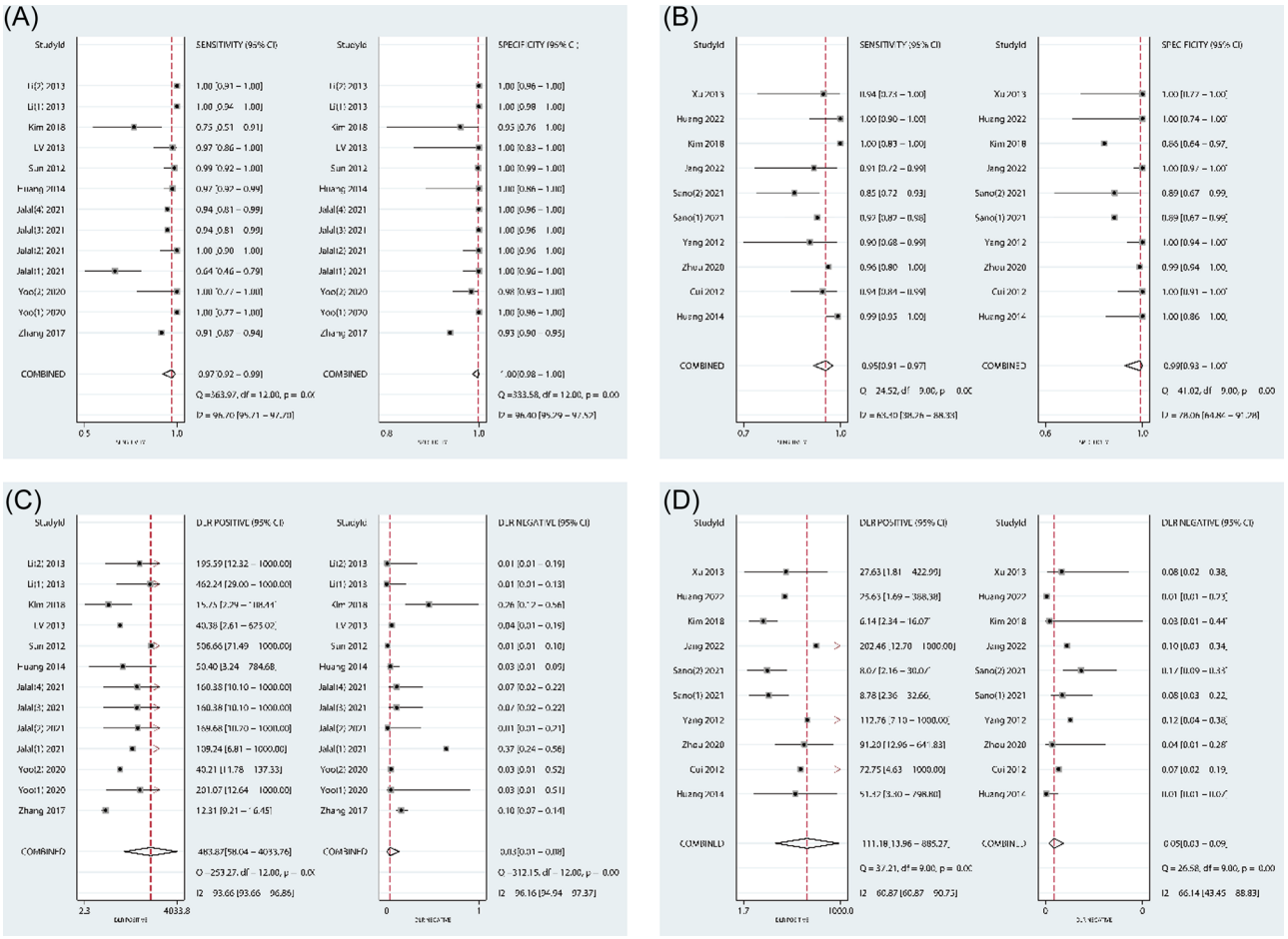

FIGURE 4 Forest plots for the pooled sensitivity and specificity of reverse-transcription polymerase chain reaction (A) and reverse-transcription loop-mediated isothermal amplification (B), positive and negative likelihood ratios of RT-PCR (C) and RT-LAMP (D). RT-LAMP, reverse-transcription loop-mediated isothermal amplification; RT-PCR, reverse-transcription polymerase chain reaction

caused by non-threshold effects. The results for RT-LAMP were $I^2 = 35.4\% < 50\%$ and $p = 0.125$, indicating no heterogeneity in RT-LAMP.

3.6 | Meta-analyses of sensitivity, specificity, PLR, and NLR

To evaluate the index of the diagnostic effects, we calculated the merged values, as shown in Figure 4. The pooled values for the sensitivity, specificity, PLR, NLR, and corresponding 95% confidence interval (CI) of RT-PCR were 0.97 (0.92–0.99), 1.00 (0.98–1.00), 483.87 (58.04–4033.76), and 0.03 (0.01–0.08), respectively. The values for RT-LAMP were 0.95 (0.91–0.97), 0.99 (0.93–1.0), 111.18 (13.96–885.27), and 0.05 (0.03–0.09), respectively. However, high heterogeneity was still observed in the pooled values ($I^2 > 50\%$).

3.7 | SROC curve

The accuracy evaluation results of the diagnostic techniques are shown in Figure 3. The AUCs of RT-PCR and RT-LAMP were 1.00 (0.99–1.00) and 0.99 (0.97–0.99), respectively, which indicated that these two detection methods had a high accuracy in diagnosing SFTS.

3.8 | Influence analysis

To identify the sources of heterogeneity, we performed a correlation analysis (Figure S2) and found that one article led to high heterogeneity in the diagnostic tests using RT-PCR and RT-LAMP. However, the heterogeneity persisted when we removed the article; thus, one or more other studies may have caused the heterogeneity.

3.9 | Subgroup analysis

As shown in Table 2, the subgroup analysis of RT-PCR revealed a lower heterogeneity among articles published before 2014 ($I^2 < 50\%$), as well as higher sensitivity, specificity, PLR, and DOR in pooled studies. In the subgroup analysis of the sample size, we found a higher sensitivity and DOR in the groups with samples > 200 but still high heterogeneity ($I^2 > 50\%$). Notably, heterogeneity among studies

using or including RT-PCR as a reference standard was higher, and the effect of the pooled studies was lower.

As shown in Table 3, the subgroup analysis of RT-LAMP revealed lesser heterogeneity, higher pooled effect, and more reliable diagnostic value in studies published before 2015. The same results were also observed in groups with sample size >80. However, for the selection of genes detected by the index test, we found that the difference between L genome group and other genomes group was not significant and still had high heterogeneity ($I^2 > 50\%$). Interestingly, we found that heterogeneity among studies from China was lower, whereas the effect of the pooled studies was higher.

3.10 | Publication bias

We used the Deeks' funnel plot to explore the publication bias in the studies on these two diagnostic techniques. As shown in Figure S3, no evident publication bias was found in RT-PCR and RT-LAMP studies ($p > 0.05$).

4 | DISCUSSION

SFTS is a serious threat to human health and has been listed among the priority diseases in the 2018 Blueprint list of the World Health Organization.[35] The report stated that SFTS cases have gradually increased, and the susceptible population were farmers and those who live in remote areas that lack medical resources,[36,37] such as mountainous, wooded, and hilly regions. Obtaining an early diagnosis of the disease is thus essential to prevent the spread of the disease and provide prompt treatment to affected individuals.

In our study, we evaluated two commonly used nucleic acid detection techniques. PCR is a classic nucleic acid detection technology with the advantages of higher sensitivity and specificity and faster processing time[38] compared with other conventional assays. In our research, the pooled sensitivity, specificity was high, PLR > 10, and NLR < 0.1, indicate that RT-PCR is highly reliable and has a lower probability of misdiagnosis or missed diagnosis.[17] Therefore, for patients suspected of SFTS based on clinical symptoms, such as fever and leukopenia, RT-PCR can be used to obtain a diagnosis quickly, thereby enabling timely treatment and qualitative testing of virus loads to help clinicians distinguish the severity and prognosis of the disease. This is because a high viral load is a risk factor for poor prognosis.[39] Additionally, researchers can also develop new and more effective primers/probes for PCR research and develop more precise commercial kits for the diagnosis of SFTS. However, currently, conventional RT-PCR, nested RT-PCR, and real-time RT-PCR are used for the detection of SFTS.[19]

In our study, we found heterogeneity in RT-PCR caused by threshold effects. This may be because of the different cycle threshold (Ct) values used as criteria for determining positivity in the studies analyzed. In some studies, the threshold values for commercial kits were not clearly indicated. Thus, further studies are needed to establish a standard threshold value for RT-PCR.

LAMP is a new isothermal amplification nucleic acid technique that provides rapid results at a low cost while reducing the incidence of contamination in the closed-tube system.[21] In our study, the pooled sensitivity, specificity, PLR, NLR, and AUC of RT-LAMP were 0.95, 0.99, 111.18, 0.05, and 0.99, respectively, which also indicates a high accuracy. RT-LAMP can qualitatively determine SFTS infection by identifying discoloration and precipitation,[34] making it suitable for developing regions, primary care facilities, small clinical laboratories, and other applications in the diagnosis of various viral diseases.[40–42] Even if the conditions are limited, primary clinical decisions can still be implemented. However, for use in scientific research, more sensitive multiplex detection experiments still need be developed for the more rapid detection of multiple viral diseases, as demonstrated in the study by Jang et al.,[16] in which the simultaneous detection of SFTS and scrub typhus was attempted.

The population included in our meta-analysis consisted of patients suspected of SFTS who presented with fever and other typical symptoms, as well as a history of engaging in outdoor activities; patients clinically diagnosed with SFTS; patients suspected of tick-borne diseases; patients with laboratory-confirmed SFTS; patients with other laboratory-confirmed hemorrhagic fever diseases, such as hemorrhagic fever with renal syndrome; SFTS contacts; and healthy donors. Two studies also collected consecutive samples during the acute and convalescent phases of the patients included. Most of the patients included in this study were clinically febrile or presented with other diseases similar to SFTS. Furthermore, nearly half of the studies included healthy individuals. Thus, our study population encompasses a wide range of cases and laboratory diagnostic methods.

While the heterogeneity of the sensitivity, specificity, PLR, NLR values for the two methods was high, most of the results were $I^2 > 50\%$ and $p < 0.1$. Particularly, those for RT-PCR were greater than 90%. Influence analysis revealed only one study on RT-PCR and RT-LAMP as a source of heterogeneity. After removing the article, heterogeneity in the RT-PCR and RT-LAMP analyses remained high. Chen et al.[17] obtained similar results for hand, foot, and mouth disease using RT-LAMP. The studies of Boger et al.[43] on RT-PCR for diagnosing COVID-19, Mustafa et al.,[44] and that of Pu et al.[45] on RT-LAMP and RT-PCR for diagnosing COVID-19, all showed high sensitivity and specificity but also high heterogeneity.

Subgroup analysis in the present study revealed that the source of heterogeneity may be related to sample size. RT-PCR and RT-LAMP studies with a large sample size tended to have high sensitivity, PLR, and DOR but low NLR. Furthermore, no heterogeneity was found in the RT-LAMP studies, suggesting that larger sample size can affect the outcomes of heterogeneity analyses. In analyzing the included studies according to year of publication and country, we found that RT-PCR and RT-LAMP studies in China had no heterogeneity. In the analysis based on reference standards, we found that, although RT-PCR is considered as the gold standard, the

TABLE 2 Subgroup analysis results of RT-PCR

Variables	Study	Sensitivity	Specificity	PLR	NLR	DOR
Publication year						
<2014	4	0.99 (0.97, 1.00, 0.0%)	1.00 (0.99, 1.00, 0.0%)	245.96 (71.51, 846.00, 0.0%)	0.02 (0.01, 0.06, 0.0%)	12856.29 (2007.41, 82336.87, 16.5%)
2014–2018	3	0.92 (0.89, 0.94, 82.4%)	0.93 (0.91, 0.95, 49.4%)	12.56 (9.45, 16.71, 0.0%)	0.10 (0.04, 0.25, 0.0%)	153.81 (45.42, 520.81, 37.0%)
>2018	6	0.90 (0.85, 0.94, 84.8%)	1.00 (0.99, 1.00, 25.4%)	79.11(33.08, 189.15, 0.0%)	0.07 (0.01, 0.30, 86.0%)	1783.52 (473.69, 6715.26, 0.0%)
Index test target						
S	7	0.94 (0.92, 0.96, 71.0%)	0.96 (0.95, 0.97, 90.7%)	100.2 (17.58, 571.15, 79.2%)	0.05 (0.03, 0.10, 39.6%)	2522.99 (311.97, 20404.63, 77.1%)
Other	6	0.91 (0.86, 0.94, 88.5%)	1.00 (0.99, 1.00, 40.4%)	71.16 (23.81, 212.65, 39.3%)	0.07 (0.02, 0.32, 90.5%)	1259.6 (156.73, 10123.36, 66.4%)
Sample size						
<120	4	0.93 (0.85, 0.97, 74.5%)	0.99 (0.96, 1.00, 35.6%)	38.86 (15.57, 96.98, 0.0%)	0.07 (0.01, 0.37, 72%)	564.72 (72.15, 4419.92, 45.0%)
120–200	4	0.88 (0.82, 0.93, 88.7%)	1.00 (0.99, 1.00, 0.0%)	147.85 (37.06, 589.79, 0.0%)	0.09 (0.02, 0.47, 89.3%)	1638.82 (337.22, 7964.29, 0.0%)
>200	5	0.95 (0.93, 0.96, 81.9%)	0.97 (0.96, 0.98, 94.5%)	111.21 (10.5, 1177.44, 87.8%)	0.03 (0.01, 0.10, 71.3%)	4606.00 (202.77, 104625.05, 87.4%)
Reference method						
Other	3	0.99 (0.97, 1.00, 0.0%)	1.00 (0.99, 1.00, 0.0%)	390.1 (97.74, 1556.97, 0.0%)	0.01 (0.00, 0.05, 0.0%)	32717.81 (4574.71, 233994.00, 0.0%)
RT-PCR	3	0.93 (0.90, 0.95, 72.0%)	0.93 (0.91, 0.95, 70.0%)	13.63 (7.85, 23.65, 6.0%)	0.06 (0.02, 0.13, 59.9%)	345.19 (57.2 , 2083.18, 51.7%)
RT-PCR and other	7	0.89 (0.83, 0.93, 83.4%)	0.99 (0.98, 1.00, 37.9%)	60.17 (27.19, 133.17, 0.0%)	0.09 (0.03, 0.28, 83.4%)	952.89 (217.87, 4167.61, 37.6%)

Abbreviations: DOR, diagnostic odds ratio; NLR, negative likelihood ratio; PLR, positive likelihood ratio; RT-PCR, reverse-transcription polymerase chain reaction.

TABLE 3 Subgroup analysis results of RT-LAMP

Variables	Study	Sensitivity	Specificity	PLR	NLR	DOR
Publication year						
<2015	4	0.97 (0.93, 0.99, 48.6%)	1.00 (0.97, 1.00, 0.0%)	58.1 (14.7, 229.61, 0.0%)	0.06 (0.03, 0.14, 39.3%)	1072.22 (223.25, 5149.66, 0.0%)
>2015	6	0.93 (0.88, 0.96, 59.8%)	0.97 (0.94, 0.99, 73.2%)	16.62 (6.01, 46.02, 57.5%)	0.09 (0.04, 0.18, 37.4%)	293.2 (71.04, 1208.64, 47.4%)
Index test target						
Other	3	0.98 (0.95, 0.99, 53.2%)	0.96 (0.90, 0.99, 76.9%)	22.93 (2.06, 255.84, 74.1%)	0.04 (0.01, 0.11, 32.1%)	907.33 (153.39, 5367.17, 0.0%)
L	7	0.92 (0.88, 0.95, 37.2%)	0.99 (0.97, 1.00, 60.7%)	26.67 (9.83, 72.41, 40.5%)	0.11 (0.07, 0.17, 3.5%)	346.82 (94.4, 1274.14, 42.8%)
Sample size						
<80	5	0.92 (0.87, 0.96, 66.8%)	0.95 (0.90, 0.98, 67.1%)	9.64 (4.57, 20.34, 19.7%)	0.10 (0.05, 0.20, 31.9%)	144.78 (45.12, 464.59, 16.8%)
>80	4	0.97 (0.93, 0.99, 43%)	1.00 (0.98, 1.00, 0.0%)	90.91 (26.49, 312.04, 0.0%)	0.05 (0.02, 0.12, 32.5%)	2017.44 (447.04, 9104.51, 0.0%)
Country						
China	6	0.97 (0.94, 0.99, 38.5%)	1.00 (0.98, 1.00, 0.0%)	58.58 (20.74, 165.47,0.0%)	0.05 (0.03, 0.11, 18.5%)	1321.12 (361.86, 4823.34, 0.0%)
Other	4	0.91 (0.85, 0.95, 49.4%)	0.96 (0.92, 0.98, 80.8%)	10.5 (3.86, 28.53, 50.5%)	0.12 (0.07, 0.20, 7.8%)	139.98 (35.69, 549.04, 33.9%)

Abbreviations: DOR, diagnostic odds ratio; NLR, negative likelihood ratio; PLR, positive likelihood ratio; RT-LAMP, reverse-transcription loop-mediated isothermal amplification.

heterogeneity of this method as a reference standard is higher than that of sequencing, clinical diagnosis, and comparison of virus isolation methods. Furthermore, the sensitivity and specificity are lower, which are consistent with the findings of Pu et al.[45]

Subgroup analysis showed the heterogeneity in this study was still high, which may also be related to the individual differences among the included patients' diseases, such as the disease severity, sex, and age, the collection of samples, RNA extraction, and researchers' action.[17,46]

Our study has some limitations. First, the number of included studies is small, which may lower the reliability of the results. Second, the high heterogeneity of pooled studies in our study was not accounted for even by subgroup analysis. Lastly, some of the included studies were case-control studies, which may have affected the accuracy of the experiments.[47]

5 | CONCLUSION

Our systematic review and meta-analysis showed that RT-PCR and RT-LAMP have high sensitivity and specificity in the diagnosis of SFTS, as well as a wide range of applications. RT-PCR is suitable for the diagnosis of patients in the laboratory or hospital and for research and commercial purposes, whereas RT-LAMP can be used for on-site clinical screening of patients. However, the number of included studies is small, warranting the need for further high-quality literature reviews.

AUTHOR CONTRIBUTIONS

Wen Tian and Xingxiang Ren were responsible for the construction and design, screening and extraction of articles, Xu Gao was responsible for data extraction, Wen Tian was responsible for the writing of manuscripts, Yuanyuan Zhang and Zhihai Chen were responsible for quality evaluation, Wei Zhang designed the study and reviewed the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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