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Diagnostic Efficacy of LAMP Assay for Human Fungal Pathogens: a Systematic Review and Meta-analysis

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Abstract

Purpose Human fungal infections particularly caused by *Candida* and *Aspergillus* have emerged as major public health burden. Long turnaround time and poor sensitivity of the conventional diagnostics are the major impediments for faster diagnosis of human fungal pathogens.

Recent Findings To overcome these issues, molecular-based diagnostics have been developed. They offer enhanced sensitivity but require sophisticated infrastructure, skilled manpower, and remained expensive. In that context, loop-mediated isothermal amplification (LAMP) assay represents a promising alternative that facilitates visual read outs. However, to eradicate fungal infections, all forms of fungi must be accurately detected. Thus, a need for alternative testing methodologies is imperative that should be rapid, accurate and facilitate widespread adoption. Therefore, the aim of the present study is to conduct a meta-analysis to assess the diagnostic efficiency of LAMP in the detection of a panel of human fungal pathogens following PRISMA guidelines using scientific databases viz. PubMed, Google Scholar, Science Direct, Scopus, BioRxiv, and MedRxiv.

Summary From various studies reported on the diagnosis of fungi, only 9 articles were identified as eligible to meet the criteria of LAMP based diagnosis. Through this meta-analysis, it was found that most of the studies were conducted in China and Japan with sputum and blood as the most common specimens to be used for LAMP assay. The collected data underlined that ITS gene and fluorescence-based detections ranked as the most used target and method. The pooled sensitivity values of meta-analysis ranged between 0.71 and 1.0 and forest plot and SROC (summary receiver operating characteristic) curve revealed a pooled specificity values between 0.13 and 1.0 with the confidence interval of 95%, respectively. The accuracy and precision rates of eligible studies mostly varied between 70 to 100% and 68 to 100%, respectively. A quality assessment based on QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) of bias and applicability was conducted which depicted low risk of bias and applicability concerns. Together, LAMP technology could be considered as a feasible alternative to current diagnostics considering high fungal burden for rapid testing in low resource regions.

Keywords Fungi · *Candida* · *Aspergillus* · LAMP · Meta-analysis · Diagnosis

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Introduction

Invasive fungal infections are life-threatening due to occurrence of diabetes and immunocompromised conditions caused by HIV, cancer, transplants, corticosteroid use, postsurgical intensive care, broad-spectrum antibiotic use, etc. [1] Among the various nosocomial infections, fungal infection rates as the 4th most common with the diagnosis of fungal infections being challenging. Despite significant advances being made in the improvement of antifungal drugs, only a limited number of antifungal drugs are currently available [2]. Among the different mycotic infections caused by these opportunistic fungi, *Candida* and *Aspergillus* cause the

majority of fungal infections, globally. *Candida albicans* accounts for approximately 50–60% or more causes of candidiasis in humans. Similarly, *Aspergillus fumigatus* accounts for majority of cases of aspergillosis. The advent of new medical therapies and procedures to treat cancer, the increase in invasive medical procedures, and the widespread use of broad-spectrum antibiotics have all been linked with this increase in fungal infections. The emergence of HIV has also increased the incidence of mucosal candidiasis caused by *Candida* species [3]. Moreover, the emergence of drug resistant strains has further complicated the problem and has become a rising obstacle against efficient therapeutics [4]. Despite availability of therapeutics, due to the lack of rapid and accurate diagnostics, the effective control of the disease is impeded.

Traditional methods are culture-based or through microscopic examination but lack accuracy and time consuming as well [5]. Additionally, various non-culture-based diagnostic methods are available such as immunoassay (mannan, anti-mannan antibodies, and (1–3)-D-glucan (BDG) assay) [6–8] and PCR [9]. The immuno and BDG assays have low specificity [7, 10] while PCR-based diagnosis is not only time-consuming but also costly, despite the detection specificity is from moderate to high depending upon the cross-contamination. Sophisticated methods such as MALDI-TOF are useful only when proper database of all fungal pathogens is available [11, 12]. Similarly, sequencing-based methods for D1/D2 or internal transcribed spacer regions of rDNA are reliable options along with real-time PCR-based methods [13, 14]. However, due to technical and financial constraints these cannot be applied in resource limited places and delay in diagnosis may lead to poor outcome in patients with fungal infections since the therapy cannot be initiated. This represents strong limitation of the current diagnostic techniques to use in general and particularly in tier II and III cities. Due to these laborious and cumbersome requirements, the number of detection tests per day is limited. Under such significant circumstances, there is an urgent need for rapid, accurate, and cost-effective diagnosis of prevalent human fungal pathogens to rapidly identify new cases and reduce the time-to-treatment and prevention of further transmission.

LAMP is an isothermal DNA amplification method which relies on four or six pairs of primers to amplify minute quantities of DNA within a shorter period with simple operation making it more suitable for low-resource regions [15]. Thus, research in fungal diagnostics aims to find an efficient, reproducible, cost-effective tool with minimal infrastructure requirements. LAMP is a popularly adopted new age technology for rapid nucleic acid amplification which is widely used as pathogen (virus, bacteria, and malaria) detection tool including SARS CoV-2 [16–18]. However, the efficiency of LAMP assay in diagnosis of human fungal pathogens is still in infancy and not utilized fully.

In pursuit of developing better diagnostics, which are crucial for achieving faster and accurate detection of human fungal pathogens, we performed a systematic review and meta-analysis to access the diagnostic accuracy of LAMP to detect major fungi. Therefore, the present study not only offers an up-to-date diagnostic performance of LAMP for prevalent human fungi (*Candida* and *Aspergillus*) detection but also covers other fungal species such as *Histoplasma* and *Trichophyton*. The pooled sensitivity and specificity of LAMP were analyzed against different references. Further, diagnostic efficiency was determined based on reference methods, target genes and detection methods of LAMP. Taken together, we aimed to evaluate the diagnostic potency of LAMP as a tool for detection of fungal pathogens to address the current fungal diagnosis burden in low-resource places.

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [19] was followed for identification of eligible studies in the present systematic review and meta-analysis.

Search Strategy

Diverse scientific databases, e.g., PubMed, Google Scholar, Science Direct, Scopus, BioRxiv, and MedRxiv, were searched to screen for studies performed using LAMP for fungal diagnostics from the year June 2000 to September 2022. The terms such as LAMP, fungi, and human fungi were used in various combinations during our research without any limitations such as "LAMP + fungi," or "LAMP + *Candida*," or "LAMP + *Aspergillus*," or "LAMP + *Histoplasma*," or "LAMP + *Trichophyton*," or "LAMP + *Mucor*," or "LAMP + *Cryptococcus*" for PubMed, Science Direct, and Google Scholar without using any language restriction. The retrieved results were screened for duplication and conformity with the pre-specified eligibility criteria. The duplications were discarded from the search and proceeded with screened results.

Study Eligibility Criteria

Inclusion Criteria This systematic review and meta-analysis included the following: (1) both peer-reviewed and preprint original articles on LAMP technology used for detection of any prevalent human fungal pathogens such as *Candida*, *Aspergillus*, *Cryptococcus*, *Mucor*, *Histoplasma*, and

Trichophyton; (2) only full-text articles written in English language; and (3) articles that contain data on true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values for the assay or have sufficient data so that the number of TP, FP, FN, and TN could be determined.

Exclusion Criteria Exclusion was made for (1) studies based on non-isothermal amplification; (2) studies where data are irretrievable; (3) review articles, editorials, commentaries, and proceedings, etc.; (4) foreign language articles (other than English) based on LAMP mediated detection of fungi.

Data Extraction

Potential articles after reviewing titles and abstracts followed by full text for inclusion were extracted by two authors (GSB and SS). Consultation from two independent authors (SH and ZF) was made to eliminate the doubt about any discrepancy. The extracted information from included studies had authors, year of publication, location of study, sample size, types of specimens, target genes, detection method, and standard reference method. The data extracted for evaluation of diagnostic accuracy for LAMP was performed by comparison with the reference methods such as microscopy, culture, biochemical tests, and PCR. The important parameters in this meta-analysis such as TP, TN, FP, and FN of all studies were either extracted or calculated to provide their sensitivity and specificity values. The included studies ($n=9$) were then assessed for their methodological quality to reduce systematic biases and inferential errors from the collected data.

Statistical Analysis

The quantitative analysis of the included studies ($n=9$) from the data extracted such as the values of TP, FP, TN, FN, and sample size was performed. Furthermore, the values of sensitivity and sensitivity were mined or calculated from the available data. Moreover, pooled sensitivity and specificity of LAMP associated with 95% CI were estimated. To maintain the accuracy and precision, the following formulas were used: Accuracy = [TP + TN/TP + TN + FP + FN] × 100 and Precision = [TP/TP + FP] × 100 [20, 21]. Forest plot for sensitivity and specificity were plotted using R-software along with summary receiver operating characteristic (SROC) for the given study.

Quality Assessment

Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the methodological quality of the eligible studies. The risk of bias in the included studies ($n=9$) was assessed from four areas of bias, e.g., patient selection, index test, reference standards, and flow/timing [22, 23]. Furthermore, we also judged to generate low, unclear, or high-risk applicability. For each QUADAS-2 domain specific yes/no questions were tailored. Following these criteria, the eligible studies were then refereed for low, unclear, or high risks of bias. Two authors (ZF and SH) independently judged the quality of each study. The disagreements if any were resolved with additional input from GSB by consensus.

Results

Literature Survey

We followed the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19] to search the literature for the present study (Fig. 1). The major scientific databases viz. PubMed, Science Direct, Scopus, BioRxiv, and MedRxiv have been extensively searched applying the above inclusion criteria and 1985 articles were extracted which included the ones that were published only after the year 2000 since the inception of LAMP technology [15]. Further, only articles written in English language were considered and thus we excluded 47 articles. Reading the titles and abstracts of these studies allowed to exclude further 880 articles comprising the review articles, editorials, proceedings, etc. Following this exclusion, another 252 articles were eliminated from 1058 studies as they were not specific to fungal diagnostics. From remaining 806 studies, additional 776 articles were irrelevant as they did not used LAMP technology for the diagnosis of any fungal species and were excluded, leaving a panel composed of 30 eligible studies. Lastly, from the 30 included articles, further 21 articles were also eliminated because their TP, FP, TN, and TN values were either not specified in these articles or the sensitivity and specificity values could be not calculated. Altogether, we observed that only 9 articles were eligible for detailed meta-analysis (Fig. 1) considering all the exclusion criteria.

Study Characteristics and Meta-analysis

Table 1 shows the data extracted from the eligible studies mentioning the details of authors, year of publication, country of study, types of specimens, target genes, detection method, and reference methods. Figure 2 shows the country-wise distribution of 9 identified articles included in the present study. Of the studies, 44.4% ($n=4$) were conducted in China followed by 22.2% ($n=2$) conducted in Japan. Apart from this, one study each, i.e., 11.1%, were from countries like Brazil, Iran, and Korea. Most of the included articles do not mention about the patient details, but the type of specimen (Fig. 3) used in most

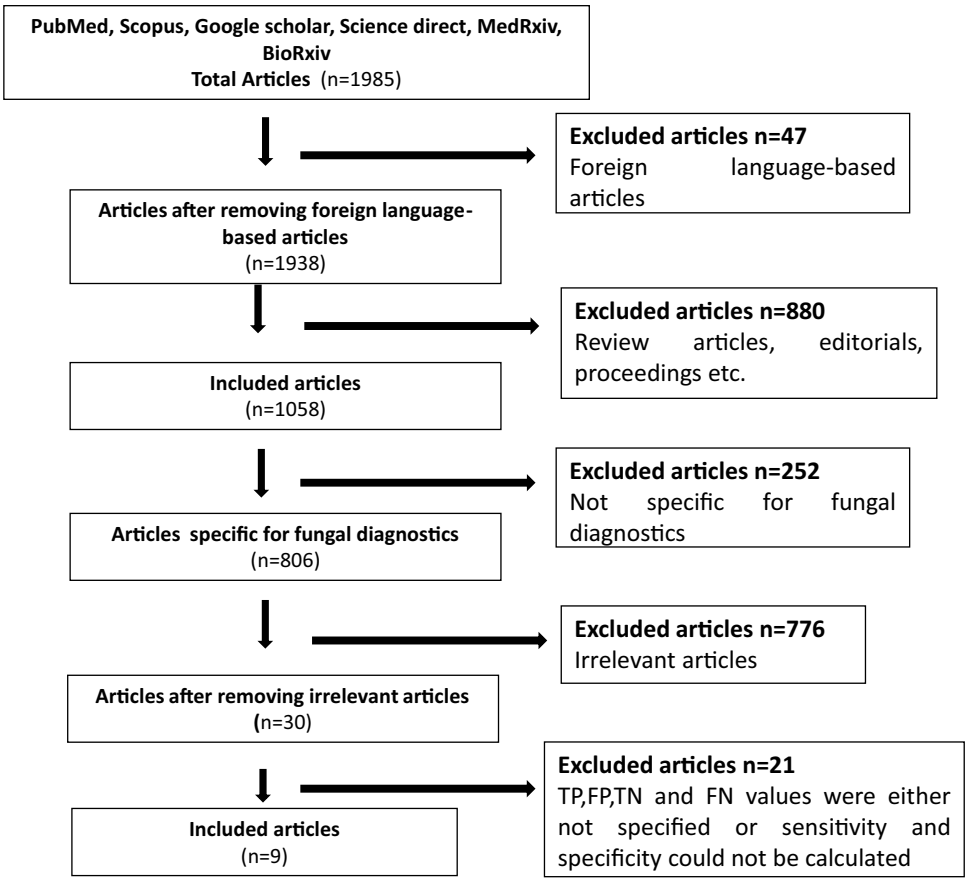

Fig. 1 PRISMA flowchart depicts search of the literature and screening strategy for meta-analysis

of the studies were sputum and blood ($n=3$), respectively. In addition to this, two studies used clinical strains ($n=2$) for fungal detection. Moreover, some studies have been tested on other specimens such as bronchoalveolar lavage ($n=1$), onychomycosis-derived samples ($n=1$), and bone marrow ($n=1$) for the detection of fungi by using LAMP. Furthermore, the standard culture assay and PCR-based methods were used as references either alone or in combination (Table 1). Next, we examined the various target genes used for the eligible studies. Ten different types of target genes including ACT1, Alfa, Afum, Anid, Anig, anxC4, Ater, IFA22, ITS, and S rRNA were selected by authors in the included studies ($n=9$). ITS gene was most frequently used in 21.4% ($n=3$) of included studies followed by anxC4 ($n=2$, 14.28%) and S rRNA ($n=2$, 14.28%) genes. 5.8S, 15S, and 28S variants of S rRNA gene were used among these studies (Fig. 4). Furthermore, while analyzing detection methods used for these 9 studies, fluorescence method ($n=7$, 77.7%) was most frequently used followed by colorimetry, gel electrophoresis, and turbidity ($n=4$, 44.4%) (Fig. 5). The lateral flow biosensor was used as a detection method in only two studies (22.2%). In 66.6% ($n=6$) of studies, more than one detection method was used while in 44.4% ($n=4$) studies, more than two methods were used. The combination of four different detection methods were used in 22.2% ($n=2$) of the included studies.

Furthermore, upon analysis of sensitivity and specificity using forest plot at the confidence interval (CI) of 95%, we found that the sensitivity values varied between 0.71 and 1.00 and the specificity values ranged from 0.13 to 1.00 (Fig. 6). Seven out of the 9 included studies showed pooled sensitivity greater than 80%. In terms of false-positive rate (1-specificity), 8 included studies showed a pooled false-positive rate less than 50% (Fig. 7). Additionally, the accuracy and precision rates of included studies were calculated. We observed that the accuracy rates varied between 70 and 100%. The analysis showed that 3 studies displayed 100% accuracy rate, while 4 studies depicted more than 90% accuracy and 4 studied showed less than 80% accuracy (Table 2). Likewise, the precision rates varied between 29.3 and 100%. The analysis showed that 5 studies exhibited more than 80% precision rate with only 4 studies depicting less than 80%. Of note, we observed that 4 studies displayed 100% precision rate (Table 2).

Quality Assessment of the Study

Majority of the included studies (8 out of 9 studies) have high risk of patient selection bias due to non-random patient selection and case–control study design (Fig. 8, Table 1). Only one of the included studies [24•] have low risk of

Table 1 Characteristics and outcomes of the included studies ($n=9$)

S.no	Author	Journal	Country	Reference method	Specimen	Target gene	Detection method	TP	TN	FP	FN	Sample size	Sensitivity	Specificity
1	Tang et al. (2016)	J Clin Microbiol	China	PCR	Bronchoalveolar lavage fluid, blood	anxC4	Colorimetry, fluorescence, gel electrophoresis, turbidity	33	17	15	4	69	89.19	53.12
2	Fallahi et al. (2019)	Arch Microbiol	Iran	Culture, PCR	Clinical	ITS2	Colorimetry, fluorescence, gel electrophoresis	24	46	0	0	70	100	100
3	Tone et al. (2019)	Med Mycol	Japan	Culture	Sputum	Afum, Afla, Anig, Ater, Anid	Fluorescence	15	20	3	6	44	71.4	87
4	Watanabe et al. (2019)	J Dermatol	Japan	Culture, PCR	onychomycosisderived samples	5.8S rRNA, 18S rRNA, 28S rRNA	Fluorescence	59	4	27	0	90	100	12.9
5	Zatti et al. (2019)	PLoS Negl Trop Dis	Brazil	Culture, PCR	Bone marrow, whole blood	ITS	Fluorescence, gel electrophoresis	5	24	2	1	32	83.3	92.3
6	Zhao et al. (2019)	Front Cell Infect Microbiol	China	Culture, PCR	Sputum	ACT1	Colorimetry, gel electrophoresis, lateral flow biosensor, turbidity	82	153	0	5	240	94.25	100
7	Jiang et al. (2021)	J Appl Microbiol	China	Culture, PCR	Sputum	anxC4	Colorimetry, lateral flow biosensor, turbidity	10	79	0	0	89	100	100
8	Ou et al. (2021)	Ann Palliat Med	China	Culture, PCR	Clinical	IFA22	Fluorescence, turbidity	27	184	65	2	278	93.1	73.9
9	Lim et al. (2022)	Pathogens	Korea	PCR	Blood	5.8S rRNA, ITS1, ITS2	Fluorescence	36	100	0	0	136	100	100

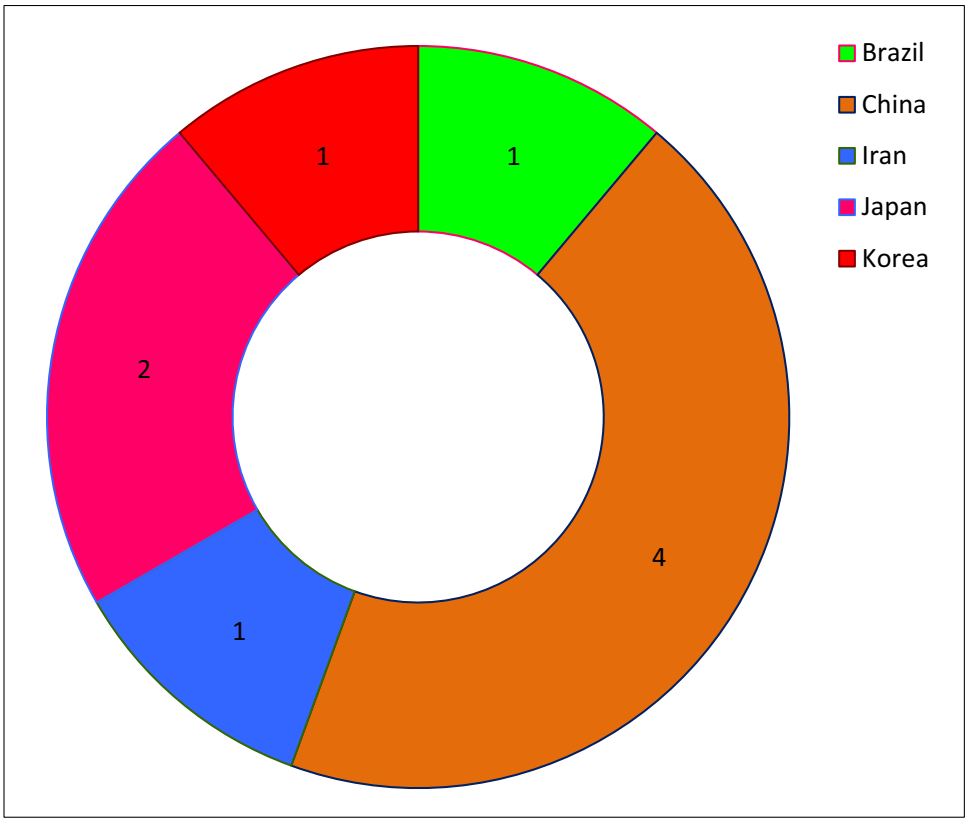

Fig. 2 Country-wise distribution of included studies ($n=9$) reported in the present investigation

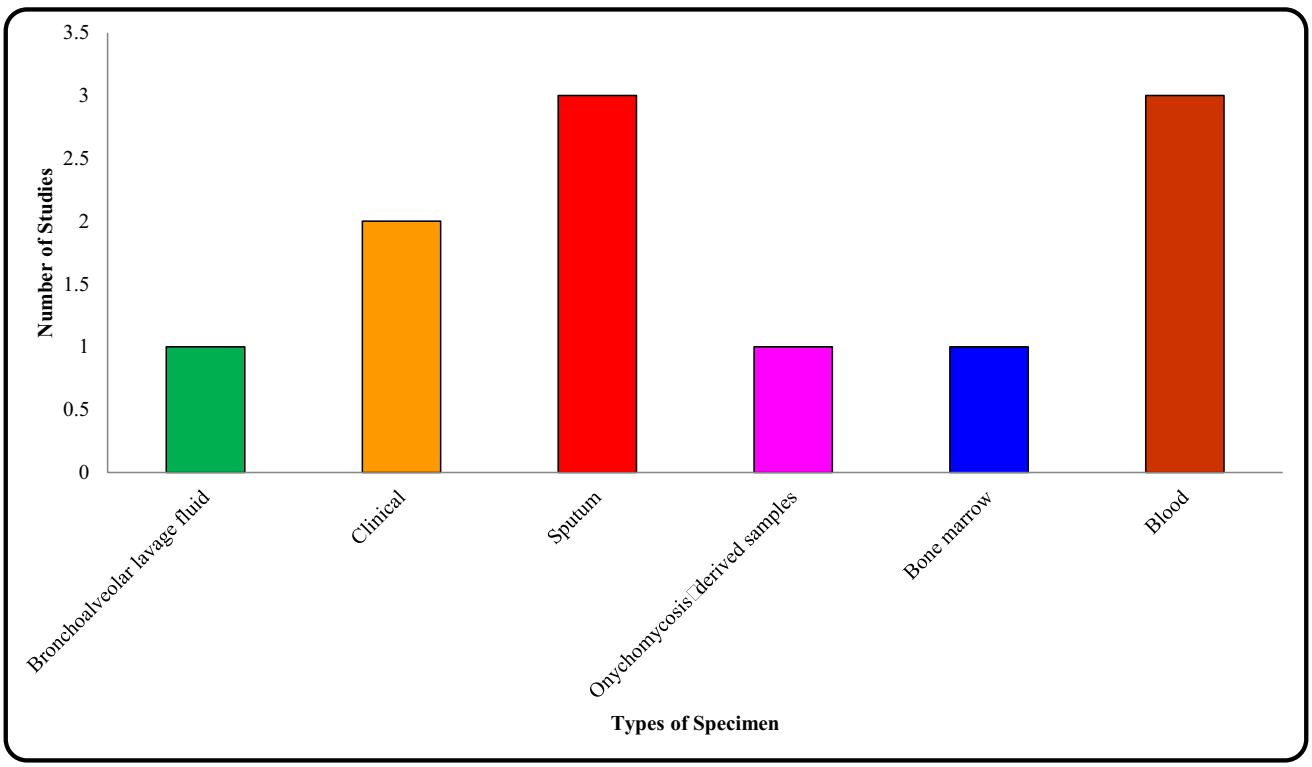

Fig. 3 Distribution of type of specimen for detection of fungi in the included studies ($n=9$)

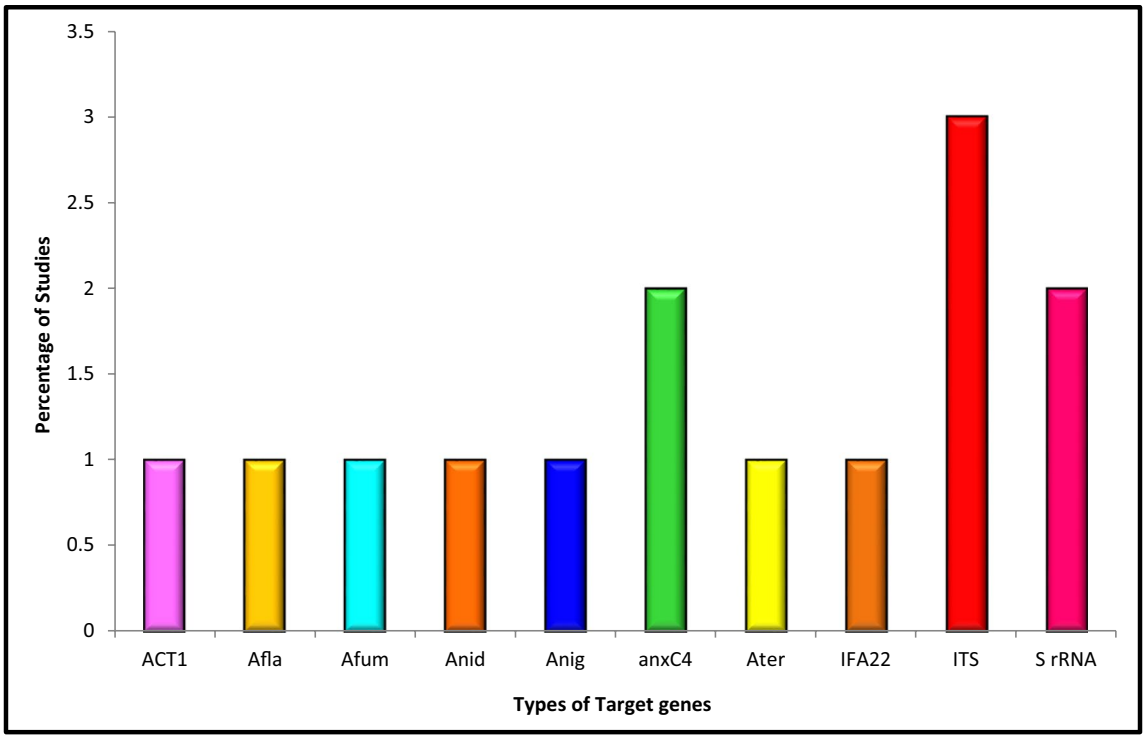

Fig. 4 Distribution of target genes reported in the included studies ($n=9$)

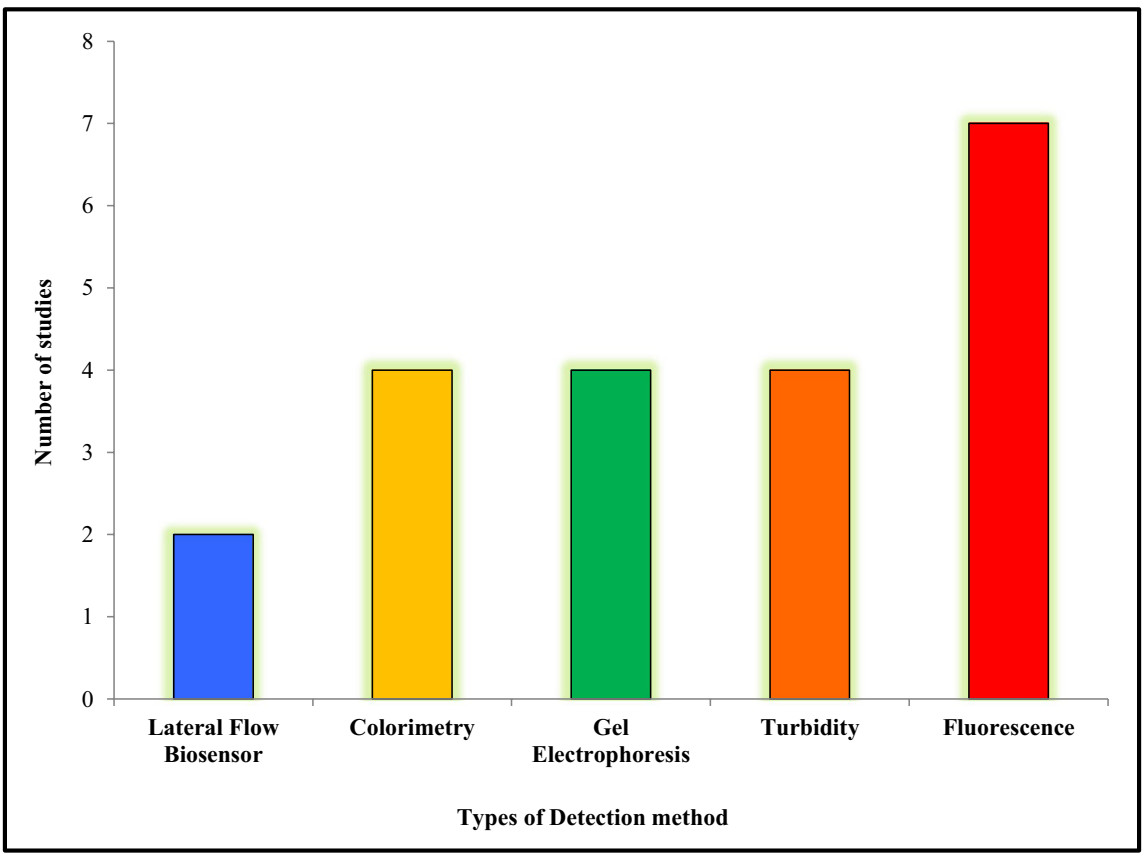

Fig. 5 Distribution of type of detection method for fungi in the included studies ($n=9$)

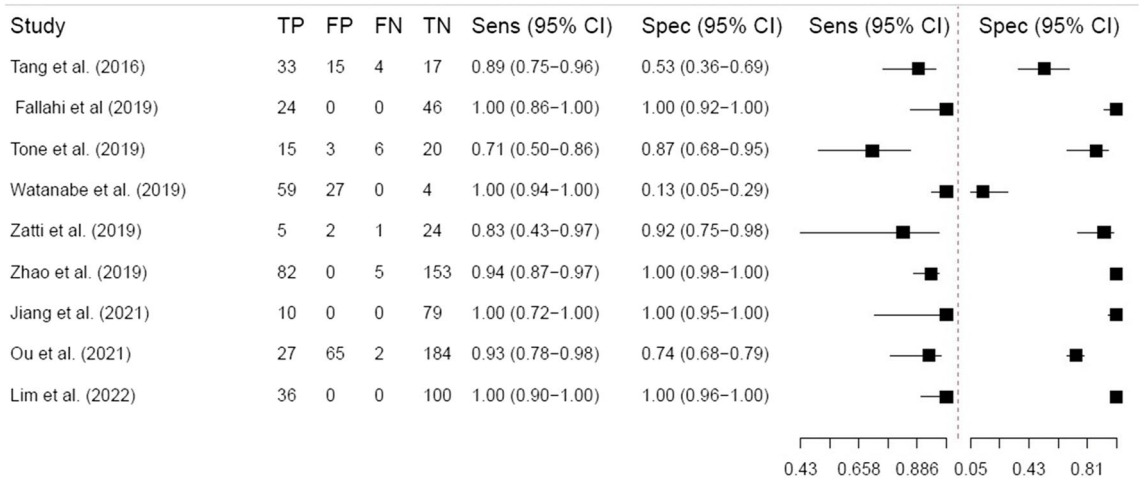

Fig. 6 The forest plot of sensitivity and specificity of included studies ($n=9$) on the diagnostic performance of LAMP technique

patient selection bias because this study provided sufficient details about patient inclusion/exclusion criteria. Further, all the included studies present low risk of index test bias because these tests clearly stated the quantitative detection readouts with reported thresholds. Moreover, these studies explicitly declared that their index and reference tests were done simultaneously in parallel to each other or that testing was blinded from each other. Similarly, all the included studies ($n=9$) have low risk of reference standard bias because they provided enough information about the standard reference test used in the study. Majority of the studies (8 out of 9) have low risk of flow and timing bias as there was enough information, whether reference standard results were interpreted with the knowledge of the results of the index test. One study [25••] was at unclear risk as it did not provide any information on whether the samples for a reference test and the index test were taken at the same time.

Index tests of all studies have generally been used for POCTs and thus have low concern of index test applicability. Reference standard tests of nearly all studies are culture-based or PCR or the combinations of them. Our review question did not focus on any patient demographics. None of the included studies attempted to exclude patients based on demographics and thus had no "concern of patient selection applicability" (Fig. 8, Table 1). Thus, we graded these studies as having low concern of standard test applicability.

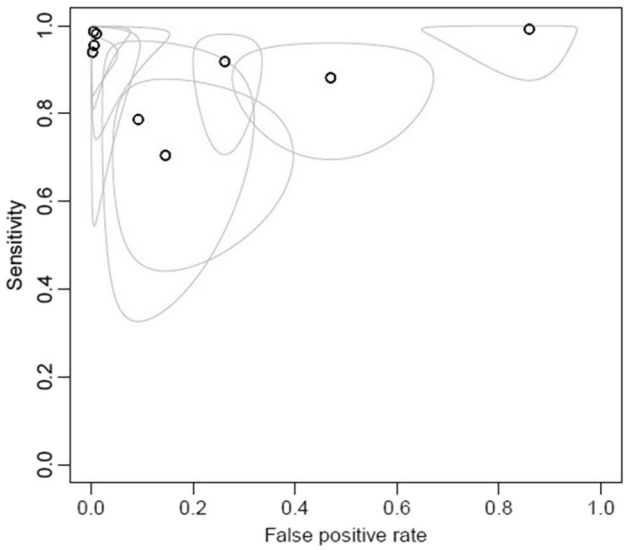

Fig. 7 Summary receiver operating characteristic (SROC) depicts LAMP diagnostic performance in fungal diagnosis

Discussion

Early and correct diagnosis of human fungal infections is pertinent for effective treatment of the disease and prevention of the spread of infection particularly in nations which have high fungal burden. The currently available diagnostics rely mostly on microscopy, culture, and PCR-based methods which are not only time consuming and less sensitive but also cumbersome and costly. LAMP assay provides a faster and innovative point of care diagnostic alternative as it is cost-effective, sensitive, and gives results in less than 1 h due to amplification under isothermal condition by strand displacement activity of Bst DNA polymerase and visual read outs. The analytical sensitivity and specificity of LAMP is higher than culture method and comparable with conventional and quantitative PCR-based techniques [26••]. The culture-based methods although serve as gold standard is time consuming and have only moderate specificity [5]. The

Table 2 Accuracy and precision of the included studies ($n=9$)

S. no	Study	Accuracy	Precision
1	Tang et al. (2016)	72.4638	68.75
2	Fallahi et al. (2019)	100	100
3	Tone et al. (2019)	79.5455	83.3333
4	Watanabe et al. (2019)	70	68.6047
5	Zatti et al. (2019)	90.625	71.4286
6	Zhao et al. (2019)	97.9167	100
7	Jiang et al. (2021)	100	100
8	Ou et al. (2021)	75.8993	29.3478
9	Lim et al. (2022)	100	100

other nonculture-based tests including the measurement of galactomannan in bronchoalveolar lavage may be promising but yet to be exploited fully [6]. Hence, the aim of the present study was to systematically review and perform the meta-analysis to assess the diagnostic accuracy of the LAMP assay for detection of prevalent human fungal pathogens.

This meta-analysis revealed that most of the studies were conducted in China and Japan (Fig. 2). We observed that for the detection of fungi sputum and blood could be considered as the most chosen samples (Fig. 3). When considering the target genes, we found a variety of genes that were used in the included studies. However, ITS ranked first among all evaluated genes in the included studies (Fig. 4). However, other target genes such as anzC4 and S rRNA were also prominent. Next, we considered the detection method that was used for assessing the LAMP results. Most of the studies used fluorescence-based methods followed by colorimetry, gel electrophoresis and turbidity, with no justification of their choices (Fig. 5). The prominence of fluorescence methods could be due to their increased sensitivity for the detection.

Forest plot was used to calculate the sensitivity and specificity. The pooled sensitivity values of meta-analysis ranged between 0.71 and 1.0 (Fig. 6), and forest plot and SROC curve revealed a pooled specificity value between 0.13 and 1.0 (Fig. 7) with the confidence interval of 95%. For the included studies, we observed that considerable specificity was reported when sputum was used as clinical sample apart from blood. Furthermore, on comparing the specificity of LAMP method based on specimen types, it is observed that specificity varies between 87 and

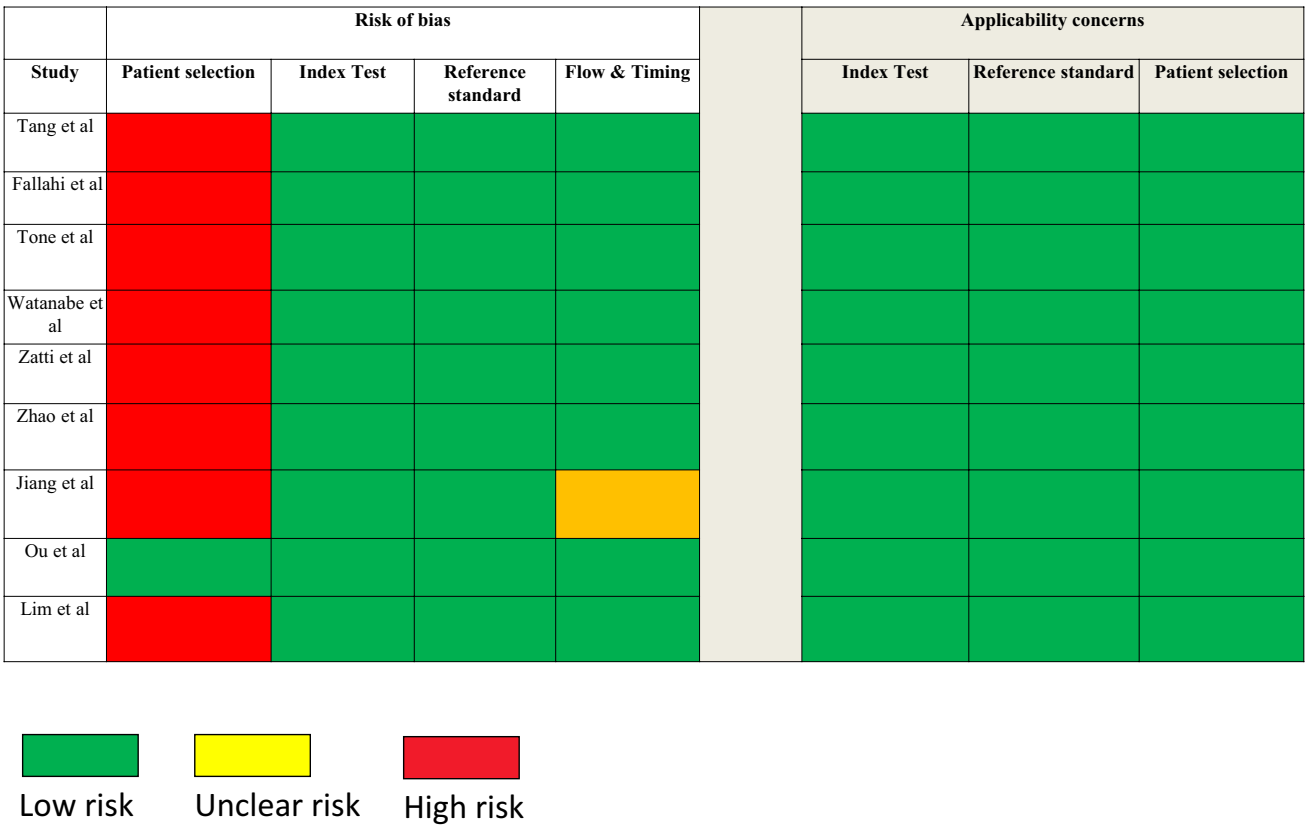

Fig. 8 Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) summary of items for risk of bias and applicability in included studies ($n=9$). Green color depicts the low risk of biasedness, yellow color depicts the unclear risk of biasedness, and red color depicts the high risk of biasedness

Table 3 Sub-group analysis representing specificities of sputum, blood, and bronchoalveolar lavage

S. no	Specimen	Specificity	References
1	Sputum	87–100	Tone et al. (2019), Jiang et al. (2021), Zhao et al. (2019)
2	Blood, bronchoalveolar lavage fluid	53–100	Lim et al. (2022), Tang et al. (2016), Zatti et al. (2019)

100% in case of sputum while it varies from 53 to 100% in case of blood and bronchoalveolar lavage fluid (Table 3). This endorses that sputum may be an easier sample to use especially in LMIC so large studies comparing sensitivity and specificity of LAMP in sputum and BAL need to be performed to see if sputum is a good alternative to use. Although the accuracy of the results could be further analyzed by increasing the sample sizes in future studies. The accuracy and precision were calculated for the included studies and for 9 studies. We found that the accuracy rate was higher than their corresponding precision rates for 4 studies and vice versa for 2 studies upon intra-comparison of accuracy with precision (Table 2). Comparison of the LAMP results have showed that the CHROMagar *Candida* and germ tube production methods are quite consistent, and the concurrence between the results of carbohydrate assimilation and chlamydoconidia generation assays with LAMP technique was 98.5% and 72.8%, respectively. The limit of detection of LAMP assay is 10 fg from the DNA of *C. albicans* strain with no amplification from other fungi [27]. Hence, it can be concluded that the LAMP method is not only specific and precise as common diagnostic methods but is faster, easier deployable, or more sensitive.

The current study also exhibited few limitations. Firstly, we observed high risk of patient selection bias in almost all the eligible studies (Fig. 8). Therefore, the use of unbias patient cohorts and double-blinded index test may be recommended for future studies. Secondly, few studies showed the highest performance with 100% sensitivity and specificity, respectively, hence displayed the lowest QUADAS risk and concerns in all the domains. Furthermore, lack of subgroup analysis and the use of solely peer-reviewed English language articles were also additional limitations. Although LAMP assay may serve as an effective method for the first line detection and identification of human pathogenic fungi in clinical samples, still further studies on the large-scale validation would be needed for confirming the suitability of LAMP to be developed for its future clinic application.

Conclusion

In a nutshell, the present study endorses the use of LAMP assay as a promising and affordable alternative for detection of human fungal pathogens, particularly in regions which are financially compromised, where drug-resistant strains are not prevalent and PCR-based tests cannot be done so frequently. However, further evaluation of LAMP assay for detection of fungal species will be required before deploying the technique for clinical surveillance.

Author Contribution GSB and SS: search, data extraction, validation. GSB and SJ: data analysis. ZF and SH: supervision. GSB and SH: writing, original draft. ZF and SH contributed to the conception and design of the study and review and editing of the manuscript.

Data availability All the data related to the study is available within the manuscript.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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