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Review

Diagnostic accuracy of polymerase chain reaction for detection of mpox in humans

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ABSTRACT

Objective. To evaluate diagnostic accuracy of polymerase chain reaction (PCR) in detecting mpox infection in humans by pooling the estimates of sensitivity and specificity across different study settings.

Methods. A systematic search was conducted in PubMed, Cochrane database, Scopus, and Google Scholar. Studies that evaluated the diagnostic accuracy of PCR test for the detection of monkeypox virus providing the sensitivity and specificity values and the total number of samples were included. The sensitivity and specificity values of PCR test were pooled for all the included studies. The meta-analysis was conducted in accordance with PRISMA guidelines using the metadta package in STATA software. A summary receiver operating characteristic (SROC) curve and forest plot were generated. The protocol was registered in PROSPERO (CRD-NIHR) database with Reference ID CRD42024590183.

Results. Twelve studies were included for meta-analysis. The pooled sensitivity and specificity estimate across all the studies using a random effects model was 0.99 (95% CI [0.95, 1.00]) and 1 (95% CI [0.96, 1.00]), respectively. The SROC curve confirmed high diagnostic accuracy of PCR. The quality assessment of diagnostic accuracy studies (QUADAS) tool depicted low risk of bias.

Conclusions. This systematic review and meta-analysis is the first study in the scientific literature to provide a pooling for diagnostic accuracy for PCR test for mpox and confirms it as an accurate tool in detecting the infection in humans.

Keywords Mpox (monkeypox); monkeypox virus; polymerase chain reaction; diagnosis; meta-analysis.

The World Health Organization (WHO) declared mpox, previously known as monkeypox, as a public health emergency of international concern (PHEIC) in 2024 with the recent upsurge of mpox infections causing more than 15 600 cases and 537 deaths so far this year, and following the emergence of a new monkeypox virus strain, clade 1b, in the Democratic Republic of the Congo (1). An earlier multi-country outbreak in 2022 was also declared as a PHEIC, when mpox was transmitted rapidly via sexual contact in endemic and nonendemic countries and warranted a worldwide public health response to contain the infection (2).

Monkeypox virus is a zoonotic double stranded DNA virus that belongs to the Orthopoxvirus genus of the Poxviridae family and is closely related to the smallpox/variola and cowpox viruses. Monkeypox virus was first identified in a laboratory monkey in 1958, but rodents are also potential hosts. Mpox is endemic in western and central Africa, where the monkeypox virus is present in wildlife but can also sporadically be transmitted to humans (3). The monkeypox virus has two phylogenetically distinct clades: clades I and II. Clade I (with subclades Ia and Ib) predominantly circulates in the Congo Basin and is believed to cause more severe disease in humans than clade II (with subclades IIa and IIb), which is more commonly seen in West Africa (4).

Exposure to the virus through physical contact with animals can occur through bites, scratches, or during activities like hunting, skinning, meal preparation, and consuming uncooked

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meat. Between humans, the spread can occur through bodily fluids, skin or internal mucosal surface lesions, respiratory droplets from infected animals or humans, and fomites (5). The virus can also be transmitted vertically through placenta to the fetus or to the newborn after birth (6). In 2022, the incidence of the mpox was more frequent among homosexual and bisexual men (7).

The typical presentation of mpox is well established, starting with a febrile prodromal phase followed by development of a characteristic rash, typically beginning on the face and spreading to the limbs and trunk. Lesions transition from macules to papules, vesicles, pustules, and finally crusts, which eventually fall off over 2–4 weeks. Other systemic symptoms such as myalgia, lymphadenopathy, and asthenia are also frequently seen (8). Some mpox cases (40% in one study) reported travel history from regions where the virus is endemic (8, 9).

Viral culture, electron microscopy, serological tests, and polymerase chain reaction (PCR) test are the various methods available for diagnosis of mpox infections (10). Viral culture should only be conducted in specified biosafety level 2 laboratories with appropriate experience and is not commonly used for diagnosis of the infection. The use of electron microscopy for routine diagnosis is also limited given the need for sophisticated laboratories and equipment. Serological tests are mostly used to detect the antibodies against the orthopoxviruses, but these tests cannot be solely relied upon as they do not detect the virus itself but only indicate exposure to the virus. Therefore, the gold standard for diagnosing mpox infection in humans, as declared by WHO, is real-time PCR, which should be the first test conducted on a suspected case (11). PCR is a nucleic acid amplification test (NAAT) through which unique sequences of viral DNA can be detected. It is a highly sensitive and specific test that can detect even small amounts of viral DNA, which is crucial for early diagnosis of the disease and therefore to reduce transmission of the infection (12).

The sensitivity of a diagnostic test is a measure of its ability to identify true positives (those with the disease are rightly identified as positive); whereas the specificity of a test is a measure of its ability to identify true negatives (those without the disease are rightly identified as negative). Several studies have reported the sensitivity and specificity of PCR in diagnosing mpox (3, 9, 13–22). However, there is no pooled evidence of the diagnostic accuracy of the sensitivity and specificity of the PCR test confirming the routine diagnosis of mpox infection. Therefore, this study aims to pool the estimates of sensitivity and specificity across different study settings and provide evidence on the diagnostic accuracy of PCR in detecting mpox infections in humans.

MATERIALS AND METHODS

Protocol and registration

This meta-analysis was conducted in accordance with PRISMA guidelines. The protocol was registered in the PROSPERO (CRD-NIHR) database with Reference ID CRD42024590183.

Eligibility criteria

Studies that met all the following criteria were included for the analysis: 1) evaluated the diagnostic performance of PCR for the detection of mpox in humans; 2) provided the sensitivity and specificity values of the PCR test used; and 3) provided the total number of samples included in the study.

Reference/index test

Reference/index test was PCR, whose sensitivity and specificity values were pooled for all the included studies to assess its diagnostic accuracy in the detection of mpox infection in human samples.

Search strategy

A systematic search of scientific literature was conducted following PRISMA guidelines to identify studies evaluating the diagnostic accuracy of PCR for detection of mpox infections in humans. The search was conducted in the electronic databases PubMed, Cochrane, Scopus, and Google Scholar. Search terms included were "diagnostic accuracy," "evaluation," "validation," "polymerase chain reaction," "PCR," "PCR assay," "monkeypox," and "mpox." These terms were combined using Boolean operators AND or OR to obtain the final search string. The search was not restricted by any date or language. Gray literature was searched through unpublished articles and manual searching of nonindexed journals at the institutional library at All India Institute of Medical Sciences (AIIMS), Bhopal, including abstracts, conference presentations, online clinical registries, but no articles were retrieved based on these criteria.

Study selection and data extraction

Two independent reviewers (GU and AS) screened the titles and abstracts of the articles for eligibility followed by a full text review of the selected articles. The reasons for the exclusion of articles were noted. Additionally, references of the selected articles were hand searched and retrieved if deemed potentially relevant. Discrepancies between the reviewers were resolved through discussion and consensus. If consensus could not be reached, a third reviewer with relevant subject expertise was available to resolve. The following details of the included studies were extracted into a pilot worksheet by the two reviewers (GU and AS): 1) author name; 2) year of publication; 3) country; 4) sample size; 5) sensitivity and specificity values of the diagnostic test (PCR). The information was rechecked for accuracy by a third reviewer.

Quality assessment

The risk of bias of the included studies was assessed using the quality assessment of diagnostic accuracy studies-2 tool (QUADAS-2) (23). The tool assesses the risk of bias for the included studies under four domains: 1) patient selection; 2) index test; 3) reference standard; 4) flow and timing. The two reviewers (GU and AS) adapted the signaling questions and assessment criteria to create a review-specific version of the tool. Once the agreement was reached it was used by the authors to assess independently the risk of bias and its applicability to all the included studies. The index test itself is the reference standard in the present study, whose diagnostic accuracy is being assessed. The term sample was used in place of patient, since only the samples were received from various laboratories and tertiary care centers for analysis.

Statistical analysis

The meta-analysis was conducted using the metadta package in STATA software (version 17; StataCorp LLC, College Station, TX, USA), which is specifically designed for meta-analysis of diagnostic test accuracy studies (24, 25). The sensitivity and specificity data were analyzed using bivariate and hierarchical models. Summary receiver operating characteristic (SROC) curve and forest plot were generated, which are essential for assessing heterogeneity and overall test performance across studies. We used the restricted maximum likelihood (REML) method for parameter estimation.

RESULTS

The search yielded 11 398 articles from the various electronic databases. After title and abstract screening by the two reviewers, 57 articles that met inclusion criteria were included for full text review. A total of 12 articles were included for the final analysis after removal of duplicates and excluding the articles that did not meet the inclusion criteria (Table 1 and 2). A PRISMA flow diagram of the study selection process is provided in Figure 1.

Eleven of the 12 included studies reported high sensitivity values with point estimates ranging from 0.93 to 1. One study reported a lower sensitivity value of 0.60 (19). The random effects model used for the meta-analysis reported a pooled estimate of 0.99 (95% CI [0.95, 1.00]) (Figure 2), which suggested that PCR demonstrated excellent diagnostic accuracy in the detection of mpox infections in humans, with a sensitivity approaching 99%.

The point estimates across different studies ranged from 0.82 to 1 with respect to the specificity of the PCR test. The estimates of three studies (9, 18, 19) revealed wider confidence intervals in comparison to other studies, indicating less precision in the specificity of the PCR test probably due to variations in PCR methodology or sample quality. The pooled estimate of specificity was 1 (95% CI [0.96, 1.00]) (Figure 2), which reflects excellent specificity of PCR test in identifying the true negatives. If a study provided multiple sensitivity and specificity values, the lower estimate was chosen to be included in the analysis to reflect the minimum possible values.

A summary receiver operating characteristic (SROC) curve was plotted to further confirm the overall diagnostic accuracy of the PCR test (Figure 3). A SROC curve consists of the following components: 1) the summary point; 2) prediction region; and 3) confidence region. The summary point provides an overall summary of the diagnostic accuracy of a test considering both sensitivity and specificity. The dotted line around the summary point represents the prediction region, which suggests the range

TABLE 1. Characteristics of studies included in the meta-analysis

Study	Country	Sample size (*n*)	Primers used	Sensitivity (%)	Specificity (%)
Peris et al., 2023	Spain	165	Sequence not provided	100	100
Sklenovska et al., 2023	Belgium	115	Primer forward: 5'-TAGTGAGTTCGGCGACAAAG-3' Primer reverse: 5'-GTATCGCATCTCTCGGGTATTC-3'	99.14	100
Velu et al., 2023	United States	97	Sequence not provided	95	100
Pond et al., 2023	United Kingdom	175	Sequence not provided	94.2	100
Mostafa et al., 2024	United States, Belgium, Spain	296	O2L gene: Primer forward: 5'-CAATAGTGAGTTCGGCGACAAAG-3' Primer reverse: 5'-TTGTATCGCATCTCTCGGGTATTC-3' F3L gene: Primer forward:5'-CATCATCTATTATAGCATCAGCATCAGA-3' Primer reverse: 5'-CGATACTCCTCCTCGTTGGTCTAC-3'	99.36	96.97
Bunse et al., 2024	Germany	63	Primer forward: GTAGTGCTATTGTTTACAGCTCC Primer reverse: GCCTTATCGAATACTCTTCCG	100	96.97
Tan et al., 2023	United Kingdom	55	Sequence not provided	92.5	82.9
Pomari et al., 2023	Italy	15	Sequence not provided	60	100
Harshani et al., 2023	Sri Lanka	25	Primer forward: 5'-GGAAAATGTAAAGACAACGAATACAG-3' Primer reverse: 5'-GCTATCACATAATCTGGAAGCGTA-3'	100	100
Elbaz et al., 2023	Israel	154	Sequence not provided	100	94
De Pace et al., 2024	Italy	37	Sequence not provided	96.3	100
Wettengel et al., 2023	Germany	246	Primer forward: 5'-GGAAAATGTAAAGACAACGAATACAG-3' Primer reverse: 5'-GCTATCACATAATCTGGAAGCGTA-3'	100	100

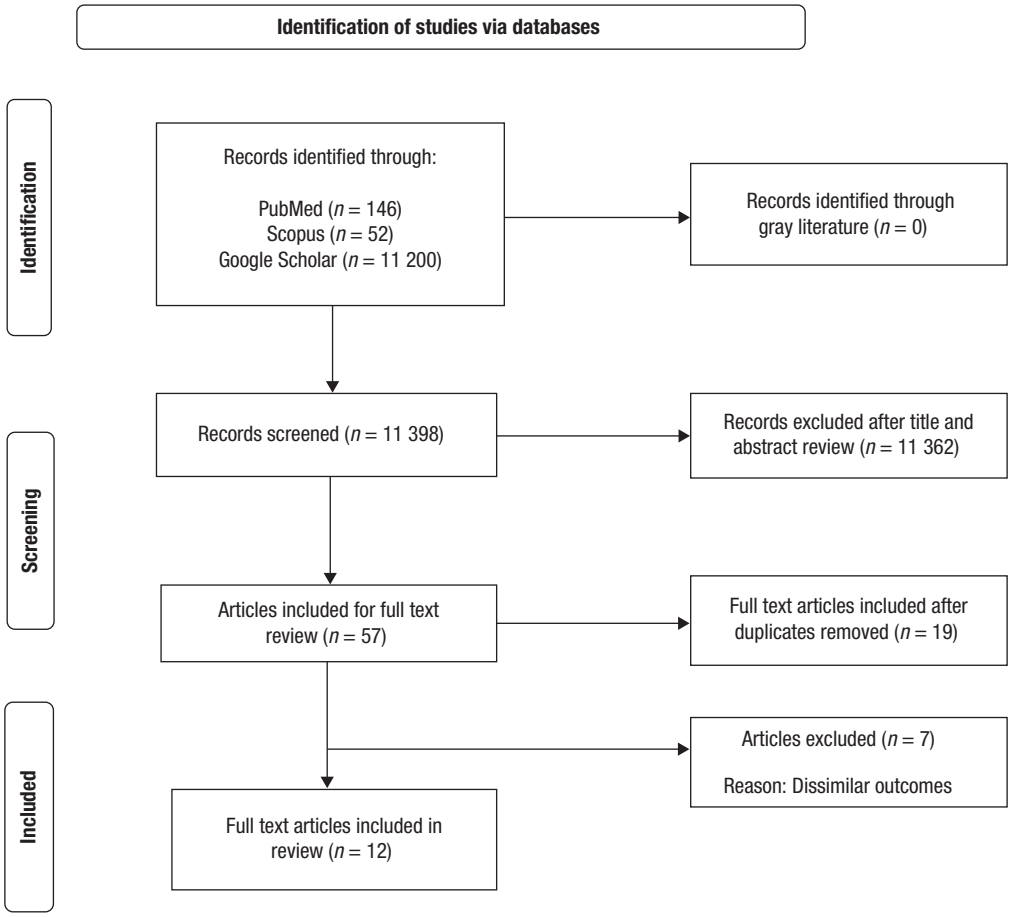
Source: Prepared by the authors based on the study data.

TABLE 2. Characteristics of studies excluded from the meta-analysis

Study	Reason for exclusion
Davi et al., 2019	
Li et al., 2024	
Mancon et al., 2024	
Liotti et al., 2023	Dissimilar outcome measures
Uhteg and Mostafa, 2023	
Thomas et al., 2023	
Porzucek et al., 2023	

Source: Prepared by the authors based on the study data.

FIGURE 1. Flow diagram of the study selection process



Source: Prepared by the authors based on the study data

of likely values of sensitivity and specificity for future studies. A narrow prediction region suggests consistent performance of a diagnostic test. The dashed line around the summary point is the confidence region, which represents the uncertainty in the pooled estimates of sensitivity and specificity values. A smaller confidence region reflects lesser variability or more precision of the estimates. The positioning of the summary point of the SROC curve near the top left corner, and the narrow prediction region and confidence region, reflects the high sensitivity and specificity values, which further reiterates the robust and consistent performance of PCR in diagnosing mpox infections in different study settings.

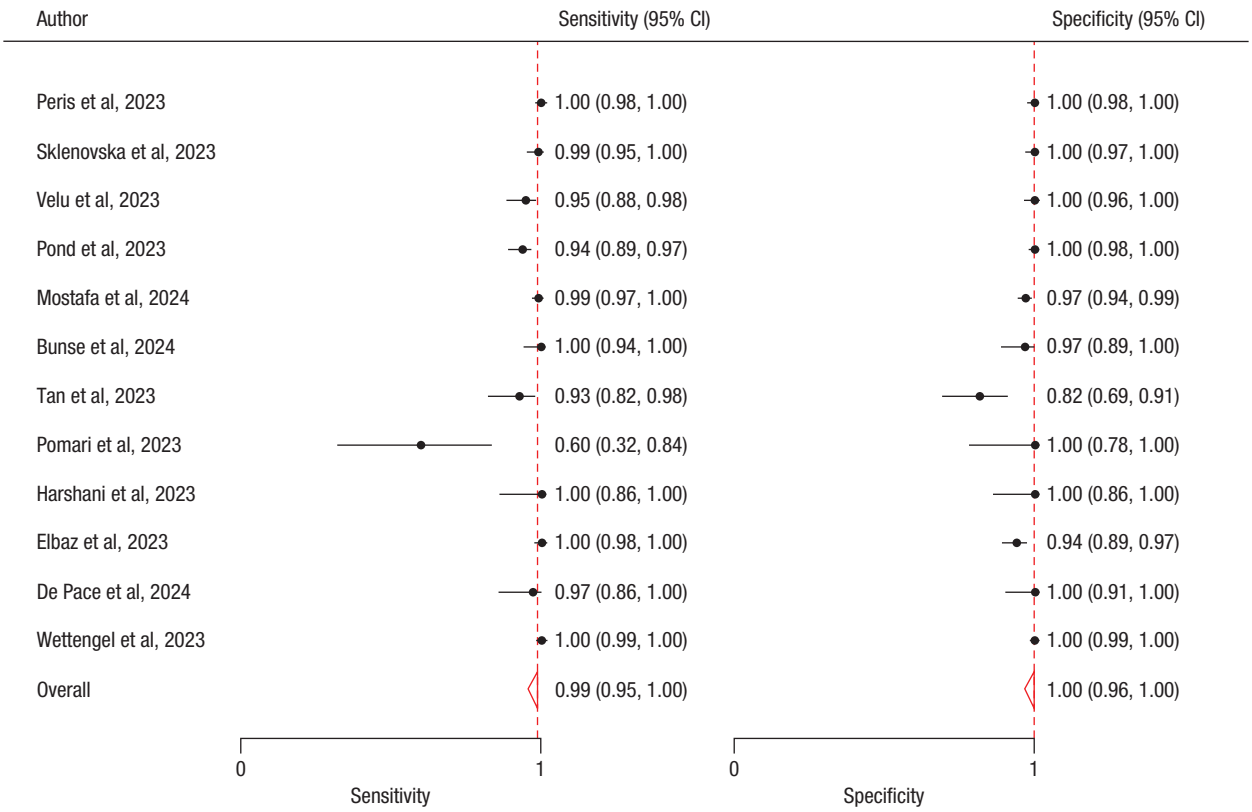
The quality of the included studies was assessed utilizing the QUADAS-2 tool. The signaling questions of the tool were adapted to the needs of the review, as the index test was the reference standard. A low risk of bias was observed for estimating the diagnostic accuracy of the index/reference test (Table 3).

DISCUSSION

This systematic review and meta-analysis evaluated the diagnostic accuracy of PCR test in detecting mpox infections in humans. The pooled estimate of sensitivity and specificity of PCR test demonstrated excellent diagnostic performance of the test with a pooled sensitivity of 0.99 (95% CI [0.95, 1.00]) and a specificity of 1 (95% CI [0.96, 1.00]). A SROC curve with summary point positioned in the top left corner, along with narrow confidence and prediction regions, confirms the diagnostic accuracy of PCR in the detection of mpox infection in humans across diverse study settings.

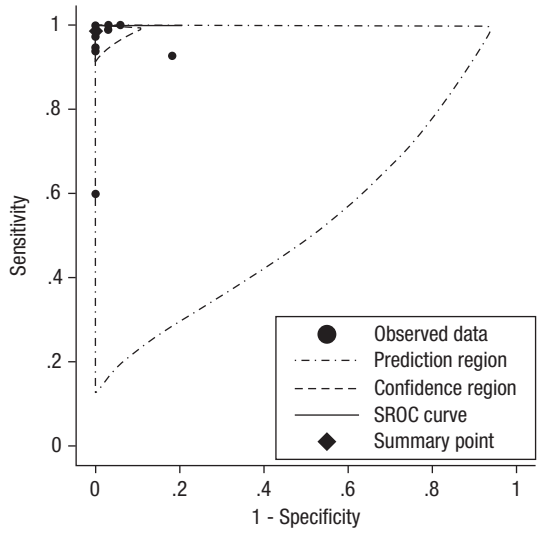
The ability of PCR to detect low viral loads early in the infection is indispensable for early-stage diagnosis to provide timely treatment and prevent further transmission of the infection. During an outbreak, early and specific identification is of paramount importance to public health. In populations at high risk

FIGURE 2. Pooled estimate of sensitivity and specificity of PCR test



Source: Prepared by the authors based on the study data.

FIGURE 3. Summary receiver operating characteristic (SROC) curve



Source: Prepared by the authors based on the study data.

for coinfection or presenting undifferentiated rashes, an assay of high specificity is crucial. Among the included studies, the most common coinfections reported were HIV, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, herpes simplex virus 1 and 2, varicella zoster virus, and *Treponema pallidum* (3, 15, 21).

In the included studies, samples analyzed were mainly obtained from skin lesions (13, 19, 20), oropharynx (18, 19, 20), and rectum (3, 19, 20). Pomari et al. (19) collected samples from whole blood along with samples from other sites, and Peris et al. (3) collected swabs from the genital area as well. According to WHO standards, the specimens from skin lesion surface or lesion crusts from various sites including genital, oropharyngeal, and perianal areas are the most preferred specimens for detection of mpox infection by PCR (8). Blood samples are not preferred, as the shedding of virus in the blood happens during the prodromal period typically before the appearance of the skin lesions. Additionally, antigen and antibody assays are often unsuitable, as monkeypox virus exhibits cross-reactivity with other orthopoxviruses (20).

Although WHO has declared PCR as the gold standard for the detection of mpox infection based on expert consensus,

TABLE 3. Summary of QUADAS-2 quality appraisal of included studies

Study	Risk of bias			Applicability concerns			
	Patient selection	Index test	Reference standard (PCR)[a]	Flow and timing[b]	Patient selection	Index test	Reference standard
Peris et al., 2023	Samples collected from various laboratories and tertiary centers. Randomization is not applicable.	Index test used is the reference standard. The aim of the study was to pool the diagnostic accuracy for PCR test, which is the reference standard.	+	+	+	+	+
Sklenovska et al., 2023			+	+	+	+	+
Velu et al., 2023			+	+	+	+	+
Pond et al., 2023			+	+	+	+	+
Mostafa et al., 2024			+	+	+	+	+
Bunse et al., 2024			+	+	+	+	+
Tan et al., 2023			+	+	+	+	+
Pomari et al., 2023			+	+	+	+	+
Harshani et al., 2023			+	+	+	+	+
Elbaz et al., 2023			+	+	+	+	+
De Pace et al., 2024			+	+	+	+	+
Wettengel et al., 2023			+	+	+	+	+

Notes: + : Low risk; [a] Index test was the reference standard; [b] Index test being pooled is the reference standard, signaling that question 1 is not applicable and questions 2 and 3 refer to the sample rather than the patients.
Source: Prepared by the authors based on the study data.

to our knowledge, no single study has comprehensively evaluated the overall diagnostic accuracy of PCR in the detection of mpox across varied study settings. This review provides the pooled estimates of sensitivity and specificity of the test across different studies conducted from different samples and confirms the diagnostic accuracy of the test. This study also serves as a foundation for future diagnostic research and sets a stage for monitoring the accuracy of PCR as new variants of monkeypox virus emerge.

Limitations of the study included lack of randomization or blinding process, as these are lab-based studies. Secondly, this review does not evaluate the diagnostic accuracy of PCR for different clades of monkeypox virus separately due to the limited number of studies that give sufficient information on the different clades tested. Only two of the included studies elaborated on the diagnostic performance of PCR on different clades of monkeypox virus (13, 15). Future research must focus on large-scale prospective studies evaluating the diagnostic accuracy of PCR in diverse real-world clinical environments. Studies must also evaluate the diagnostic accuracy of PCR in detecting multiple clades of the virus. Standardization of PCR protocols across laboratories is necessary to reduce the variability and ensure consistent findings in different study settings. In spite of PCR being highly sensitive and specific in detecting mpox, it requires sophisticated laboratory settings, tools, and trained personnel, which might not be feasible in low resource settings where an mpox outbreak has occurred and the availability of PCR is limited. Therefore, alternative diagnostic tools must still be explored to complement PCR in these settings.

Conclusion

This systematic review confirms PCR as an accurate tool in detecting mpox infections in humans, with a high sensitivity and specificity across varied study settings. PCR demonstrated excellent diagnostic accuracy, making it indispensable for clinical and public health responses during outbreaks. However, lack of data on clade-specific performance highlights the need for further research to ensure robustness of PCR test across all variants of monkeypox virus.

Author contributions. GU conceived the idea. GU and AS conducted the literature search and extracted the data. AP, AS, and GU analyzed the data. GU and AS drafted the manuscript. All authors revised and approved the final manuscript.

Conflict of interest. None declared.

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Exactitud diagnóstica de la reacción en cadena de la polimerasa para la detección de la mpox en el ser humano

RESUMEN

Objetivo. Evaluar la exactitud diagnóstica de la reacción en cadena de la polimerasa (PCR) en la detección de la infección de mpox en el ser humano agrupando las estimaciones de sensibilidad y especificidad obtenidas en diferentes entornos de estudio.

Métodos. Se realizó una búsqueda sistemática en PubMed, la base de datos Cochrane, Scopus y Google Scholar. Se incluyeron los estudios que evaluaron la exactitud diagnóstica de la prueba de PCR para la detección del virus de la mpox y proporcionaron los valores de sensibilidad y especificidad, así como el número total de muestras. Se agruparon los valores de sensibilidad y especificidad de la prueba de PCR de todos los estudios incluidos. El metanálisis se llevó a cabo siguiendo lo establecido en las directrices PRISMA, con el empleo del conjunto de metadatos, mediante el programa STATA. Se generó una curva de características operativas del receptor resumida (SROC) y un diagrama de bosque. El protocolo se registró en la base de datos PROSPERO (CRD-NIHR) con la identificación de referencia CRD42024590183.

Resultados. Se incluyeron doce estudios en el metanálisis. La estimación agrupada de la sensibilidad y la especificidad en el conjunto de los estudios, con un modelo de efectos aleatorios, fue de 0,99 (IC del 95%: [0,95; 1,00]) y 1 (IC del 95%: [0,96; 1,00]), respectivamente. La curva SROC confirmó la gran exactitud diagnóstica de la PCR. La herramienta de evaluación de la calidad de los estudios de exactitud diagnóstica (QUADAS) mostró un riesgo bajo de sesgo.

Conclusiones. Esta revisión sistemática y metanálisis es el primer estudio científico publicado que utiliza una agrupación de estudios para determinar la exactitud diagnóstica de la PCR en la mpox, y confirma que se trata de un análisis exacto para la detección de la infección en el ser humano.

Palabras clave Mpox; monkeypox virus; reacción en cadena de la polimerasa; diagnóstico; metaanálisis.

Acurácia diagnóstica da reação em cadeia da polimerase para detecção da varíola símia em humanos

RESUMO

Objetivo. Avaliar a acurácia diagnóstica da reação em cadeia da polimerase (PCR) para detectar a infecção pelo vírus da varíola símia (mpox) em humanos, combinando as estimativas de sensibilidade e de especificidade de estudos em diferentes contextos.

Métodos. Foi realizada uma pesquisa sistemática das bases de dados PubMed, Cochrane, Scopus e Google Acadêmico. Foram incluídos na análise estudos que avaliaram a acurácia diagnóstica do teste de PCR para a detecção do vírus da varíola símia e que apresentavam os resultados de sensibilidade e especificidade e o número total de amostras. Os dados de sensibilidade e especificidade de todos os estudos incluídos na revisão foram combinados. A metanálise foi conduzida conforme as diretrizes PRISMA com o uso do pacote de metadados do software STATA. Os dados foram representados em uma curva característica de operação do receptor sumarizada (sROC) e um gráfico de floresta. O protocolo da revisão foi registrado na base PROSPERO (CRD-NIHR), sob o número de referência CRD42024590183.

Resultados. Doze estudos foram incluídos na metanálise. As estimativas combinadas de sensibilidade e especificidade dos estudos com o uso de um modelo de efeitos aleatórios foram 0,99 (IC 95% [0,95, 1,00]) e 1 (IC 95% [0,96, 1,00]), respectivamente. A curva sROC confirmou a elevada acurácia diagnóstica do teste de PCR. A ferramenta de avaliação da qualidade dos estudos de acurácia diagnóstica (QUADAS) indicou baixo risco de viés.

Conclusões. Esta revisão sistemática e metanálise é o primeiro estudo da literatura científica a combinar os resultados de acurácia diagnóstica do teste de PCR para varíola símia, confirmando que este é um instrumento preciso para detectar essa infecção em humanos.

Palavras-chave Mpox; monkeypox virus; reação em cadeia da polimerase; diagnóstico; metanálise..