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RESEARCH ARTICLE

Diagnostic accuracy of serological tests for the diagnosis of Chikungunya virus infection: A systematic review and meta-analysis

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Abstract

Background

Chikungunya virus (CHIKV) causes febrile illnesses and has always been misdiagnosed as other viral infections, such as dengue and Zika; thus, a laboratory test is needed. Serological tests are commonly used to diagnose CHIKV infection, but their accuracy is questionable due to varying degrees of reported sensitivities and specificities. Herein, we conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of serological tests currently available for CHIKV.

Methodology and principal findings

A literature search was performed in PubMed, CINAHL Complete, and Scopus databases from the 1st December 2020 until 22nd April 2021. Studies reporting sensitivity and specificity of serological tests against CHIKV that used whole blood, serum, or plasma were included. QUADAS-2 tool was used to assess the risk of bias and applicability, while R software was used for statistical analyses.

Thirty-five studies were included in this meta-analysis; 72 index test data were extracted and analysed. Rapid and ELISA-based antigen tests had a pooled sensitivity of 85.8% and 82.2%, respectively, and a pooled specificity of 96.1% and 96.0%, respectively. According to our meta-analysis, antigen detection tests serve as a good diagnostic test for acute-phase samples. The IgM detection tests had more than 90% diagnostic accuracy for ELISA-based tests, immunofluorescence assays, in-house developed tests, and samples collected after seven days of symptom onset. Conversely, low sensitivity was found for the IgM rapid test (42.3%), commercial test (78.6%), and for samples collected less than seven of symptom onset (26.2%). Although IgM antibodies start to develop on day 2 of CHIKV infection, our meta-analysis revealed that the IgM detection test is not recommended for acute-phase samples. The diagnostic performance of the IgG detection tests was more than 93% regardless of the test formats and whether the test was commercially available or developed in-

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house. The use of samples collected after seven days of symptom onset for the IgG detection test suggests that IgG antibodies can be detected in the convalescent-phase samples. Additionally, we evaluated commercial IgM and IgG tests for CHIKV and found that ELISA-based and IFA commercial tests manufactured by Euroimmun (Lübeck, Germany), Abcam (Cambridge, UK), and Inbios (Seattle, WA) had diagnostic accuracy of above 90%, which was similar to the manufacturers' claim.

Conclusion

Based on our meta-analysis, antigen or antibody-based serological tests can be used to diagnose CHIKV reliably, depending on the time of sample collection. The antigen detection tests serve as a good diagnostic test for samples collected during the acute phase ($\leq$7 days post symptom onset) of CHIKV infection. Likewise, IgM and IgG detection tests can be used for samples collected in the convalescent phase (>7 days post symptom onset). In correlation to the clinical presentation of the patients, the combination of the IgM and IgG tests can differentiate recent and past infections.

Author summary

Chikungunya virus (CHIKV) causes non-specific symptoms such as fever, and the infection is sometimes misinterpreted as other viral infections, such as dengue and Zika. Although serological tests are commonly used to diagnose CHIKV infection, the reliability of these tests is questionable due to their highly variable performance. A systematic review and meta-analysis were performed to determine the diagnostic accuracy of these serological tests. As the analytes (antigen and antibodies) are present in the patient's sample at different time points of CHIKV infection, we analysed the diagnostic performance of serological tests detecting CHIKV antigen, IgM, and IgG antibodies. Our meta-analysis showed that antigen or antibody-based serological tests could reliably be used to diagnose CHIKV, depending on the time of sample collection. Antigen detection test serves as a good diagnostic test for samples collected within the acute phase (1 to 7 days) of CHIKV infections. On the other hand, the IgM and IgG tests can be used for convalescent-phase (>7 days of symptom onset) samples, differentiating recent and past CHIKV infections. Although IgM antibodies start to develop as early as 2 to 4 days of CHIKV infection, our result showed that the IgM detection tests for acute-phase samples exhibited low accuracy. Thus, the IgM detection test is not recommended for samples collected <7 days of symptoms onset.

1. Introduction

Chikungunya virus (CHIKV) is transmitted to humans by Aedes mosquito bite. First isolated in Tanzania in 1953 [1], CHIKV was restricted to sporadic outbreaks in Africa and Asia. The three genotypes of CHIKV are designated after its geographical origins: East/Central/South/African (ECSA), West African, and Asian [2]. A genotypic shift of the CHIKV from Asian to ECSA was observed during the massive Indian Ocean outbreak in 2004, affecting millions of people [3]. ECSA genotype of CHIKV then continues to cause outbreaks in India and other parts of Asia [4,5]. Due to increased human movement and virus adaptability inside vectors,