

Original Research Article

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Evaluation of the Rapid Card Test and Capture ELISA Tests in Diagnosis of Dengue Infection

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ABSTRACT

Dengue Fever is a Flaviviral infection transmitted by the Aedes mosquitoes. It is a major public health issue in tropical and subtropical countries. Dengue virus is having four serotypes. It may progress to Dengue Hemorrhagic Fever, which can lead to Dengue Shock Syndrome and death. The study was conducted in the Department of Microbiology, K S. Hegde Medical Academy with the blood samples collected from the patients with clinical diagnoses of Dengue without any age or gender restriction. The samples were collected from the period of October 2015 to April 2017. Two blood samples were collected from each patient. First sample collected between 1-5 days of appearance of clinical symptoms and second sample between 15-21 days. 67 samples were collected and tested with Rapid test (Dengue Day 1Test) and ELISA test for the detection of NS1Ag, IgM and IgG antibody. Results from both methods were compared for evaluation considering Elisa as a gold standard. 67 samples from Dengue positive patients were collected in the time period of study and processed. In first sample, Rapid test showed 54 NSI Ag positive cases, 13 NS1Ag negative, 9 IgM positive, 10 IgG positive and 1 case positive for both IgM and IgG. In ELISA test, no positive cases for IgM and IgG together, but other reports were same. In second sample out of 67 samples 41 were positive for NS1Ag, 26 were negative. IgM positive in 27, IgG positive in 21 and both IgM and IgG positive in 9. In Elisa tests NS1Ag positive in 40 negative in 27. IgM positive in 31 and IgG positive in 25. Both IgM and IgG was positive in 17 cases. Statistical analysis and Evaluation of kits was done considering ELISA as gold standard comparing sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. Dengue infection is a vector borne disease and it has to be diagnosed early so that control measures can be taken at the earliest to prevent epidemics. Accurate and early diagnoses will decrease the mortality by giving adequate medical care. In a developing country like India most of the hospitals are not well equipped and resource setups are not standardized. So the diagnostic strategy should be based on accuracy and cost effectiveness without causing heavy financial burden to the community and Government.

Keywords

Dengue, NS1Ag,
IgM, IgG, ELISA

Article Info

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Introduction

Dengue is one of the most rapidly spreading arthropod borne viral disease, which is becoming a major public health problem in tropical and subtropical regions. Dengue virus belongs to family Flaviviridae and it is a positive sense single stranded RNA (ssRNA+)¹.

Dengue virus has got four serotypes (DENV-1, DEN-2, DEN-3, DENV-4). Dengue is transmitted by the bite of infected female mosquitoes of the genus *Aedes aegypti* and also *Aedes albopictus*. This disease causes varying clinical symptoms from mild asymptomatic illness to fatal dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)². Fever, headache, myalgia/arthralgia, nausea, vomiting and maculo-papular rashes are the clinical symptoms of classic dengue fever presentation⁴. Other infections like malaria, typhoid, and leptospirosis can mimic dengue and laboratory investigations are essential for an early definite clinical diagnosis⁶.

The diagnoses can be done with different biomarkers. They include isolation of virus in culture or mosquitoes or detection of viral genomic RNA, capture and detection of viral products (NS1 protein) or the host immune response to viral infection (measurement of virus specific immunoglobulin M and G (IgM and IgG)¹⁰. A significant rising IgM levels 3-5 day after the onset of symptoms shows a primary infection. This can persist for 1-3 months. In secondary infection there will be elevated levels of IgG at 6-15 days of symptoms and IgM can also be detected in secondary infection¹¹. As per the World Health Organization (WHO) dengue case definition in acute febrile illness 2 blood samples to be collected. First sample in 1-5 days of onset of symptoms and second sample 6-14 days after the onset of symptoms during

the convalescent phase¹². This study was done for the evaluation of rapid card tests and capture ELISA tests.

Materials and Methods

The study was conducted in the department of microbiology laboratory, KS HEGDE MEDICAL ACADEMY, with the blood samples collected from the patients of febrile illness (0-15 days) with clinical diagnosis of dengue (Sample size of 50) from the period of October 2015 to April 2017.

Method of processing

Collection and transport of samples

Blood samples were collected in red-capped vacutainer with all aseptic preparations. Samples were centrifuged and plasma separated. Samples were processed according to the manufacturer's instruction. Those samples not processed within 6 hours were refrigerated at 2-8 degree centigrade and were processed within 3 days. From each patient 2 blood samples (Sample 1 between 1-5 days of clinical symptoms and sample 2 between 15-21 days of clinical Symptoms) were collected.

Dengue day 1 rapid test

Dengue Day 1 Test kit contains two devices; one device for Dengue NS1 antigen detection and other device is for the differential detection of Dengue IgM / IgG antibodies in human serum/ plasma. Dengue IgM/IgG test device is containing three lines; Control line "C", IgM test line "M" and IgG test line "G". IgM and IgG test line test line are coated with anti-human IgM monoclonal antibodies and anti-human IgG monoclonal antibodies respectively.

Test was done as per the manufacturer's instruction. The results were read after 20

minutes (Positive results will appear as early as 2-10 minutes. Negative results were confirmed after 20 minutes only).

ELISA tests

Specimen processing

Frozen sample

Dengue ELISA tests will give the best performance if tests are done with fresh samples that have not been frozen and thawed. In this study few samples were run fresh and the remaining was kept in the refrigerator at 2-8 degree. Kit & its components were stored at 2-8°C. (Expiry date on the kit indicates the date beyond which kit should not be used).

Test principle

(A) NS1Ag MICROLISA is a solid phase enzyme linked immunoassay (ELISA) based on the "Direct Sandwich" principle. (B) DENGUE IgM MICROLISA is an enzyme immunoassay based on "MAC Capture ELISA". (C) DENGUE IgG MICROLISA is an enzyme immunoassay based on "GAC-Capture ELISA". Tests were done as per the manufacturers instruction.

Results and Discussion

Patients admitted in the hospital with a clinical history suggestive of dengue fever and a positive dengue test (NS1Ag / IgM/ IgG) from the period of October 2015-April 2017 were included. Initial study population was 132 dengue positive cases. For the fulfillment criteria of this study 2 blood samples had to be collected from each patient. First blood sample was collected from all the 132 patients. Despite all efforts for adequate sample collection, 11 serum samples received were inadequate to proceed with ELISA tests. From the remaining 121 patients only 67 patients were attending for a follow up and second

sample were collected only from these patients only. So the final numbers were restricted to 67 cases though the sample size in the study criteria was only 50. First sample was collected between 1-5 days of the onset of symptoms and the second sample 15-21 days later. Relevant clinical history was collected from the patient or patient party and there after serum sample was collected. For all these patients both and Rapid and ELISA tests were done.

Age distribution

27(40.3%) patients out of the 67 cases were in the age group of 31-45 followed by 24 cases (35.8%) in the age group of 46-60yrs. Only 4 (6%) cases were seen in >15 yrs age and 3(4.5%) patients were >61 yrs. In 16-30 yrs age group 9 patients (13.4%) were having dengue fever in our study.

In another study by Solanke et al showed 81.9%(127/155) of their dengue positive cases were in the age group of 0-20 years, followed by the age group of 21-40 years¹⁴.

Sex distribution

Males were more affected with dengue fever in this study, 36 (53.7%) of 67 cases. Females were 31 (46.3%). In a study by Jigna karia et al, out of the 78 dengue positive cases 53(67.94%) were males and 25(32.05%) were females⁴⁴.

In the study by Tabasum begum et al conducted in Mysore, which is belonging to the state of Karnataka in the year 2013, showed 104 (66.24%) male cases and 53 (33.76%) females out of the 157 dengue fever cases³⁶.

Clinical symptoms

In our study fever was the commonest presenting symptom in 64 (95.5%). Other

symptoms like headache in 60(89.6%), myalgia /arthralgia in 55 (82.1%), retro-orbital pain in 27(40.3%). Less common symptoms like abdominal pain was seen in 15 (22.4%) nausea /vomiting was present in 10 (14.9%) and skin rash was seen in 8(11.9%) cases. Dengue Hemorrhagic Fever (DHF) was present in only 1 case (1.5%).

In a study by Gopalakrishna S and Mohan K, from Bangalore Karnataka in the year 2012 during an epidemic, all the patients were presenting with fever(100%). Other symptoms were headache (95.7%), myalgia/arthralgia (92.1%), retro-orbital pain (78%), hemorrhagic manifestation (29.7%)⁴⁷. Most of the findings in this study favor our study findings.

Laboratory findings

In this study thrombocytopenia was present in 27(40.3%) patients. Thrombocytopenia (Platelets <50,000/ μ l) is a very significant indicator in dengue fever. Another findings were leukopenia (WBC < 4000/ μ l) in 8 (11.9%) cases, SGPT >55 u/l in 5 (7.4 %), SGOT > 45u/l in 7 (10.4 %) and Total bilirubin >2 mg/dl in 1 (1.5%). Increased Hematocrit values were seen in 12 (17.9 %) cases. In our study DHF was diagnosed in, 1 (1.5%) patient only. No cases of DSS or death were reported in our study. In a study by Aswinikumar et al, 8% showed DHF and 7.3% with DSS and 3 deaths were also reported⁴⁷.

In case of DSS there will be severe plasma leakage, which can cause shock or accumulation of fluid and can cause a respiratory distress, bleeding and organ damage (due to metabolic acidosis). So DSS patients should be closely monitored. Management protocols of DSS patients are given in WHO handbook for the management of Dengue¹⁰.

Serological tests

NS1 Ag Detection by Dengue day 1 (Rapid test) and ELISA tests

Non-structural protein1(NS1) is a glycoprotein, produced in secretory and membrane associated forms by the virus⁴⁸. The NS1Ag levels can be detected by immunochromatography and sandwich Elisa. In the diagnosis of acute dengue infection NS1Ag detection represented a newer approach⁴⁹.

Acute serum sample (Sample 1: Between 1-5 days)

Rapid test

In this study out of 67 dengue positive patients, Rapid test showed 54 NS1Ag positive and 13 NS1Ag negative.

NS1 MICROLISA-ELISA was showing 54 NS1Ag positive and 13 negative. Comparative evaluation of the rapid test was done considering ELISA as the gold standard. Rapid test was showing 98.1% sensitivity, 92.3% specificity with PPV 98.1% and NPV 92.3% and diagnostic accuracy of 97.01%.

Convalescent serum sample (Second sample: between 15-21 days)

RAPID TEST-The second sample showed 41(61.19%) NS1Ag positive cases by Dengue day 1 test and 26(38.8%) negative cases.

ELISA test was giving 40(59.70%), positive case and 27(40.29%) negative. However 1 patient with NS1Ag negative report detected by rapid test was giving NS1Ag positive report in capture ELISA test. This can be due to a false negative report. At the same time one case with NS1Ag positive report given by

Rapid test was giving report by capture Elisa. The sensitivity and specificity of Rapid test was 97.5% and 92.6% with a PPV of 95.1% and NPV of 96.2% with a diagnostic accuracy of 95.52%.

In a study done in Maharashtra India, NS1Ag immunochromatographic test was compared with capture ELISA. It was showing 90.11% sensitivity and 98.45% specificity with a PPV of 98.15% and a NPV of 91.57%⁵¹. This is similar to the findings in our study. However we cant exclude dengue infection immediately after a negative NS1Ag report by rapid test. These reports along with antibody detection assays will provide a higher diagnostic yield³⁴.

IgM Antibody (Acute serum sample)

dengue day 1 test and MAC ELISA test: A comparative evaluation

In the Rapid test for detecting IgM antibody from the 67 acute serum samples 9(13.4%) were positive for IgM. Out of this 9 IgM positive cases 3 were positive for NS1Ag also. 5 IgM positive cases were negative for NS1Ag. One patient with NS1Ag positivity was found to be positive for both IgM and IgG.

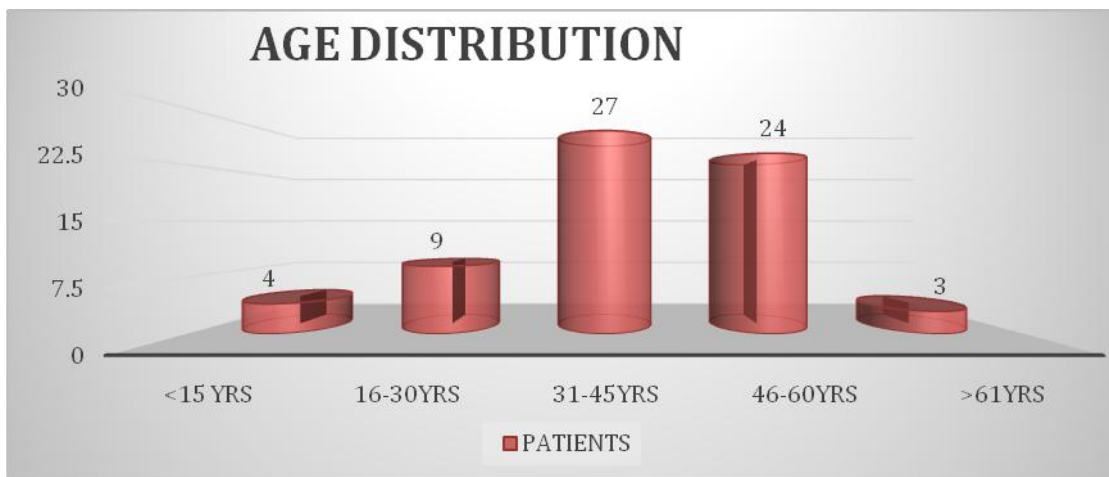
MAC ELISA

In the MAC ELISA test for detecting IgM antibody from the 67 acute serum samples 9 (13.43%) were positive for IgM antibody. Out of this 9 IgM positive cases 4 cases were having positive NS1Ag also. 5 IgM positive cases were NS1Ag negative. MAC ELISA test has been taken as the gold standard for a comparative evaluation.

Dengue DAY 1 test for was showing at 88.9 % and a specificity of 98.3%. The PPV was 88.9% and NPV at 98.3 % with a diagnostic accuracy of 97.01%.

Convalescent serum (Day 15-21)

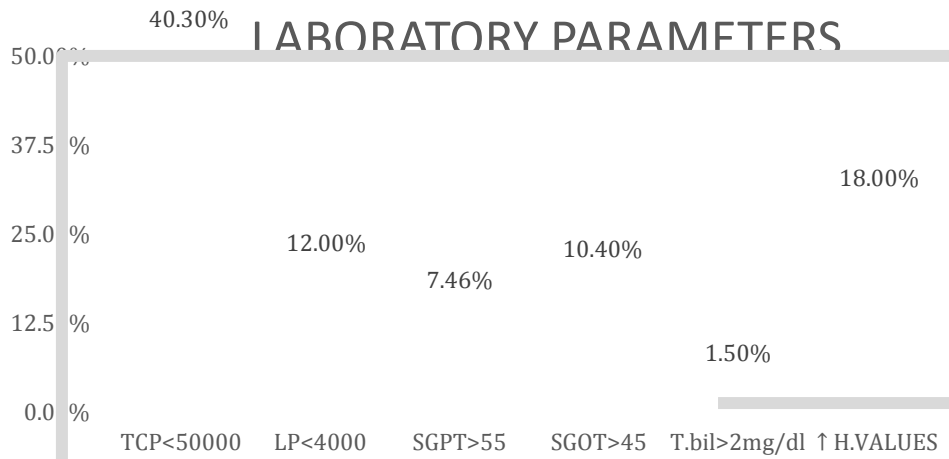
Dengue day 1 test- In the Rapid test for detecting IgM antibody from the convalescent serum samples 27 (40.3%) were positive for IgM antibody, 10 cases from this were having positive NS1Ag also. 8 IgM positive cases were seen with NS1Ag negative patients. 9 patients were found to be positive for both IgM and IgG, out of this 1 patient was NS1Ag positive while 8 were NS1Ag negative.



SEX DISTRIBUTION IN DIFFERENT AGE GROUP

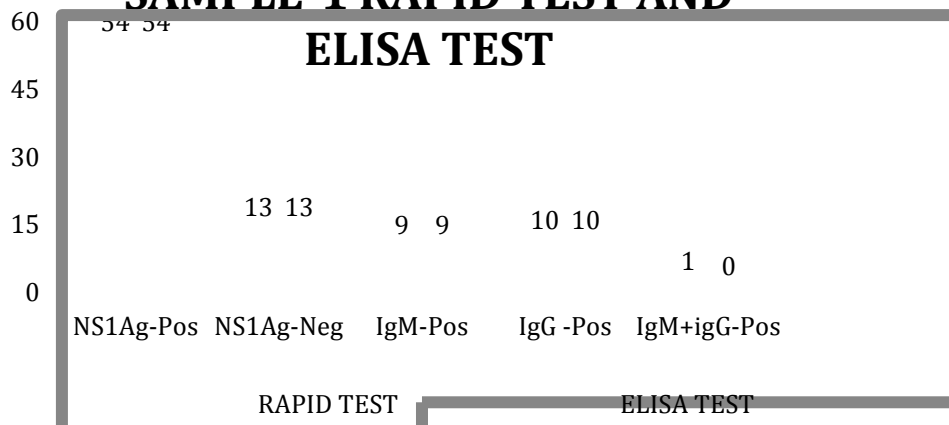


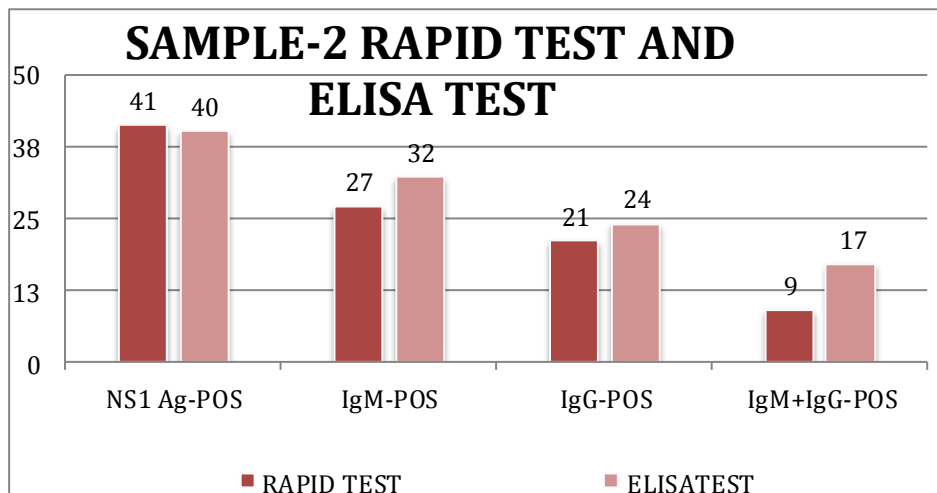
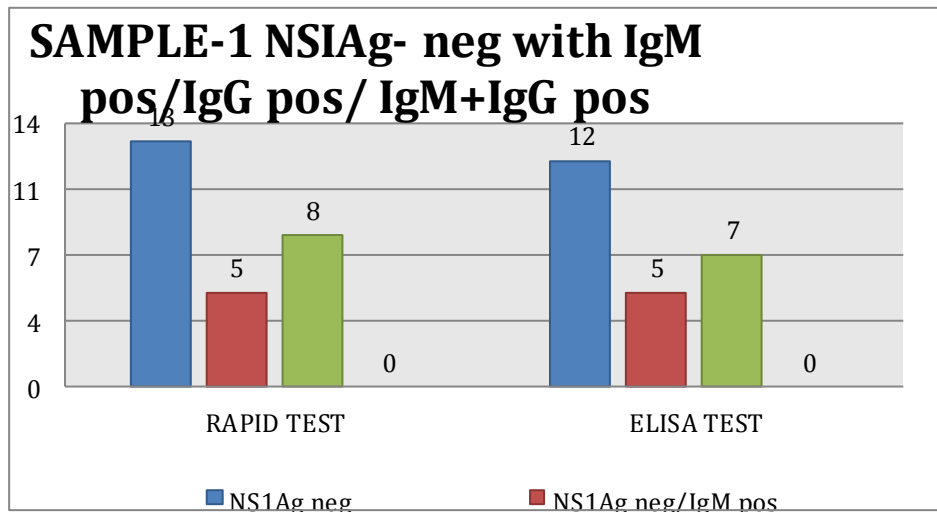
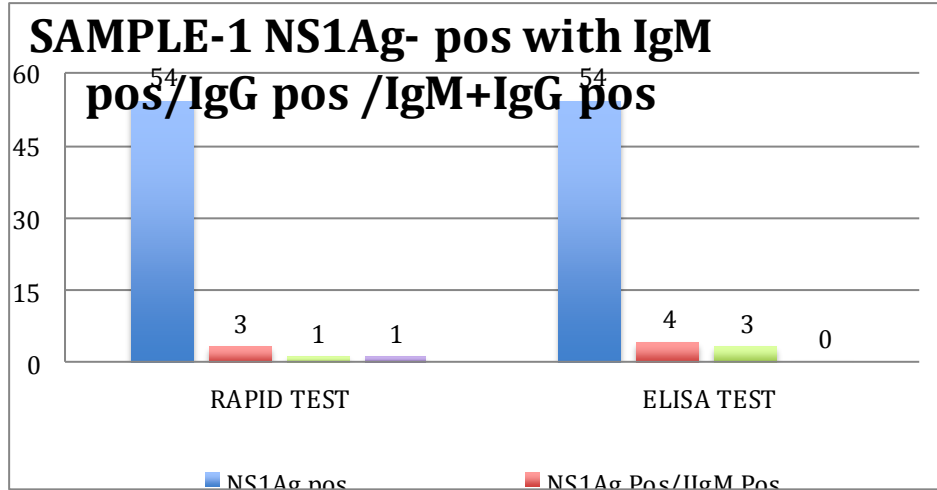
LABORATORY PARAMETERS

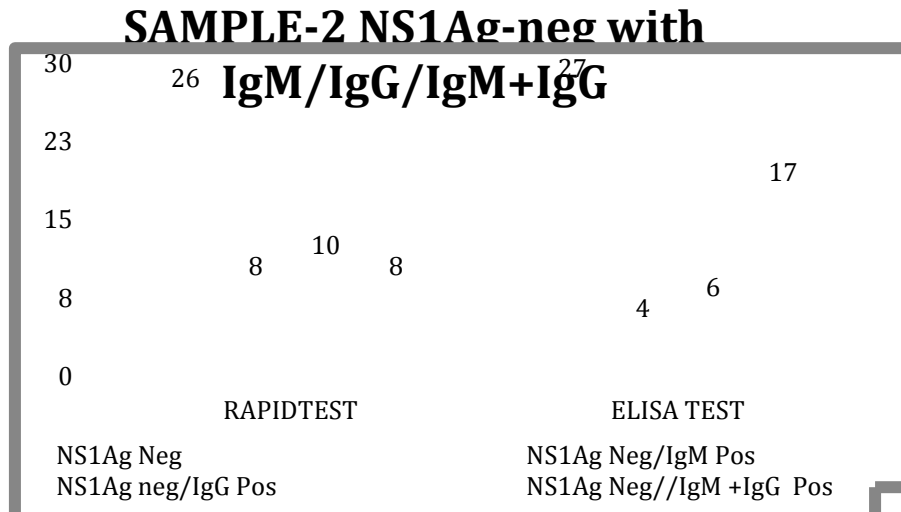
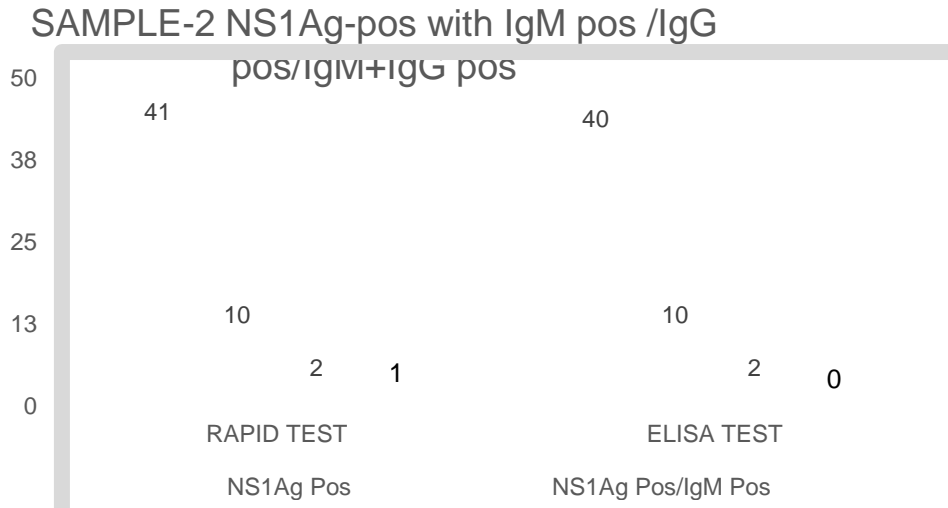


Abbreviations; TCP; thrombocytopenia, LP;leukopenia, SGPT;alanine aminotransferase(ALT), SGOT; aspartate amino tranferase(AST), T.Bil; Total bilerubin, ↑ H.value; increased hematocrit values

SAMPLE-1 RAPID TEST AND ELISA TEST







MAC ELISA-A comparative evaluation

In the MAC ELISA test for IgM antibody from the convalescent serum samples 31 (46.2%) of 67 cases were found positive for IgM antibody. Out of these 31 cases 10 cases were positive for NS1Ag. 4 NS1Ag negative patients were IgM positive. At the same time 17 NS1Ag negative patients were having both IgM and IgG positivity.

The Dengue Day 1 test was found to have a sensitivity of 83.9% and a specificity of 97.2% with a PPV of 96.3% and a NPV of

87.5%. The diagnostic accuracy was 91.04%.

In some studies increased sensitivity of the RAPID test devices were seen in primary infection comparing to secondary infection. During the time period of 0-3 days; sensitivity of IgM rapid tests increased. Appearance of IgM antibody and the absence of IgG indicate a primary infection. At the same time presence of IgG antibody is indicative of secondary infection. Moreover the duo cassettes have a draw back of misdiagnosing primary as secondary dengue infection¹³.

IgG Antibody

Dengue day 1 Rapid test and GAC ELISA a comparative evaluation:

Acute serum sample: Rapid day 1 test

From the 67 acute serum samples 10 (14.9%), were positive for IgG antibody. Out of the 10 IgG positive cases; 1 case was positive for NS1Ag showing a probable recent infection. But presence of IgG antibodies in the early stage could be due to a past infection with another strain. 1 patient with NS1Ag positivity was showing IgM and IgG antibody. 8 IgG positive cases were found to be negative for NS1Ag.

Acute serum sample: GAC ELISA a comparative evaluation

In the GAC ELISA test for IgG antibody from the 67 acute serum samples 10 (14.9%) patients were positive for IgG antibodies. Out of this 10 IgG positive 3 were NS1Ag positive while 7 cases were negative for NS1Ag.

Dengue day1 test showed 90% sensitivity and 98.2% specificity, with a PPV of 90% and NPV of 98.2% with a diagnostic accuracy of 97.01%.

Convalescent serum: Dengue DAY 1 Test

In the Rapid test for detecting IgG antibody from the convalescent serum samples 21 (31.3%) patients were positive for IgG antibody. Out of these 21 IgG positive cases, 2 cases were found to be positive for NS1Ag also. 10 IgG positive cases were from NS1Ag negative patients and 1 patient with NS1Ag positivity was showing IgM and IgG antibody positivity. At the same time 8 NS1Ag negative patients were found to be positive for both IgM and IgG.

Convalescent sera GAC ELISA a comparative evaluation

25 (35.8%) patients were positive for IgG antibody. Out of this only 2 cases were positive for NS1Ag. 6 IgG positive cases were found to be negative for NS1Ag. At the same time 17 NS1Ag negative patients were found to be positive for both IgM and IgG on ELISA. This test showed a sensitivity of 80% with a specificity of 97.6%. The PPV was 95.2% with a NPV of 89.1%. The diagnostic accuracy was 91.04%.

In a multi country study by Subhamoy Pal claimed that IgM and IgG with NS1Ag were giving a higher overall sensitivity for rapid test kits. They claimed that the sensitivity increased upto 93.5% in day 4-7, 98.6% in day 8-14 and 93.9% from day 15. In the same study MAC Elisa and GAC Elisa sensitivity reached upto 100% for the samples collected between the days 8-14. The specificity of IgM Elisa, was 88.1% in these samples, IgG specificity was 88.4%. IgG Elisa was showing a lower sensitivity range in all serotypes. In secondary infection IgG showed still lower sensitivity (69.6%). In contrast to this in primary and secondary infection IgM was having the similar sensitivity¹³. This was similar to our findings.

Dengue hemorrhagic fever is characterized by increase in vascular permeability and coagulopathy. In the acute phase of Dengue disease NS1 protein is highly conserved and circulated in high levels in all dengue serotypes. Development of DHF is in correlation with this⁴¹. In this study there was one case of DHF. This case was showing NS1Ag positivity in acute serum sample by both Day 1 test and ELISA. This patient was showing thrombocytopenia.

In conclusion, rapid tests for dengue diagnoses, which are based on immune-

chromatography, are mainly used in common clinical practice. Rapid tests are easy to use, cheap, need less expertise and another important factor behind is less turn over time. Performance of this RDT kits varies. Dengue fever is common in tropical regions where temperature and humidity is high. So storage temperature is a factor in kit performance. For easy diagnoses in a resource limited setups RDTs will be useful. Sensitivity and specificity of rapid kits still remains as a major issue and standardized approaches should be implemented while performing the diagnostic assessments. However ELISA has got a better sensitivity and specificity especially in secondary infections.

Elisa can be used in hospital when there is an outbreak of dengue as the format enables testing of multiple samples. At the same time it is a huge logistic burden for the laboratory when the time and training requirements are considered. The low specificity of the rapid tests will necessitate confirmatory test for all the RDT positive samples with ELISA tests.

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