Evaluation of Rapid Antibody Test Compatibility in COVID-19 Cases Confirmed by RT-PCR Assay

RT-PCR Testi ile Doğrulanmış COVID-19 Olgularında Hızlı Antikor Testi Uyumluluğunun Değerlendirilmesi

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Aim: This study aimed to determine the reliability of rapid antibody detection test (RADT; Weimi Bio-Tech COVID-19 Antibody test) results and their compatibility with RT-PCR test in screening and control of COVID-19 infection.

Material and Methods: Our study was conducted with the permission of the Ministry of Health and the local ethics committee of our hospital. Laboratory results of 624 healthcare personnel were recorded between May 2020 and November 2020. Two nasopharyngeal specimens were collected from each case to perform RT-PCR. Simultaneously serum/plasma samples were collected for RADT testing. Our hospital's data processing system (HIS) and laboratory information system (LIS) records were used for data collection. The level of agreement between the tests was calculated using Cohen's κ index. Statistical analyses were performed using SPSS software.

Results: The mean age of the patients included in the study was 28.46 ± 2.35 years. Of all cases, 54% were female (n=337) and 46% (n=287) were male, and none of the cases had any comorbidity. Both RT-PCR and RADT were negative in 86% of the cases (n=540). RT-PCR results were positive in 13.6% (n=102) of the included cases. Of the 102 RT-PCR positive cases, 84 were positive by RADT and there were no false positive results with RADT. Sensitivity and specificity for all cases were 84.7% and 100%, respectively. In symptomatic cases, sensitivity was >95%.
Conclusion: We consider that antibody tests may be useful in screening for COVID-19 in circumstances where access to RT_PCR testing may be limited, particularly in cases in the first or second week of symptomatic infection.

Keywords: COVID-19; RT-PCR test; Rapid antibody test

Amaç: Bu çalışma COVID-19 enfeksiyonunun tarama ve tanısında hızlı antikor testi (RADT; Weimi Bio-Tech COVID-19 Antibody test)'nin güvenilirliğini ve RT-PCR testi ile uyumluluğunu belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Çalışmamız sağlık bakanlığından ve hastanemizin etik komitesinden gerekli izinler alınarak yapılmıştır. Mayıs 2020 ve Kasım 2020 arasında, 624 sağlık çalışanının laboratuvar sonuçları kaydedilmiştir. RT-PCR testi yapmak üzere her bireyden iki nazofarengeal sürüntü örneği ve eş zamanlı olarak RADT testi için kan serum örneği alınmıştır. Veri toplamak amacıyla hastanemizin veri giriş sistemi ve laboratuvar bilgi sistemi kayıtlarından yararlanılmıştır. Testler arası uyum seviyesi (level of agreement) Cohen's κ index kullanılarak hesaplanmıştır. İstatistiksel analizler DPSS programı kullanılarak yapılmıştır.

Bulgular: Çalışmada yer alan hastaların ortalama yaşı 28,46 ± 2,35. Tüm hastaların 54%'ü kadın (n=337), 46%'sı (n=287) erkektir ve bunların hiçbirinin herhangi bir komorbiditesi bulunmamaktadır. Hem RT-PCR hem de RADT testleri tüm popülasyonun 86%'sında (n=540) negatif saptandı. RT-PCR popülasyonun 13,6%'sında (n=102) pozitif saptandı. Bu 102 adet RT-PCR pozitif hastanın 84'ü RADT pozitif saptandı ve RADT testi ile yanlış pozitiflik olmadı. Tüm vakalar için sensitivite ve spesifisite sırasıyla 84,7% ve 100% olarak hesaplanmıştır. Semptomatik vakalarda sensitivite >95% olarak hesaplanmıştır.

Sonuç: RT-PCR testine erişimin olmadığı durumlarda, semptomatik COVID-19 enfeksiyonunun taramasında, özellikle birinci ve ikinci haftalarda antikor testlerinin faydalı olabileceğini düşünülmektedir.

Anahtar Kelimeler: COVID-19; RT-PCR testi; Hızlı antikor testi

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INTRODUCTION

The SARS-CoV-2 virus caused the pandemic that spread rapidly around the world called coronavirus disease. The COVID-19 epidemic caused by the novel coronavirus disease caused a health crisis surrounding the whole world in 2019 and 2021. COVID -19 is an infectious disease in heterogeneous forms, with a variety of signs and symptoms, including severe and mild forms (Lawandi & Danner, 2020; Sethuraman et al., 2020). However, in cases of COVID-19, timely diagnosis is necessary to ensure accurate diagnosis and optimal management, as well as isolation, especially in the hospital setting. Rapid antibody detection test (RADT) for the detection of COVID-19 infection is simpler, easier to perform, and less expensive than reverse transcription-quantitative polymerase chain reaction (RT-qPCR), which is considered the gold standard in definitive diagnosis. RT-PCR testing requires advanced molecular technical facilities, trained personnel, and equipment, and turnaround time can often be longer (Lawandi & Danner, 2020; Sidiq et al., 2020). RADT tests are considered less sensitive but have the advantages of a simple operating environment and short turnaround time. Evaluating the sensitivity and specificity of antibody tests for symptomatic and asymptomatic COVID-19 patients is of great priority for medical strategies that include antibody testing. Antibody tests for COVID-19 detect the presence of IgM or IgG antibodies secreted by B cells. There are 4 different antibody tests: rapid diagnostic tests, ELISA, measurement of neutralization antibodies, and chemiluminescence immunological tests (Lawandi & Danner, 2020; Sidiq et al., 2020). Currently, no standard antibody test has been reported to detect antibodies against SARS-CoV-2 during or after COVID-19 infection. The specificity of most antibody tests for SARS-CoV-2 is lower in the first week of exposure and increases in the second week. The bias of antibody tests, especially in asymptomatic cases, has several limitations Generally, high false negative rates and high biases have been recorded in COVID-19 antibody tests, depending on the stage and timing of the infection (Dortet et al., 2021; Sidiq et al., 2020).

This study aimed to compare the results of COVID-19 IgM, IgG antibodies (Colloidal Gold, lateral flow immunochromatography test) in the Wiemi Diagnostic Kit test with the results of the RT-PCR test, which is considered the gold standard in diagnosis.

MATERIALS AND METHODS

This retrospective study was performed with the permission of the local and central ethics committee (EC. 28.052020-34) during the COVID 19 screening of healthcare workers in our hospital, which is the reference center, from May 2020 to November 2020. Upper respiratory tract swab samples were taken from all cases and tested for SARSCoV-2 RNA by reverse transcription polymerase chain effect analysis. RT-PCR tests were performed in the Islab-2 laboratory at Göztepe Prof. Dr. Süleyman Yalçın City Hospital. Patients with positive RT-PCR test results for COVID-19 were included in the study. According to the protocol determined in the approach to cases, cases were tested for health screening either because they had symptoms suggestive of the disease or because they were at high risk of infection. Samples were obtained from both nostrils separately and as a deeper sample, a nasopharyngeal swab was used. The samples were transported to the central virology laboratory in a standard transport medium (vNAT (Bioeksen, Istanbul, Turkey) for RT-PCR application. They were delivered in a transport box kept constant at 4 °C. They were extracted with the M14 automatic nucleic acid extraction separation system. The presence of SARS-CoV-2 in the isolated samples was confirmed by a commercial kit (Bio-Speedy, Bioeksen, Turkey), one-step reverse transcription with SARS-CoV-2 Dual Gene RT- and results were obtained by applying real-time PCR. Using the qPCR kit targeting the N and Orf1ab gene region specific to SARS-CoV-2, the threshold cycle number was recorded as 0.05 cycle threshold (Ct). If $Ct \geq 38$, the result is negative, $Ct<38$ was considered positive. RT-PCR was performed using the BIO-RAD CFX96 instrument.

Immunochromatographic test and its application

included the following steps: 1. Recombinant novel coronavirus antigen with colloidal gold labeling and control antibody gold marker. 2. Nitrocellulose membrane with two built-in test lines (T1 and T2) and control line (C). T2 line with a built-in reagent for antibody M. T1 line with a built-in reagent for IgG antibody test and C with built-in control antibody. It will be absorbed by the device by the capillary effect that occurs when the appropriate sample is added to the test device. The antibody will combine with the colloidal gold-labeled COVID -19 antigen with the IgM antibody, the immune complex will be captured by the settled anti-human IgM antibody, a colored line will appear on the test line (T2) where the M antibody is located, it will be captured by the precipitated reagent and IgG on the test line (T1). A colored line will appear indicating positive for the antibody. If there is no appearance of T1 and T2, it means a negative result. There is a control zone C within the cassette; the colored line appears at control line C whether the test line is visible or not. (If the test is completed as required and without errors, a color change line will appear) All RADT tests were performed immediately upon admission, according to the testing rules (Figure 1).

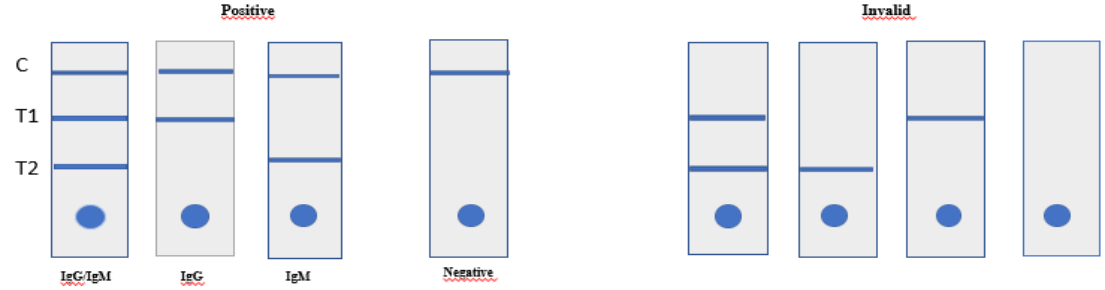

Figure 1. Explanation RADT results T1: IgG, T2: IgM, C: Control line

The sensitivity and specificity of Weimi Bio-Tech COVID-19 Ag RADT with a 95% confidence interval (CI) were calculated regarding RT-PCR test results as the standard. Sensitivity was calculated based on the presence of symptoms and RT-PCR values of all patients with positive results. The level of agreement between the tests was calculated using the κ (kappa) index. Statistical analyses were performed using open-source software. Continuous variables were presented as median and range, and categorical variables were presented as number and percentage. Interobserver reliability for CT diagnosis was assessed using Cohen'sκ calculation ($0 \leq \kappa \leq 0.20$, $0.20 \leq \kappa \leq 0.40$, no agreement, poor agreement, $0.40 \leq \kappa \leq 0$) .60, moderate There is (adequate) compatibility, $0.60 \leq \kappa \leq 0.80$ there is very good (high) compatibility, $0.80 \leq \kappa \leq 1.00$ there is excellent compatibility. Statistical analysis was based on IBM Corp. published in 2013. was carried out using. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. A p-value of less than 0.05 indicated a significant difference.

RESULTS

A total of 624 cases were included; 56% (n=337) were female and 46% were male (n=287). The median age was 28.46 ± 2.35 years. While 45.1% (n=284) of 624 cases applied with findings suggestive of COVID-19, 54% of 340 (n=340) had no symptoms suggestive of COVID-19. RT-PCR was positive in 13.6% (n=102) of 624 cases. Of the RT-PCR-positive cases, 82.3% (n=84) were symptomatic. Cases presenting any of the symptoms of cough, sore throat, fever, nasal congestion, dyspnea, headache, loss of taste or smell, nausea, vomiting, and fatigue were considered symptomatic. The median symptom duration was 6.8 days (0,5–14). 84 patients with positive RT-PCR, 96.4% (n=81) were mild cases and 3.7% (n=3) cases were treated in hospital. The RADT was positive in 97.6% (n=82) of 84 symptomatic RT-PCR positive cases, while the RADT was false negative in 2.44% (n=2) cases. While the RADT was positive in 6 (3.33%) of 18 asymptomatic cases, the RADT was false negative in 66.6% (n=12).

Among all RT-PCR positive cases, the RADT gave false negative results in 11.7 (n=12) cases (Figure 2).

The highest sensitivity level for IgM, IgG, and IgM/IgG was reached on the 9th day of symptom onset (Figure 3).

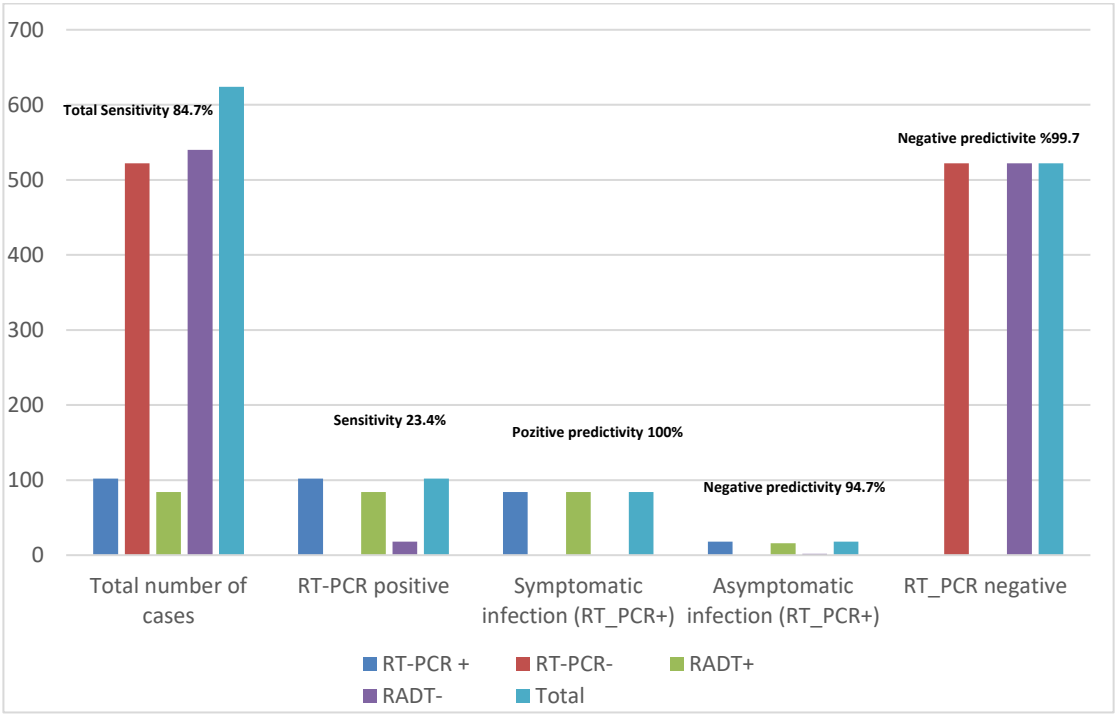

Figure 2. Distribution of RADT positive and negative cases according to RT-PCR results

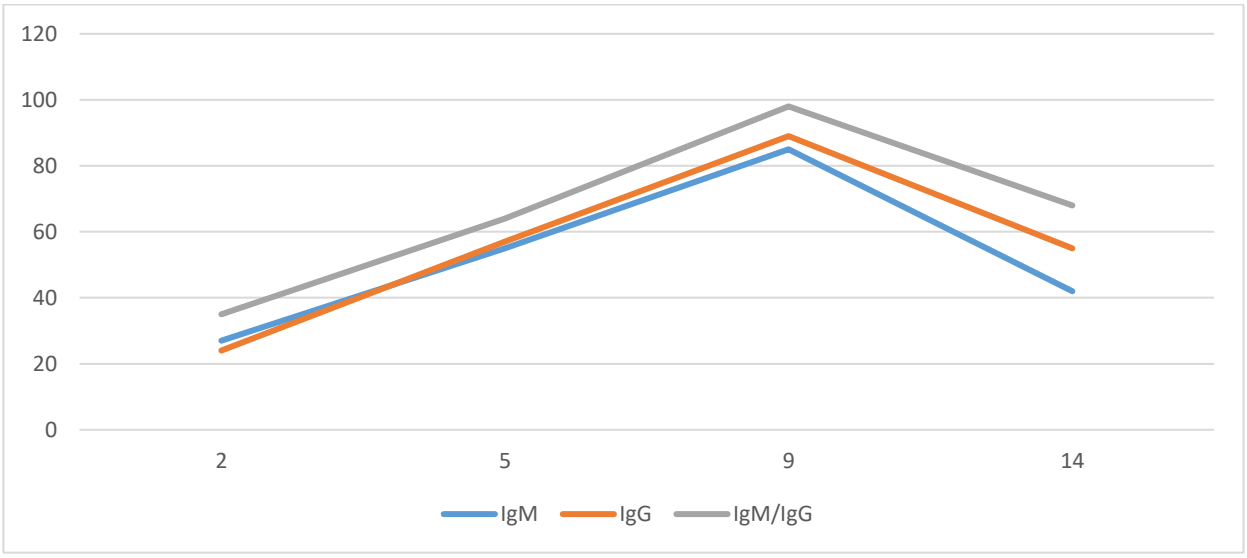

Figure 3. Sensitivity of the RADT days since onset of symptoms among cases who reported at least one symptom before testing stratified by antibody types

RADT was negative in all RT-PCR negative cases (n = 312). Agreement between the two methods was 98.9% (0.923–1) κ score: 0.89 (0.83–0.96) 95%CI (Figure 2). The overall sensitivity and specificity of the Weimi Bio-Tech test were 84.7% (73%-94.2%), 95% CI, and 100%, respectively. Its positive predictive value and negative predictive value were 95% CI of 100% and 98.72% (98.9%-99.6%) respectively, with a prevalence of 16.3%. Some significant differences were observed in the diagnostic performance of the test subject to our research between symptomatic cases and asymptomatic but infected individuals (Table 1,2,3).

Table 1. Comparison of casess with demographic and clinical features on admission RT-PCR positive.

	Male	**Female**	***P* value[a]**
Age, years	27.46 ± 3.4	29.55± 2.8	*NS*
Symptomatic infection	41 (48.8%)	43 (51.2%)	*NS*
Asymptomatic infection	8 (44.4%)	10 (55.6%)	*NS*

a Wilcoxon- Mann Whitney Test comparing medians

Table 2. COVID-19 symptoms and duration, RT_PCR+among RADT positive and negative cases.

	RADT+ (n=84) IgM(n=21), IgG(n=24), IgG+IgM(n=39)	**RADT- (n=540)**	**Total (n=624)**
Number of cases	84	540	624
RT-PCR positive	84	18	102
RT-PCR negative	0	522	522
Symptomatic infection	82	2	84
Asymptomatic infection	2	16	18
Durations of symtoms (days)	8.3 (1.5-14)	3.2 (0.5-7)	6.8 (0.5-14)

Table 3. Diagnostic performance of RADT in cases who had symptoms suggestive of COVID-19 and asymptomatic cases

	Symptomatic cases	**Asymptomatic cases**	**Total**
Prevalence of infection	13.5%	2.9%	16.3%
Sensitivity (95%CI)	96.3% (89-100)	23.4% (-3.9-48.9)	84.7% (73-94.2)
Specificity (95%CI)	100%	100%	100%
Positive predictive value	100%	100%	100%
Negative predictive value	99.7	94.2	98.9
κcsore	0.986 (0.923-1)*	0.373 (-0.005-0.721)	0.89 (0.82-0.97)*

DISCUSSION

Even though it does not continue as a pandemic, there is still a need for tests that are less complex, low-cost, simple to perform, and require fewer personnel for the early detection of SARS-CoV-2 infection. Point-of-care rapid antigen and antibody tests can fill a major gap

in diagnostic needs without burdening laboratory testing capacity. The tests can be easily administered by healthcare personnel, even without special training. They are also cheaper, performed at the point of care, and results are almost instantaneous. However, it should be kept in mind that there may be poor performance of RADTs for SARS-CoV-2 diagnosis in some early studies (Dortet et al., 2021; Sidiq et al., 2020).

In our study, it can be said that the Weimi Bio-Tech COVID-19RADT test has a not-bad clinical performance with an overall sensitivity of 84.7% (73-94.2) and a specificity of 100%. According to some guidelines published by the World Health Organization, it is acceptable that the sensitivity of these tests should be ≥80% and the specificity should be ≥97% compared to the RT-PCR test (Mina et al., 2020). The results of our current study appear generally consistent with previously reported findings in adults. However, some differences were observed in the test results reported for children. Publications are reporting that the sensitivity of rapid antibody tests in primary care is significantly lower in pediatric patients than in adults (Santos et al., 2021; Zhao et al., 2020).

Masiá et al. reported poorer testing and unreliable performance in pediatric participants. Researchers emphasized that it is difficult to collect upper respiratory tract swabs in young cases, RT-PCR tests may be more difficult to apply and standardize, and the onset, severity, and variety of symptoms may be evaluated incorrectly. Moreover, it has been reported that RT-PCR values in children may differ from adults due to unpredictable reasons (Masiá et al., 2021). In many cases, symptoms may be subtle or no COVID-19 symptoms. However, in case of suspicion of COVID-19, accurate testing and diagnosis are important, especially for the need for timely isolation to ensure accurate diagnosis and optimal treatment. The majority of symptomatic COVID-19 patients can be diagnosed with RADT tests within the week of illness (Masiá et al., 2021). In our study, only 2 (4.8%) of 42 cases with symptomatic SARS-CoV-2 infection had false-negative RADT. In one of these cases, with moderate disease, the test was performed approximately 24 hours after the onset of symptoms. In general, high false negative rates and high biases have been noted in antibody tests depending on the stage and timing of COVID-19 infection (Masiá et al., 2021; McAloon et al., 2020). This study was conducted at a time when the COVID-19 vaccine had not yet been administered. Therefore, rapid antibody production did not lead to any interference with vaccine-associated antibodies.

Another important consideration is that the potential risks of using rapid antibody tests in terms of variants of SARS-CoV-2 that will develop should not be ignored. As the virus continues to differentiate, there will always be concern that some variants may affect the performance of diagnostic tests, including rapid antibody tests. Variants may change the antibody profile as viruses emerge, potentially affecting the sensitivity and specificity of tests. These variations can lead to changes in the immune response and potentially affect the accuracy of antibody tests in detecting past infections or ongoing immunity. In a similar study, Sabat et al. emphasized that there were COVID-19 cases that gave false negative results even among symptomatic cases (Sabat et al., 2023; Yuan et al., 2020). For these reasons, antibody tests can provide valuable information about the presence of antibodies against SARS-CoV-2, especially in symptomatic cases. Continuous monitoring of results and evaluation of their performance against emerging variants is vital. In the face of evolving and differentiating viral dynamics, it will be necessary to constantly monitor and adapt diagnostic strategies to the new situation to ensure effective control and accurate management of COVID-19, like all viral infections

In a study conducted in the same period, Kaçmaz et al. concluded that although there were problems in the validation of antibody tests in COVID-19, especially for healthcare personnel, they could prevent nosocomial infections (Kaçmaz et al., 2020). Tanrıverdi et al. also reported false negatives in asymptomatic cases but emphasized that the use of rapid antibody tests in COVID-19 would be useful (Tanrıverdi Çaycı et al., 2023).

Our study had several limitations that we could see. First, the symptom description was self-reported and there is a potential risk of subjectivity bias. Additionally, we need to acknowledge that the estimated mean incubation period for COVID-19 is 5.1 days (95% CI, 4.5-5.8 days). This means that we must recognize that the optimal timing of the onset of symptoms is delayed by an average of five days from the actual onset of infection. This feature is an important limitation of antibody testing. This possibility may have resulted in poor predictive accuracy in identifying and isolating infectious cases. With the findings in mind, our study shows that the Wiemi Diagnostic Kit conditionally detects COVID-19 in symptomatic and asymptomatic cases. It may entail positive and negative predictive value and clinically poor performance, especially in infected cases that remain asymptomatic. Rapid antibody tests showed an overall sensitivity of up to 84.7% in adult cases. Additionally, in the presence of symptoms suggestive of COVID-19, sensitivity increased to 96.3%. Although the Wiemi Diagnostic Kit test meets the criteria set by WHO, we believe that it cannot replace RT-PCR, especially in hospital environments where high sensitivity is required for the correct diagnosis and prevention and early isolation of SARS-CoV-2 spread. However, the turnaround time for rapid antibody tests is much shorter than RT-PCR for eligible symptomatic cases hospitalized with COVID-19.

CONCLUSION

Therefore, we think that COVID-19 screening, which allows diagnosis, isolation, and management, may be useful in patients presenting with symptoms suggestive of the disease, especially in the first week of infection. Plans for future epidemics require mechanisms to ensure faster and more convenient delivery of gold-standard diagnostic tests. We think this planning will be important along with prevention, vaccination, and treatment.

Abbreviations:

RADT: rapid antibody detection test
RT-PCR: reverse transcription-quantitative polymerase chain reaction
HIS: hospital information system
LIS: laboratory information system
EC : ethics committee
CI: confidence interval

Authorship Contributions: Idea/Concept: A.A.F., H.K., Design: A.A.F, H.K., S.E., Data Collection: H.K. U.B., H.A.Y., Writing: A.A.F., E.T.K., U.A., Literature Review: A.A.F., S.E., E.T.K., U.A.

All authors reviewed the results and approved the final version of the manuscript.

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