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Evaluation of Rapid Antigen Test Results and Real-time Reverse Transcription Polymerase Chain Reaction for the Laboratory Diagnosis of SARS-CoV-2

SARS-CoV-2'nin Laboratuvar Tanısında Hızlı Antijen Testi ve Gerçek Zamanlı Ters Transkripsiyon Polimeraz Zincir Reaksiyonu Sonuçlarının Değerlendirilmesi

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Abstract

Introduction: Real-time reverse transcription-polymerase chain reaction (RT-PCR) is the gold standard method for the diagnosis of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection. However, real-time RT-PCR is time-consuming, expensive, and requires special laboratory conditions and experienced personnel. Thus, the diagnostic importance of faster and easier-to-perform antigen-detecting rapid diagnostic tests (Ag-RDTs) has increased. With on-site application and fast turnaround time, Ag-RDTs provide quick isolation, minimizing the risk of transmission. We aimed to compare the results of the Mö-Screen Corona Antigen Test (MöLab, Langenfeld, Germany) and real-time RT-PCR.
Materials and Methods: Nasopharyngeal swabs from 863 patients from January 2022 to March 2022 were included in the study. The SARS-CoV-2 antigen was assessed for using the Mö-Screen Corona Antigen Test. The SARS-CoV-2 real-time RT-PCR results were obtained within two days in 417 patients.
Results: The agreeability of the real-time RT-PCR and Ag-RDT results was 96.2%. The sensitivity and specificity of Ag-RDT were 84.8% and 100%, respectively. The test sensitivity increased to 92% in specimens with Ct value <25.
Conclusion: The Mö-Screen Corona Antigen Test (MöLab, Langenfeld, Germany), an Ag-RDT test with a high specificity and sensitivity, may be an alternative to real-time RT-PCR for the diagnosis of SARS-CoV-2.
Keywords: SARS-CoV-2, antigen test, COVID-19

Öz

Giriş: Şiddetli akut solunum sendromu-Koronavirüs-2 (SARS-CoV-2) enfeksiyonunun tanısında altın standart yöntem olarak gerçek zamanlı ters transkripsiyon polimeraz zincir reaksiyonu (RT-PZR) önerilmektedir. Ancak bu yöntem zaman alıcı ve pahalı olması, özel laboratuvar koşulları ve deneyimli personel gereksinimi gibi dezavantajlara sahiptir. Bu nedenle, daha hızlı ve gerçekleştirilmesi daha kolay antijen tespit eden hızlı tanı testlerinin (Ag-RDT'ler) tanısal önemi artmıştır. Yerinde uygulama ve hızlı geri dönüş süresiyle Ag-RDT'ler hızlı izolasyon sağlayarak bulaşma riskini en aza indirir. Bu çalışmanın amacı Mö-Screen Corona Antigen Testi (MöLab, Langenfeld, Almanya) ve gerçek zamanlı RT-PZR sonuçlarının karşılaştırılmasıdır.
Gereç ve Yöntem: Ocak-Mart 2022 tarihleri arasında 863 farklı hastadan alınan nazofaringeal sürüntü çalışmaya dahil edildi. Tüm sürüntü örneklerinde Mö-Screen Corona Antigen Testi ile SARS-CoV-2 antijeni arandı. Aynı zamanda bu hastaların 417'sinin iki gün içinde elde edilmiş SARS-CoV-2 gerçek zamanlı RT-PZR sonuçları mevcuttu.
Bulgular: Gerçek zamanlı-PZR ve Ag-RDT sonuçları %96,2 uyumlu bulunmuştur. Ag-RDT için duyarlılık ve özgüllük değerleri sırasıyla %84,8 ve %100 olarak belirlenmiştir. Ct değeri <25 olan örneklerde duyarlılığın %92'ye yükseldiği belirlenmiştir.
Sonuç: Mö-Screen Corona Antigen Test (MöLab, Langenfeld, Almanya) sonuçları göz önüne alındığında, özgüllüğü ve duyarlılığı yüksek olan bu Ag-RDT testinin, SARS-CoV-2 tanısında gerçek zamanlı RT-PZR'ye bir alternatif olabileceği düşünülmektedir.
Anahtar Kelimeler: SARS-CoV-2, antijen testi, COVID-19

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Introduction

The outbreak of the Coronavirus disease-2019 (COVID-19), which is caused by the novel Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2), has become a global public health concern[1]. According to the World Health Organization (WHO), more than six million people have died from COVID-19. The disease spreads rapidly to susceptible individuals via mildly symptomatic or asymptomatic carriers, despite efforts to contain the disease[2-4].

The development of tests that accurately detect COVID-19 to prevent the spread of the virus and that rapidly detect acute cases is a priority[5]. The gold standard test for the diagnosis of SARS-CoV-2 is the real-time reverse transcription-polymerase chain reaction (RT-PCR) test[6]. However, real-time RT-PCR tests require professional personnel and specialized laboratory equipment. Furthermore, it is expensive, and has a long turnabout time[7,8]. Therefore, faster and simpler tests are needed to rapidly detect and control the disease in infected individuals. Recently, SARS-CoV-2-specific antigen-detecting rapid diagnostic tests (Ag-RDTs) have become available, which provide a simple and rapid alternative to nucleic acid amplification tests[9].

In this study, we aimed to compare the Ag-RDT and real-time RT-PCR testing methods for the detection of SARS-CoV-2.

Materials and Methods

The results of the SARS-CoV-2 Ag-RDT and real-time RT-PCR tests using nasopharyngeal swabs of patients with suspected COVID-19 between January 2022 and March 2022 at the Faculty of Medicine of Ondokuz Mayıs University were compared. This retrospective a study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (number: B.30.2.ODM.0.20.08.151; decision number: 2022/118; date: 16/03/2022).

Nasopharyngeal swabs for both methods were obtained by experienced personnel. Viral transfer tubes (vNAT; Bioeksen R&D Technologies INC, İstanbul, Turkey) were used to transfer the specimens for real-time RT-PCR. For Ag-RDT, the samples were collected in a sterile tube without any transport medium and delivered immediately (maximum within 1 hour) to the laboratory. Subsequently, the COVID-19-related symptoms (fever, loss of taste and smell, cough, dyspnea) of patients whose real-time RT-PCR test was positive were obtained retrospectively from the hospital database. The dual-gene kit DS Coronex RT-PCR (DS Bio and Nano Technologies INC, Ankara, Turkey), targeting the SARS-CoV-2-specific gene regions ORF1ab and N (nucleocapsid) (FAM), and CFX96 RT-qPCR system (Bio-Rad Laboratories INC, California, USA) was used for RNA amplification. The human RNase P gene (HEX) was used for nucleic acid extraction and inhibition control. Non-sigmoidal curves were considered as "negative" results. Sigmoidal curves with a cycle threshold (Ct) ≤33 for FAM were considered as "positive" results. The Ct values of all positive results were recorded. The real-time RT-PCR amplification program steps are as follows; 5 minutes at 45 °C, five cycles at 95 °C for 5 seconds and 55 °C for 10 seconds, followed by 35 cycles at 95 °C for 5 seconds and 55 °C for 1 second (Table 1).

The Ag-RDT kit (Mö-Screen Corona Antigen Test; MöLab GmbH, Langenfeld, Germany) uses the colloidal, gold-enriched, double-antibody sandwich method to determine the presence of SARS-CoV-2 antigen. Results were read manually 15 minutes after adding the sample to the test well. Cards that showed both control (C) and test (T) lines were considered as "positive" results.

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) statistics (version 22.0; SPSS Inc., Illinois, USA). Demographic data are presented as percentages. The relationships between real-time RT-PCR and Ag-RDT, Ct values, and Ag-RDT and between symptom status and Ag-RDT results were analyzed using Pearson's chi-squared test. Statistical significance was set at $p<0.05$.

Results

Nasopharyngeal swab samples from 863 patients with suspected COVID-19 were studied using Ag-RDTs. The Ag-RDT results of 417 patients whose real-time RT-PCR results were available within 48 hours were included in the study. The median age was 38 years [interquartile range (IQR), 10-0]. Of the included patients, 138 were <18 years old, 100 were >65 years-old. Furthermore, 210 patients were males (Table 2).

Table 1. Real-time RT-PCR amplification program

Cycle	Temperature	Time
1	45 °C	5 min
1	95 °C	1 min
5	95 °C	5 s
	55 °C	10 s
35	95 °C	5 s
	55 °C	1 s

RT-PCR: Real time reverse transcription-polymerase chain reaction, s: Second, min: Minute

Table 2. Sex and age distribution of the included patients

Variables		n (%)
Sex	Female	207 (49.6)
	Male	210 (50.4)
Age	0-17	138 (33.1)
	18-64	179 (42.9)
	>65	100 (24)

Compared with real-time RT-PCR, the sensitivity and specificity of Ag-RDT were determined as 84.8% and 100%, respectively. Furthermore, its positive and negative predictive values were 100% and 96.5%, respectively. The number of samples with positive Ag-RDT results was 67 (16.1%). The real-time RT-PCR results of 64 samples were positive on the same day with Ag-RDT. The real-time RT-PCR results of three samples were negative on the same day with Ag-RDT. However, the real-time RT-PCR performed the next day with a new sample from the three patients was detected as positive. Since our study was based on real-time RT-PCR results obtained within 48 hours, these patients were included in the real-time RT-PCR-positive patient group. Approximately 18.9% (79/417) of samples were detected to be COVID-19-positive by real-time RT-PCR. Comparison of the real-time RT-PCR and Ag-RDT results of 417 patients indicated an agreeability of 96.2%; discordant results were obtained in 16 patients, among these patients, 12 had negative Ag-RDT results and positive real-time RT-PCR results. In three patients, the Ag-RDT were positive and same day real-time RT-PCR results were negative. However, the real-time RT-PCR results of these patients were positive when new samples obtained the next day were used. In one patient, the Ag-RDT result was invalid (no control line was observed) and real-time RT-PCR was negative. Furthermore, in four patients, a weak test line appeared; the real-time RT-PCR results of these patients were positive. Based on the manufacturer's recommendations, the Ag-RDT results of these patients were considered to be positive (Table 3).

The median Ct value of real-time RT-PCR results was 23.3 (IQR, 17.8-25.8) among Ag-RDT-positive samples and 25.9 (IQR, 24.9-30.2) among Ag-RDT-negative samples. The sensitivity of Ag-RDT increased to 92% in samples with a Ct value <25. However, the sensitivity was 79.1% in samples with 25 < Ct < 30 and 0% in samples with 30 < Ct < 33 (Table 4). A significant difference in the sensitivity based on a Ct cutoff of 25 was identified between Ag-RDT-positive and Ag-RDT-negative samples ($p<0.05$).

Patients with at least one of the following symptoms were grouped as symptomatic patients: fever, cough, dyspnea, and loss of taste and/or smell. Approximately, 75.9% (60/79) of the real-time RT-PCR-positive patients were symptomatic. Approximately 80% of symptomatic patients developed only one symptom; the remaining 20% developed more than one symptom. The most common symptom was fever (60%). Ag-RDT sensitivity was 88% and 52.7% in the real-time RT-PCR-positive symptomatic and asymptomatic patients, respectively. Ag-RDT-positivity was significantly higher among the symptomatic patients than among the asymptomatic patients ($p<0.00001$) (Table 5). The real-time RT-PCR Ct values of symptomatic and asymptomatic patients were 21.5 and 24.9, respectively.

Table 3. Comparison of the real-time RT-PCR and Ag-RDT results

		Ag-RDT			Total n (%)
		Positive n (%)	Negative n (%)	Invalid n (%)	
Real-time RT-PCR	**Positive n (%)**	67* (16.1)	12 (2.9)	-	79 (18.9)
	Negative n (%)	-	337 (80.8)	1 (0.2)	338 (81.1)
Total n (%)		67 (16.1)	349 (83.7)	1 (0.2)	417

*Three patients who were Ag-RDT-positive and real-time RT-PCR-negative on the same day, but real-time RT-PCR-positive the next day, were included in this group. $p<0.05$.

RT-PCR: Real-time reverse transcription-polymerase chain reaction, Ag-RDT: Antigen-detecting rapid diagnostic tests

Table 4. Ct values in real-time RT-PCR-positive samples

Ct values	Real-time RT-PCR-positive			
	Ag-RDT-positive		Ag-RDT-negative	
	n (%)	Median Ct (range)	n (%)	Median Ct (range)
Ct < 25	48* (71.7)	20.45 (13.7-24.9)	4 (33.3)	23.3 (22.3-24.6)
25 ≤ Ct < 30	19 (28.3)	27.85 (25-29.9)	5 (41.7)	26.4 (25.6-29.3)
30 ≤ Ct ≤ 33	-	-	3 (25)	31.9 (30.8-32.5)
Total	67 (100)	23.3 (13.7-29.9)	12 (100)	25.9 (22.3-32.5)

*Three patients who were Ag-RDT-positive and real-time RT-PCR-negative on the same day, but real-time RT-PCR-positive the next day, were included in this group. $p<0.05$

Ct: Cycle threshold, RT-PCR: Real time reverse transcription-polymerase chain reaction, Ag-RDT: Antigen-detecting rapid diagnostic tests

Table 5. Symptom status in real-time RT-PCR-positive samples

Symptom status	Real-time RT-PCR-positive	
	Ag-RDT-positive	Ag-RDT-negative
Symptomatic (n=60)	58* (96.7%)	2** (3.3%)
Asymptomatic (n=19)	9 (47.3%)	10 (52.7%)

*Three patients who were Ag-RDT-positive and real-time RT-PCR-negative on the same day, but real-time RT-PCR-positive the next day, were included in this group.

**Patients with symptom persisting >10 days. p<0.05.

RT-PCR: Real time reverse transcription-polymerase chain reaction, Ag-RDT: Antigen-detecting rapid diagnostic test

Discussion

The priority in controlling the spread of COVID-19 is based on rapid and cost-effective detection in symptomatic patients and their contacts. The appropriate application and interpretation of Ag-RDTs can help detect positive cases faster and at a lower cost than real-time RT-PCRs, especially in symptomatic individuals[10,11]. This increases the importance of Ag-RDTs in the diagnosis of COVID-19.

Several studies have evaluated antigen tests, and depending on the commercial kits used, different sensitivity and specificity results have been obtained. In India, France, and Japan, the sensitivity of antigen tests is reportedly 63.3%, 69.6%, and 84.7%, respectively, and the specificity is reportedly 96.8%, 99.9%, and 94.9%, respectively[12-14].

The results of the Sofia SARS-CoV-2 rapid antigen test kit was compared to that of real-time RT-PCR results in a German study with 7877 patients. The study revealed that the Sofia SARS-CoV-2 rapid antigen test kit had an overall sensitivity of 62.9% and specificity of 99.4%. Furthermore, the sensitivity increased to 94.2% in samples with Ct values ≤25. Additionally, the sensitivity of Ag-RDT in real-time RT-PCR-positive symptomatic patients was 72.1%[15]. Another study compared the results of the third-generation antigenic swab LumiraDx with that of real-time RT-PCR results. Of the 282 patients included in the study, 80.9% (n=228) were real-time RT-PCR-positive. Of the 228 RT-PCR-positive patients, 174 had positive LumiraDx results. The sensitivity and specificity of LumiraDx were 76.3% and 94.4%, respectively. Test sensitivity within the first 10 days of onset of symptoms increased to 91%, and determined as 95%at the specimens withCt was <25[16]. In another study, the performance of an Ag-RDT, RapidForTM Antigen Rapid Test Kit, for detecting SARS-CoV-2 nucleocapsid antigen in nasopharyngeal swab samples was evaluated. A total of 346 real-time RT-PCR-positive and 98 real-time RT-PCR-negative samples were included and the overall sensitivity and specificity were 80.3% and 87.8%, respectively. Furthermore, the sensitivity increased to 95.7% in samples with 20 ≤ Ct <25 and 100% in samples with Ct < 20[17]. In our study, the sensitivity and specificity of the Ag-RDT were 84.8% and 100%, respectively. Furthermore, similar to previous studies, the test sensitivity increased to 92% in samples with Ct < 25.

According to WHO, the minimum sensitivity and specificity requirements for rapid antigen tests for the diagnosis of SARS-CoV-2 are 80% and 97%, respectively[18]. The test sensitivity of most of the previous studies are below the WHO-recommended value. However, the overall sensitivity and specificity obtained in our study are above WHO-recommended values.

In our study, 12 patients were the real-time RT-PCR-positive and Ag-RDT-negative. Of these patients, two were symptomatic, with symptoms persisting for >10 days, and 10 were asymptomatic. This suggests that antigen tests are more reliable in the early stages of infection than in the late stages of infection. Furthermore, Ag-RDTs may produce false negative results in asymptomatic patients. In our study, the Ag-RDT sensitivity was 88% and 52.6% in the real-time RT-PCR-positive symptomatic and asymptomatic patients, respectively. Similarly, in the study by Bornemann et al.[15] and Pray et al.[19] the Ag-RDT sensitivity in the real-time RT-PCR-positive symptomatic patients was 89% and 72.1%, respectively, and in the real-time RT-PCR-positive asymptomatic patients was 41.2% and 46.8%, respectively. Additionally, in our study, the median Ct value was significantly lower in the real-time RT-PCR-positive symptomatic patients than in the real-time RT-PCR-positive asymptomatic patients. Thus, contagiousness and viral load may be higher in symptomatic patients, and thus may be associated with low Ct values. Studies have shown that a high viral load in COVID-19 is associated with high disease infectivity and predisposition to a symptomatic illness. Ag-RDTs perform best in individuals with high viral loads and in the early stages of an infection. Furthermore, they are most reliable when the prevalence of SARS-CoV-2 is >5%. The easy applicability, cost-effectiveness, and quick turnaround time of Ag-RDTs allow a large number of individuals to be screened in a short time. However, it has a lower sensitivity than the real-time RT-PCR in asymptomatic individuals[11,20,21]. Furthermore, the relationship between Ct and infectivity could not be proven in our study. The virus can reportedly be cultured even with samples with Ct values >30 or after day 10 of symptom onset[22-24]. These studies indicate that there may not be a relationship between Ct values

and contagiousness. Thus, Ag-RDTs may produce false positive and false negative results, which is a disadvantages of the test.

There may be an increase in false negativity in asymptomatic individuals or when the disease frequency is low. In these conditions, the first-line test should be the real-time RT-PCR. Alternatively, negative Ag-RDT results should be confirmed by the real-time RT-PCR. Current guidelines recommend using Ag-RDTs in patients with symptoms consistent with COVID-19 and retesting after 1-2 days in asymptomatic patients with negative Ag-RDT results[25]. In the study conducted by Park et al.[26] with an Ag-RDT similar to ours, the positive and negative predictive values of the test were 90.3% and 97.9%, respectively. In our study, the positive and negative predictive values of the test were 100% and 96%, respectively.

Study Limitations

The limitations of our study were that no additional procedures were performed for viscous samples and some results were invalid. In further studies, preprocessing steps can be made using dithiothreitol, N-acetyl-L-cysteine, or proteinase K to reduce viscosity and their effects on the study can be investigated.

Conclusion

The Mö-Screen Corona Ag-RDT kit was useful in t:he rapid diagnosis of COVID-19. It can be a good diagnostic tool, especially when the number of positive patients and the importance of early isolation measures increase. However, considering the test's false-positivity and false negativity, a negative result cannot exclude the possibility of a COVID-19 infection. In such instances, the patient should be evaluated based on clinical findings and the diagnosis should be confirmed with the real-time RT-PCR.

Ethics

Ethics Committee Approval: This retrospective a study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (number: B.30.2.ODM.0.20.08.151; decision number: 2022/118; date: 16/03/2022).

Informed Consent: Informed consent form was not received due to the retrospective nature of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Y.T.Ç., Design: Y.T.Ç., Z.S., K.H.Ü., Data Collection or Processing: Y.T.Ç., Z.S., K.H.Ü., H.U.A., E.A.Ö., Analysis or Interpretation: Y.T.Ç., Z.S., K.H.Ü., D.G.V., K.B., Literature Search: Y.T.Ç., Z.S., K.H.Ü., Writing: Y.T.Ç., Z.S., K.H.Ü.

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