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COVID-19 Real Time PCR Test Sonuçlarının PCR Cihazı ve CAtenA Smart PCR Bioinformatik Programı Üzerinden Değerlendirme Sürelerinin Karşılaştırılması

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ÖZET

İlk kez Aralık 2019'da Çin'in Wuhan eyaletinde ortaya çıkan SARS-CoV-2 kaynaklı COVID-19 enfeksiyonu, tüm dünyada yıkıcı etkisini hala sürdüren bir pandemiye neden olmuştur. COVID-19 tanısında kullanılan standart tanı yöntemi nükleik asit çoğaltma yöntemidir. CAtenA Smart PCR, yapay zekâ kullanarak PCR veri analizi yapan ve kullanıcıya sonuç önerisinde bulunan bioinformatik bir programdır. Bu çalışmanın amacı, uzman hekimin PCR test verilerini cihaz başında değerlendirerek, sonuçları laboratuvar bilgi yönetim sistemine aktarma süresi ile CAtenA Smart PCR üzerinden değerlendirme süresi arasındaki farkın kıyaslanmasıdır. Konya Meram Devlet Hastanesi COVID-19 PCR Tanı Laboratuvarında 1 Eylül-30 Kasım 2021 tarihleri arasında çalışılmış ve her biri 94 farklı örnek ve iki iç kalite kontrolden oluşan 139 PCR çalışma verisi uzman hekimler tarafından PCR cihazından (Bio-Rad CFX96 Touch, Singapore) ve CAtenA programı (Ventura, Ankara, Turkey) üzerinden değerlendirilerek analiz süreleri kayıt altına alınmıştır. PCR cihazı üzerinden yapılan 139 teste ait ortalama analiz süresi 14,05 ± 7,55 dakika, CAtenA programı üzerinden yapılan ortalama analiz süresi 8,04 ± 3,93 dakika olarak bulunmuştur. Wilcoxon signed ranks testi ile istatistiksel analiz yapılmıştır. Analiz süreleri arasında anlamlı bir fark olduğu belirlenmiştir (p = 0,0001). Çalışma süreci, pozitiflik oranlarının veri analiz süresine etkisini görmek için yüksek pozitiflik ve düşük pozitiflik dönemi olmak üzere ikiye ayrılmıştır. İki grubun analiz süreleri arasında anlamlı fark olduğu belirlenmiştir (p = 0,0001). Bulguların vaka pozitiflik oranlarının PCR cihazı ve CAtenA üzerinden yapılan analiz sürelerini etkilediği görülmüştür. Sonuç olarak, PCR verilerini ön analizden geçirerek uzman onayına sunan ve sonuçları web tabanlı sonuç sistemine doğrudan aktarabilen CAtenA Smart PCR yapay zekâ programının, veri analiz süresini kısalttığı ve kullanıcıya kolaylık sağladığı belirlenmiştir.

Comparison of the Turnaround Times of COVID-19 Real Time PCR Data on the PCR Instrument and the Catena Smart PCR Bioinformatics Program

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ABSTRACT

The COVID-19 pandemic, which was caused by the SARS-CoV-2 virus, emerged in Wuhan, China in December 2019, and has had a detrimental impact worldwide. The nucleic acid amplification tests are the recommended method for the diagnosis of COVID-19. CAtenA Smart PCR is an artificial intelligence-based bioinformatics tool that assists with PCR data interpretation

CAtenA Smart PCR
COVID-19
Data analysis
Artificial intelligence
Turnaround time

and offers conclusion preferences before transaction to the web-based result systems. The aim of this study was to compare the turnaround times between the data analysis on a PCR instrument, including result submission, and the CAtenA Smart PCR-assisted analysis. The specialists assessed 139 PCR data sets, each with 94 samples and two internal controls, that were performed in the COVID-19 PCR Diagnostic Laboratory at Meram State Hospital in Konya between 1 September and 30 November 2021. The data analysis times for the PCR tool (Bio-Rad CFX96 Touch, Singapore) and the CAtenA Smart PCR Bioinformatics Program (Ventura, Ankara, Turkey) were recorded. The mean time duration of the 139 PCR data analyses for the PCR device was 14.05 ± 7.55 and 8.04 ± 3.93 minutes for the CAtenA. The Wilcoxon signed ranks test was used for the statistical analysis. The difference between the turnaround times for the PCR instrument and CAtenA Smart PCR was found to be statistically significant (p = 0.0001). We further divided the study period into two groups: the high-positivity phase and the low-positivity phase. We compared the two phases in order to assess the effect of the case positivity rates on the turnaround times. There was a significant difference between the turnaround times of the two groups (p = 0.0001). The findings showed that the positivity rate has affected the time duration of data analysis on both the PCR instrument and the CAtenA program. As a result, employing artificial intelligence-based CAtenA Smart PCR to interpret PCR data and send transactions to the web-based result systems reduces the time it takes to complete the task and gives the user more convenience.

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Introduction

The clinical microbiology laboratories perform a wide range of activities, from determining the pathogens in a patient's infection to assisting in the identification of global outbreaks, such as the COVID-19 pandemic. Throughout the ongoing pandemic, authorized COVID-19 diagnostic laboratories have been working as part of clinical microbiology laboratories at health care facilities. Currently, approximately 600 COVID-19 diagnostic laboratories are authorized in Turkey, with over 350,000 polymerase chain reaction (PCR) tests performed per day (URL_1). According to the World Health Organization, the PCR assay is one of the recommended diagnostic techniques for COVID-19 (URL_2). Real-time PCR technology allows for the simultaneous amplification, identification, and visualization of nucleic acids from a target microorganism. The COVID-19 has been at the forefront of research since its inception, and the real-time PCR assay is the most widely used nucleic acid amplification test in the world (Tasdelen and Ugur, 2021). Data from PCR tests are processed on the PCR device by a professional and entered into the Laboratory Information Management System (Laboratuvar Bilgi Yönetim Sistemi, LBYS), a web-based results entry and display tool. The PCR results are then automatically transmitted to the e-pulse Personal Health (e-nabız Kişisel Sağlık Sistemi, e-nabız) and Public Health Management Systems (Halk Sağlığı Yönetim Sistemi, HSYS) (Figure 1). CAtenA Smart PCR is a web-based bioinformatic application that uses artificial intelligence (AI) and integrates data from PCR instruments without the need for installation. A professional can either analyze data without depending on artificial intelligence-based tips or approve

its suggestions. After expert approval, the PCR results are transected to the LBYS, HSYS, and e-pulse (URL_3).

Figure 1. The process of collecting data, analyzing it, and submitting the results. The specialist should manually submit the results to the Laboratory Information Management System upon completion of the analysis on the PCR instrument. On the other hand, the approved results are automatically transacted to the Laboratory Information Management System via the CAtenA.

Laboratories are required to maintain the highest level of quality while increasing efficiency. All of the procedures performed by laboratories are becoming increasingly intertwined with bioinformatics. The use of artificial intelligence and bioinformatics effectively can improve the accuracy and timeliness of assays, while reducing laboratory workload, resulting in improved laboratory efficiency and reductions in healthcare costs (Rhoads et al., 2014; Egli et al., 2020). In laboratories, there has recently been an increase in demand for high-quality digital laboratory data. The aim of this study was to compare the turnaround times between the data analysis on a PCR instrument, including result submission, and the CAtenA Smart PCR-assisted analysis.

Material and Methods

Three specialists assessed a total of 139 PCR data sets, each of which included 94 samples and two internal controls, completed in the COVID-19 PCR Diagnostic Laboratory at Meram State Hospital in Konya between September and November 2021. All specialists had equal experience in PCR laboratory management. Only full plate assays were included in the study in order to equalize the performance required for the data analysis. Each specialist evaluated the same assay both on a PCR device-connected computer (Bio-Rad CFX96 Touch, Singapore) and on the CAtenA smart PCR Bioinformatics Program (Ventura, Ankara, Turkey). All PCR experiments were performed using Diagno5 plex NS SARS-CoV-2 Real-Time PCR Kit (A1 Life Sciences, Istanbul, Turkey). The study

period was further divided into two distinct groups according to the intensity of case positivity rates in Konya: one was termed the “high-positivity phase” (n = 80) in September, and the other as the “low-positivity phase” (n = 59) in November.

The specialists recorded the performed time duration of the data analysis for the PCR instrument and for the CAtenA. The time duration of the result entry procedure to the LBYS was added to the analysis time on the PCR instrument. The transaction to the LBYS was an integral part of the data analysis of the CAtenA.

Since the data were not regularly distributed, the Wilcoxon test, which is a nonparametric test, was utilized to determine if there was any significant difference between the turnaround times. The same statistical test was used to compare the turnaround times of the high- and low-positivity phases. A *p* value of less than 0.005 was used to determine statistical significance. SPSS 26 (IBM, USA) was used to conduct the statistical analysis.

Ethics approval for this study was obtained from the Necmettin Erbakan University Ethics Committee, Reference: 2021/3510 (7807).

Results and Discussion

In the present study, we found that the mean turnaround time of the 139 PCR data sets for the PCR instrument was 14.05 ± 7.55 min. The CAtenA Smart PCR had a mean turnaround time of 8.04 ± 3.93 min. for the 139 PCR data analysis (Table 1). The turnaround times on the CAtenA Smart PCR and the PCR instrument were determined to be statistically significant ($p = 0.0001$).

Table 1. The average turnaround times for 139 data sets' analyses.

	Mean (minutes)	**N**	**SD**	**Min.**	**Max.**
AI-based evaluation (CAtenA)	8.0400	139	3.92787	2.00	19.00
Data analysis on PCR Instrument	14.0468	139	7.55001	4.00	31.00

We further divided the study period into two groups: the high-positivity phase, which was shortly after the Delta variant of SARS-CoV-2 surge in September, and the low-positivity phase, which was assigned as the case where positivity rates declined in November in Konya. We compared the two periods in order to assess the effect of the case positivity rates on the turnaround times. The mean positive results per PCR assay in the high-positivity and the low-positivity periods were 21.36 ± 8.79 and 7.15 ± 3.69, respectively (Table 2). There was a significant difference between the turnaround times of the two groups ($p = 0.0001$). The findings showed that the positivity rate has affected the time duration of data analysis on both the PCR instrument and the CAtenA program (Table 3 and 4).

Table 2. Descriptive statistics for positivity rates in high- and low-positivity phases.

	Phase			Statistic	Std. Error
POSITIVES	Low-positivity	Mean		7.15	0.480
		95% Confidence Interval for Mean	Lower Bound	6.19	
			Upper Bound	8.11	
		5% Trimmed Mean		6.94	
		Median		6.00	
		Variance		13.614	
		Std. Deviation		3.690	
		Minimum		2	
		Maximum		20	
		Range		18	
		Interquartile Range		6	
		Skewness		0.900	0.311
		Kurtosis		1.165	0.613
	High-positivity	Mean		21.36	0.984
		95% Confidence Interval for Mean	Lower Bound	19.40	
			Upper Bound	23.32	
		5% Trimmed Mean		21.18	
		Median		21.00	
		Variance		77.424	
		Std. Deviation		8.799	
		Minimum		5	
		Maximum		42	
		Range		37	
		Interquartile Range		13	
		Skewness		0.183	0.269
		Kurtosis		-0.461	0.532

Table 3. A brief summary of group statistics for both AI-based (CAtenA) and PCR instrument-based evaluation time.

	Period Name	N	Mean	SD
AI-based evaluation (CAtenA)	Low-positivity Period	59	4.9671	1.87707
	High-positivity Period	80	10.3063	3.48005
Data analysis on PCR Instrument	Low-positivity Period	59	7.4493	4.28691
	High-positivity Period	80	18.9125	5.44057

Table 4. Statistical analysis between turnaround times of analyses in the high- and low-positivity periods.

	AI-based evaluation (CAtenA)	Data analysis on PCR Instrument
Mann-Whitney U	336.500	299.500
Wilcoxon W	2106.500	2069.500
Z	-8.669	-8.809
Asymp. Sig. (2-tailed)	0.000	0.000

Despite the availability of laboratories 24 hours a day, seven days a week, the workload at COVID-19 PCR diagnostic facilities has increased throughout the pandemic. Due to the exponential development in the number of COVID-19 cases around the world, the healthcare system is overloaded (Ding et al., 2021). Also, most countries have seen a significant rise in healthcare expenses, with more than doubling in the last decade (URL_4). In addition, the clinical microbiology laboratory is essential in identifying and preventing local infectious outbreaks (Kho et al., 2013). Timeliness is critical, since reducing the time it takes to notice an outbreak can dramatically reduce its negative impact (Sintchenko and Gallego, 2009).

The prompt completion of the PCR assays, as well as their error-free transaction to the system, is critical for the diagnosis, treatment, and follow-up of COVID-19, as well as controlling the pandemics. In order to communicate effectively with public health authorities and rapidly identify outbreaks, bioinformatics tools and artificial intelligence are essential (Xu et al., 2021).

Artificial intelligence, such as machine learning and deep learning, helps to strengthen the health system by allowing for the analysis of complicated and huge data sets processed in clinical laboratories (Peiffer-Smadja et al., 2020). For instance, applications that visually analyse gram stain-based images, stool microscopy, and digital bacterial cultures from growth medium have been successfully utilized (Rhoads et al., 2015). Artificial intelligence has recently begun to replace image analysis in a variety of data sources and applications in clinical microbiology laboratories (Smith et al., 2020; Asada et al., 2021). Furthermore, MALDI-TOF mass spectrometry (matrix-assisted laser desorption-ionization/time of flight mass spectrometry) and the use of artificial intelligence in whole genome analysis have broken new ground in the field of microbiology (van Oosten and Klein, 2020).

Applications used for molecular assays may vary in their interoperability and integration with the laboratory management systems. Based on our best knowledge, there is few data concerning the tools

enabling PCR data analysis with the aid of artificial intelligence and bioinformatics. The CAtenA Smart PCR is a tool that automates data flow and eliminates post-analytical errors caused by manual data entry, providing users with quick and reliable results (URL_3). Also, we previously assessed the high consistency between the expert analysis and the analysis of CAtenA too (Uğur and Taşdelen, 2021).

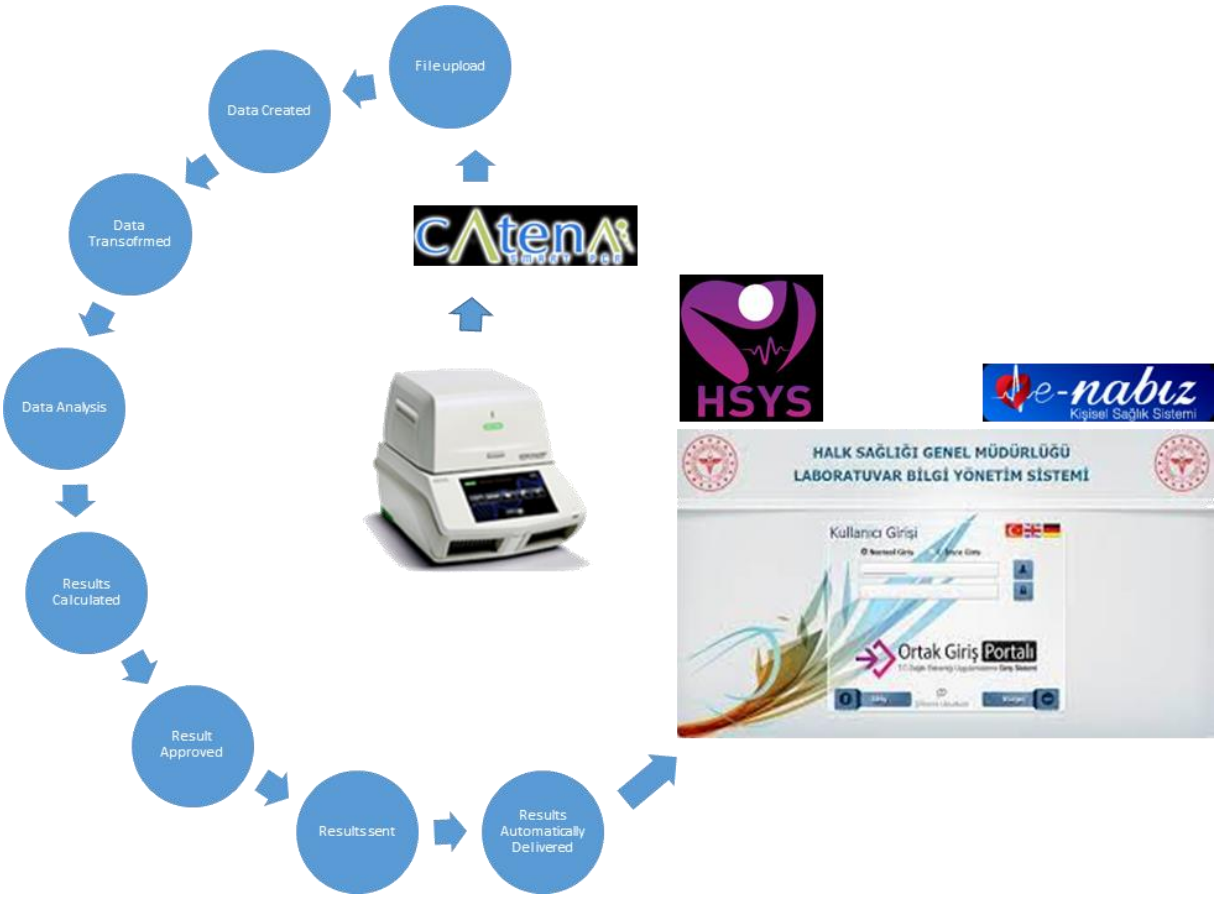

Figure 2. A schematic diagram of the workflow of the CAtenA Smart PCR.

In the present study, we found that using a bioinformatics tool integrated with artificial intelligence can significantly decrease the turnaround time of COVID-19 PCR tests, enabling more rapid completion of PCR tests. We also showed that, the duration of turnaround time decreased as the positivity rate declined. Another advantage was that the direct transaction of the results from the CAtenA to the LBYS could prevent post-analytical errors.

There are several limitations regarding our findings. The limited number of analyzed PCR data sets was one of the limitations of the present study. Our findings regarding factors affecting the turnaround times of data analyses were limited only by the positivity rates. The capacity and number of multiplex detections of SARS-CoV-2 variants, the sensitivity and specifity of the PCR kit, PCR device software specialties the quantity of inconclusive results (e.g., the recommendation of CAtenA for repeating tests), and experience of the user could all influence the length of the analysis. Another study restriction was that the data sets were examined by only three professionals. The fact that users' PCR

and program experience may have an impact on the PCR data analysis time. In the microbiology laboratory, AI has aided laboratory personnel in facilitating and speeding up diagnostic testing. The diversity, quality, and reliability of AI-based technologies, as well as the integration of AI into the clinical laboratory workflow, appear to be increasing in the not-too-distant future. Joint studies in multidisciplinary science fields such as medicine, computer, artificial intelligence, and bioinformatics are needed to develop and improve the qualification and capacity of diagnostic tests.

Conclusion

In the clinical microbiology laboratory, an ever-increasing amount of data must be created, evaluated, and interpreted. In conclusion, CAtenA Smart PCR artificial intelligence may aid users in interpreting PCR data and transacting to the LBYS, which speeds up the procedure and makes it more convenient for the user. The use of a bioinformatics tool in a laboratory allows for quick and consistent data entry. Artificial intelligence and bioinformatics tools will continue to improve patient and public health care in the future.

Statement of Conflict of Interest

Authors have declared no conflict of interest.

Author's Contributions

The contribution of the authors is equal.

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