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Comparing artificial intelligence based diagnosis with expert results in SARS-COV-2 RT-qPCR

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ABSTRACT

Objectives: Reverse transcription and real-time polymerase chain reaction (RT-qPCR) based on the SARS-CoV-2 viral RNA demonstration is the gold standard in diagnosis. Data files obtained from PCR devices should be analysed by a specialist physician and results should be transferred to Laboratory Information Management System (LIMS). CAtenA Smart PCR (Ventura, Ankara, Türkiye) program is a local bioinformatics software that assess PCR data files with artificial intelligence, submits to expert approval and transfers the approved results to LIMS. The aim of this study is to investigate its accuracy and matching success rate with expert analysis.

Methods: A total of 9400 RT-qPCR test results studied in Ankara Provincial Health Directorate Public Health Molecular Diagnosis Laboratory were compared with respect to expert evaluation and CAtenA results.

Results: It was determined that the preliminary evaluation results of the CAtenA matched 86% of the negative and 90% of the positive results provided by expert analysis. 987 tests which CAtenA determined as inconclusive and suggested repeating PCR were found either negative or positive by expert analysis. A significant difference between positive and negative matching success rates and artificial intelligence (AI) based software overall accuracy was found and associated with the missed tests of the AI.

Conclusions: As a result, it was suggested there is a low risk of confirming false positive results without expert analysis and test repetitions would cause losing time along with extra test costs. It was agreed that the PCR analysis used in CAtenA should be improved particularly in terms of test repetitions.

Keywords: SARS-CoV-2, RT-qPCR, expert analysis, CAtenA, artificial intelligence

Coronavirus disease-2019 (COVID-19), emerged in Wuhan, China in late 2019 and became a pandemic, is an infectious disease caused by SARS-CoV2 (Severe Acute Respiratory Syndrome Coronavirus-2) that affects the respiratory tract [1]. World Health Organization (WHO) declared COVID-19 pandemic on March 11, 2020 [2]. The effectiveness of variant viruses is considered as one of the reasons for increasing SARS-CoV-2 infection which is spreading steadily as is the case worldwide. Five variants in the SARS-CoV-2 have been identified as Variant of Concern (VOC) category so far including the WHO's last weekly status report published on 06 April 2022 [3]. These variants are termed as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529) [3]. WHO reported that the standard diagnosis of SARS-Cov-2 will be made by nucleic acid amplification method [4]. The most widely used

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among these methods is the SARS-CoV-2 real time polymerase chain reaction test [5]. In our country, SARSars-CoV-2 VOCs are studied by microbiology laboratories determined by the TR Ministry of Health [6] with one-step reverse transcription and real-time polymerase chain reaction (RT-qPCR) tests based on the detection of mutated regions in viral RNA vNAT (viral nucleic acid extraction buffer) transfer tubes, also provided by the Turkish Ministry of Health, are used for the transport and storage of nasopharyngeal swab samples for this purpose [7]. PCR data files should be analysed by the expert in the laboratory and the results should be transferred to the web-based Laboratory Information Management System after SARS-CoV-2 RT-qPCR test. Testing services are carried out 24/7 and an intense workflow continues in the COVID-19 PCR diagnostic laboratories which are opened with the pandemic. The rapid completion of these tests and their error-free transfer to the system are very important steps for the diagnosis, treatment, and follow-up of COVID-19 [8]. Programs with artificial intelligence such as machine learning and deep learning contribute to the development of the health system by enabling the analysis of complex and large data sets processed in clinical laboratories [9, 10]. Artificial intelligence (AI) has started to take its place in image analysis and various data sources and applications in Microbiology laboratories recently [11, 12]. Matrix-assisted laser desorption-ionization/time of flight mass spectrometry and processing of all gene analysis data with artificial intelligence has opened a new era in microbiology field [13].

CAtenA Smart PCR (Ventura, Ankara, Turkey) is a web-based bioinformatics software that evaluates PCR data files with artificial intelligence, submits them to expert approval and can transfer the approved results to the Laboratory Information Management System [14]. CatenA aims to assist the specialist physician in the rapid conclusion of the tests. The aim of this study is to investigate compatibility of the preliminary evaluation results carried out by the CatenA Smart PCR program with specialist physician analysis result.

METHODS

A hundred PCR studies, each containing 94 patient samples and two internal quality control samples, were performed at Ankara Provincial Health Directorate Public Health Molecular Diagnosis Laboratory between April 15, 2021, and November 15, 2021 and uploaded to the online CatenA (Ventura, Ankara, Turkey) artificial intelligence system. A medical virologist analyzed PCR data through the program. The preliminary evaluation results of the program and the expert results were recorded in electronic environment. Negative and positive controls which are internal quality control were excluded from the assessment. Thus, 9400 PCR test results were included in the study.

Ethical approval was obtained from Yıldırım Beyazit University Yenimahalle Training and Research Hospital Scientific Research Ethics Committee (Decision No: E-2022-22) to conduct this study. Samples were obtained after written informed consent had been obtained, and all procedures were performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical Analysis

Analysis of PCR Tests

The statistical evaluation and accuracy calculation were performed by utilizing classification matrix also known as confusion matrix. The assessments and their justification are detailed in the following section under results.

RESULTS

It was determined that the preliminary evaluation results of the CatenA Smart PCR program matched 94% of the negative and 92.5% of the positive results provided by expert analysis. 91.2% of the 987 test results for which CatenA suggested repeating PCR were found to be negative by expert analysis while 8.8% of them were positive. It has been determined that the samples for which CatenA recommends retesting have 0% match with the expert analysis.

The matching rates of CAtenA with expert analysis results with respect to negative and positive classification were almost 86% and 90% respectively (Table 1). Precise false positives (73 patients for whom unnecessary quarantine and treatment will be applied) and false negatives (166 patients who requires quar-

Table 1. Comparison of PCR test results with CAtenA smart PCR program and expert analysis.

Method	Negative	Positive	Retest	Total
Expert	6907	2493	0	9400
CAtenA	5934	2240	987 *	
Coherence	0.859	0.898	0	

*Number of patients which could not classified as either positive or negative by CAtenA AI is 987. This yields a %10 fail rate. Expert classified all these patients. AI requires more re-sampling and re-testing. Therefore, it is suggested that software needs calibration and further adaptation to reduce and eliminate inconclusive status if possible.

antine and treatment are to be discharged and cause further spreading the infection), obtained by direct comparison with expert analysis result lists, were considered to achieve a more refined analysis. These statistics do not contribute to the total number of patients in classification matrix (Table 2) which is provided as n=8413 since CatenA missed 987 patients and declared inconclusive which in return to be interpreted as a retest. They were inherently included in the calculation. The overall accuracy of CatenA is almost 97 % based on the classification matrix.

There is a substantial difference between positive and negative matching success rates and overall accuracy. Test repetition, also termed as fail rate in this study, is believed to be the main reason for this difference. AI based software seems to have a high accuracy when fail rate after initial run have been omitted but retesting requires re-sampling of patients in doubt and re-testing by AI and/or expert which will cause further use of PCR test kit, lab material and lab expert workhours. The outcome of the retest will affect the accuracy of as there is a possibility of more false positives and negatives. Even though accuracy of Catena AI based software have been declared as 97.96% according to the results of the preliminary study carried out by the manufacturer [14] and similarly calculated in this study, this accuracy rate is believed to be synthetic and do not reflect real life usage without considering repeated test results.

Table 2. Expert analysis and CAtenA smart PCR results classification summary matrix

Number of Patients (n = 8413)		Expert Results	
		Positive	Negative
CAtenA Results	Positive	2313	73
	Negative	166	6100

DISCUSSION

When the test results were grouped as negative, positive and retest, 86% matching was observed between the negative results, 90% between the positive results, and 0% matching was found between the analyszes since all the PCR tests that the artificial intelligence recommended to repeat were concluded as negative or positive by the expert. CAtenA Smart PCR software has been put into use by evaluating more than 4 million PCR test results studied in various COVID-19 diagnostic laboratories located in Turkey, Italy and Uzbekistan for trial purposes [14]. It was reported that the results of the preliminary evaluation of CAtenA were matching expert analysis at a rate of 97.96% according to the results of the preliminary study carried out by the manufacturer [14].

Even though the overall accuracy (compliance rate) we obtained was found to be similar the compliance rate reported by the company based on the comparison results in this study, it is required to inspect the fail rate and include the results of test repetitions. Overall accuracy is believed to decrease after an additional run for missed patients since the expert classified them as positive and negative. A proper comparison of AI based software and expert results stipulates covering the full set of patients.

The increased workload due to the pandemic may cause disruptions in the rapid evaluation and transfer of test results to the system in COVID-19 PCR laboratories. CAtenA Smart PCR software which is developed for this reason can help the user with fast and accurate results. It is a great advantage that the tests

performed by a specialist physician can be analysed with artificial intelligence which can offer recommendations according to the preferences of the specialist physician. On the other hand, it seems that CAtenA needs improvement on the retest recommendation considering the findings of comparison we made approximately one year after the launch of the program. In addition, the software may suggest false positive results according to our findings, albeit at a low rate. False positive results cause negative effects such as unnecessary treatment, quarantine and contact tracing, thus unnecessary economic costs and loss of workforce. Therefore, it was emphasized that artificial intelligence should also be enhanced in terms of positive result suggestions. The worst-case scenario when classifying PCR tests is false negative results. False-negative results can cause important problems such as the patient receiving inappropriate treatment and the continuation of the contagiousness of asymptomatic positive individuals in the community.

The absence of false negative results among the test recommendations provided by CAtenA Smart PCR program in our study increases the reliability of the software. It has been shown that the COVID-19 PCR test results must be checked by a specialist physician before they can be approved by utilizing the bioinformatics program when all of our findings are evaluated. Another advantage of the CAtenA Smart PCR software is the ability of transferring test results LIMS without error and therefore post-analytical errors in this regard can be avoided. Manually uploading test results to LIMS can be performed with patient-based or batch approval options. Health centers with a high-test load prefer to use the collective approval option. It is necessary to apply extreme caution and to control the accuracy of the data at every stage to avoid any mistakes in manual data entry. CAtenA Smart PCR program allows patient results to be transferred directly to LIMS without the need for any manual entry with the barcoding method included in the worklists.

Although PCR data analysis is performed with certain rules, the results are closely related to the test kit, consumables, device experience and working quality of the microbiologist [15]. Many experts using the CAtenA smart PCR program may evaluate the same study differently for this reason. For example, a sample thought to be low positive may have been run again. Comparing more analysis of PCR data by more experts will yield more precise results.

CONCLUSION

It was determined that CAtenA smart PCR, an artificial intelligence-based bioinformatics data analysis program software, was 86% successful in predicting negative results. All the samples for which CAtenA recommends a PCR retest were evaluated as negative or positive by the expert. It is thought that there is a risk of confirming false results in test approvals without expert analysis, and test repetitions will cause additional costs and loss of time considering the findings we have obtained. It has been suggested that the PCR analysis used in CAtenA, particularly in terms of false positive results and test repetitions, should be improved. In lights of these observations, it is suggested that an AI based software can be considered an asset and facilitation tool in a pandemic environment which requires rapid evaluation and firm decision making to guide quarantine processes, treatment protocols and patient follow-up. Human expert supervision would not be optional and highly recommend if/when AI based software is deployed.

Authors' Contribution

Study Conception: BGG, GGA; Study Design: BGG, GGA; Supervision: BGG, GGA; Funding: N/A; Materials: BGG; Data Collection and/or Processing: GGA; Statistical Analysis and/or Data Interpretation: BGG; Literature Review: GGA; Manuscript Preparation: BGG and Critical Review: BGG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Eng J Med 2020;382:727-33.
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19, 11 March 2020. (online). Available from: https://www.who.int/ director-general/speeches/detail/who-directorgeneral-s-opening-remarks-at-the-media-briefing-oncovid-19---11-march-2020) (cited 14 April 2022).
3. World Health Organization, Tracking SARS-CoV-2 variants (online). Available from: https://www.who.int/en/activities/tracking-sars-cov-2-variants/ (cited 14 April 2022).
4. Worl Health Organization. Laboratory testing of 2019 novel coronavirus (2019-nCoV) in suspected human cases: interim guidance, 17 January 2020. (online). Available from: https://www.who.int/publications/i/item/laboratory-testingof-2019-novel-coronavirus-(-2019-ncov)-in-suspectedhuman-cases-interim-guidance-17-january-2020). (cited 14 April 2022).
5. Sule, WF, Oluwayelu, DO. Real-time RT-PCR for COVID-19 diagnosis: challenges and prospects. Pan Afr Med J 2020;35(Suppl 2):121.
6. The Turkish Ministry of Health, COVID-19 information page (online). Available from: https://covid19.saglik.gov.tr/TR 68720/covid-19-yetkilendirilmis-tani-laboratuvarlari-listesi.html. (cited 14 April 2022).
7. Petruzzi G, De Virgilio A, Pichi B, Mazzola F, Zocchi J, Mercante G, et al. COVID-19: nasal and oropharyngeal swab. Head Neck 2020;42:1303-4.
8. Sreepadmanabh M, Sahu AK, Chande A. COVID-19: advances in diagnostic tools, treatment strategies, and vaccine development. J Biosci 2020;45:148.
9. Tasdelen A, Sen B. A hybrid CNN-LSTM model for pre-miRNA classification. Sci Rep 2021;11:14125.
10. Peiffer-Smadja, N, Dellière S, Rodriguez C, Birgand G, Lescure F. X, Fourati S, et al. Machine learning in the clinical microbiology laboratory: has the time come for routine practice? Clin Microbiol Infect 2020;26:1300-9.
11. Smith KP, Wang H, Durant TJS, Mathison BA, Sharpeh SE, Kirby JE, et al. Application of artificial intelligence in clinical microbiology diagnostic testing. Clin Microbiol Newsletter 2020;42:61-70.
12. Asada K, Kaneko S, Takasawa K, Machino H, Takahashi S, Shinkai N, et al. Integrated analysis of whole genome and epigenome data using machine learning technology: toward the establishment of precision oncology. Front Oncol 2021;11:666937.
13. van Oosten LN, Klein CD. Machine learning in mass spectrometry: a MALDI-TOF MS approach to phenotypic antibacterial screening. J Med Chem 2020;63:8849-56.
14. Ventura. CAtenA Smart PCR. (online). Available from: https://ventura.com.tr/catena (cited 14 April 2022).
15. Kuang J, Yan X, Genders AJ, Granata C, Bishop DJ. An overview of technical considerations when using quantitative real-time PCR analysis of gene expression in human exercise research. PloS One 2018;13:e0196438.