BIOMEDIKA
ISSN: 2085-8345, E-ISSN: 2541-2582
Vol 16, No. 2 Agustus 2024
doi: 10.23917/biomedika.v16i2.3940

External Validation of AI-powered GeNose C19 to Diagnose Volatile Organic Compounds in COVID-19 Patients Tested at Udayana University Academic Hospital

Cokorda Agung Wahyu Purnamasidhi[1], Agus Eka Darwinata[2], I Made Susila Utama[3], Ketut Tuti Parwati Merati[3], Saktivi Harkitasari[4], Darren Junior[5], I Gusti Ngurah Ariestha Satya Diksha[5], Richard Christian Suteja[5]

AFFILIATIONS

1. Tropical and Infectious Diseases Division Internal Medicine Department of Udayana University Academic Hospital, Medical Faculty, Udayana University
2. Clinical Microbiology Department, Medical Faculty, Udayana University
3. Tropical and Infectious Diseases Division Internal Medicine Department of Prof. dr. I.G.N.G. Ngoerah General Hospital, Medical Faculty, Udayana University
4. Neurology Department, Medical Faculty, Warmadewa University
5. Medical Faculty, Udayana University

ABSTRACT

In search for potential alternatives to RT-PCR, Gadjah Mada University developed GeNose C19 which was deemed to have high sensitivity, specificity, PPV, and NPV. The objective of this study is to contribute to the development of GeNose C19 by means of external validation conducted in Udayana University Academic Hospital, Bali. This was a cross-sectional study conducted on adults above 17 years old. Demographic variables, symptoms, vaccination status, GeNose C19 results, and RT-PCR results were measured. We analyzed the sensitivity, specificity, PPV, and NPV using respective appropriate formulas and the impact of other variables gathered towards accuracy by means of Chi-squared test, Mann-Whitney U test and independent-samples T test. The results showed that the subjects included in this study were 50.8% female and had a mean (IQR) age of 23.0 (21.0-27.5) years old. Only three subjects (2.5%) showed COVID-19-related symptoms such as cough (1.7%), flu (0.8%), fever (0.8%), and headache (0.8%). GeNose C19 yields a sensitivity of 83.1%, a specificity of 73.6%, PPV of 79.4%, and NPV of 78.0%. There were no variables that significantly affect the accuracy of GeNose C19. Further study is still required to validate GeNose C19's performance in different environmental conditions and multiple different races.

KEYWORDS:

COVID-19; GeNose C19; RT-PCR; External Validation

CORRESPONDING AUTHOR:
Cokorda Agung Wahyu Purnamasidhi
E-mail purnamasidhi@unud.ac.id

INTRODUCTION

The COVID-19 pandemic has been an ongoing phenomenon for more than two years in Indonesia. A total of 6.702.132 cases, with the number of mortalities reaching 160.287, was reported on 13th December 2022 [1]. The lack of availability of healthcare facilities in several provinces may have also contributed to the inaccuracy of reported cases [2,3]. Furthermore, low rates of diagnoses were caused by the lack of laboratories' capacity, reagents availability, workers' capabilities, and rules regarding lab workers and specimen collectors [4,5].

A crucial aspect during the course of the COVID-19 pandemic has been the process of detection and diagnosis. Early detection and diagnosis could help in determining patients' treatments. Until now, several modalities have been used to detect COVID-19 in patients. These

modalities include reverse transcription-quantitative polymerase chain reaction (RT-PCR) or antigen-based rapid tests [6]. The RT-PCR is still widely accepted as the gold standard in diagnosing COVID-19. However, RT-PCR comes with its disadvantages, which include the need for special equipment and trained staff, being an invasive method in procuring samples, and higher costs [7–9].

As the search for a more effective and cost-efficient alternative ensues, Gadjah Mada University developed a new modality called Gadjah Mada Electronic Nose (GeNose C19), which implemented e-nose technology by utilizing gas sensors and Artificial Intelligence (AI) [10]. Through a three-stage clinical trial, it was found that GeNose C19 had high sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). GeNose C19 works by analyzing the 'digital breathprint' of its users, mimicking human olfactory perfection when analyzing volatile organic compounds within air exhaled into plastic bags. Users were initially asked to exhale air into a custom-made plastic bag specially manufactured using materials with enough inert properties so as not to confound the composition of molecules within the bag. These bags were then run through a machine running multiple sensors on different distinct molecules. Signals were then inputted into a custom-made machine, which then ran an updated AI version of the machine to process inputs generated earlier by the sensors. This AI was important, as these input sensors tend to have a cross-sensitivity drawback. Analysis was then reported in a binary form of positive/negative. The full mechanism behind how the hardware works can be seen in papers made by Nurputra *et al.* (2022) and Hidayat *et al.* (2022).

Despite all the advantages GeNose C19 offers, RT-qPCR remains the gold standard. The GeNose C19 is currently used as a method for early detection of SARS-CoV-2 infection in patients. Still, it needs further studies regarding its accuracy before being able to be fully implemented in society [11]. Therefore, through this study, we would like to contribute to the development of GeNose C19 by means of external validation conducted in Udayana University Academic Hospital, Bali.

METHODS

This cross-sectional study was conducted in Udayana University Academic Hospital, Bali, Indonesia, from March to October 2023. The study samples were adults above 17 years old who underwent voluntary COVID-19 RT-PCR testing at Udayana University Academic Hospital with or without COVID-19-like symptoms. We measured demographic variables (age, sex), presence of symptoms (cough, flu, fever, headache), comorbidities, doses of vaccination received, GeNose C19 diagnostic results, and COVID-19 RT-PCR diagnostic results. RT-PCR as the gold standard

was conducted on all the study samples and independent to the GeNose C19 test.

All variables, excluding GeNose C19 and RT-PCR diagnostic results, will be reported according to their data distribution. A cross-tabulation and calculation of sensitivity, specificity, PPV, and NPV using their respective formula will be reported to compare the diagnostic accuracy of GeNose C19 to COVID-19 RT-PCR diagnostic result. Furthermore, demographic variables, symptoms, comorbidities and vaccination status will be analyzed for their effect on accuracy using Chi-squared test for categorical data, independent-samples T test for normally distributed numerical data and Mann-Whitney U test for abnormally distributed numerical data. All statistical analyses were done on IBM SPSS ver. 20. This study had been approved by the Ethical Committee of Gadjah Mada University (IRB# KE/0489/05/2020).

RESULT AND DISCUSSION

Subjects included in this study had a mean (IQR) age of 23.0 (21.0-27.5) years old and 50.8% comprised of females. Mean (± SD) BMI was reported to be 22.3 (± 4.9), and only one patient (0.8%) smokes. Only three subjects (2.5%) showed COVID-19-related symptoms such as cough (1.7%), flu (0.8%), fever (0.8%), and headache (0.8%). Three subjects (2.5%) had comorbidity, which included hypertension (1.7%) and gastritis (1.7%). Sixteen (13.6%) subjects were unvaccinated, while six (5.1%) subjects received one dose, ninety-five (80.5%) subjects received two doses, and one (0.8%) subject received three doses of COVID-19 vaccine. The full demographic, clinical, and vaccination profile can be seen in Table 1.

Table 1. Demographic, Clinical, and Vaccination Profile (*n*=118)

Parameter	*n* (%)
Age, years	**23.0 (21.0-27.5)**[a]
Sex	
Male	58.0 (49.2)
Female	60.0 (50.8)
Body Mass Index (BMI)	**22.3 (± 4.9)**[b]
Smoking	**1.0 (0.8)**
Symptoms	**3 (2.5)**
Cough	2.0 (1.7)
Flu	1.0 (0.8)
Fever	1.0 (0.8)
Headache	1.0 (0.8)
Comorbidity	**3 (2.5)**
Hypertension	2.0 (1.7)
Gastritis	2.0 (1.7)
Vaccination Status	
Unvaccinated	16.0 (13.6)
1	6.0 (5.1)
2	95.0 (80.5)
3	1.0 (0.8)

[a] Median (interquartile range); [b] mean (standard deviation)

A cross-tabulation of the number of positive and negative results on both GeNose C19 and RT-PCR testing can be seen in Table 2. Results, as seen in Table 2, yielded a sensitivity of 83.1% and a specificity of 73.6%. Positive predictive value (PPV) was at 79.4%, whereas negative predictive value (NPV) at 78.0%.

We further analyzed demographic variables, symptoms, and vaccination status for its impact on the accuracy of GeNose C19. We found that there were no variables that significantly affect the accuracy of GeNose C19. Results from the bivariate analysis can be found in Table 3.

Table 2. Cross-Tabulation GeNose C19 to RT-PCR

		RT-PCR		Total
		Positive	Negative	
GeNose C19	Positive	54	14	68
	Negative	11	39	50
Total		65	53	118

Table 3. Variables Affecting Accuracy of GeNose C19

Variables	*p*-value
Age, years	**0.879[a]**
Sex	**0.422**
Body Mass Index (BMI)	**0.590[b]**
History of smoking	
Smoking	1.000
Symptoms	
Flu	0.381
Fever	0.381
Cough	0.143
Headache	0.381
Comorbidities	
Hypertension	1.000
Gastritis	0.143
Respiratory infection within 4 weeks	0.381
History of vaccination	**0.532**
Vaccination dosage	**0.198**

[a] Mann-Whitney U test; [b] independent-samples T-test

The sensitivity, specificity, PPV, and NPV values obtained in this study were lower when compared to the study by Nurputra *et al*. (2022) which was conducted in Bhayangkara General Hospital and Bambanglipuro COVID-19 Hospital and consisted of 83 subjects. The study by Nurputra *et al.* (2022) processed all their datasets utilizing the DNN model and showed a sensitivity value of 95.5% and specificity value of 95.7%. Another study conducted in a public hospital in Yogyakarta which consisted of 460 breath samples also showed all sensitivity, specificity, PPV, and NPV value to be 87% which is lower than the previous mentioned study but still higher that this study [12]. Gadjah Mada University as the developer of the GeNose C19 also stated that they obtained sensitivity, specificity, PPV, and NPV results of 89-92%, 95-96%, 87-88%, and 97% respectively from a three-stage clinical trial [11].

As means to determine the factors that might have impacted the accuracy of GeNose C19 testing in this study, we analyzed demographic variables, symptoms, comorbidities, and vaccination status of the samples enrolled in our study but found that they had no significant effect. This may be due to fact that there were only a few subjects who experienced symptoms and suffered from comorbidities. However, this condition was actually similar to the clinical characteristics of the subjects in the study by Nurputra *et al*. (2022), where it was found that 79-80% of the enrolled subjects were asymptomatic and the rest only exhibited mild symptoms.

One factor which could have contributed to the lower accuracy of GeNose C19 when compared to RT-PCR, which is still regarded as the gold standard in COVID-19 testing, was the analysis of VOCs. In contrast to RT-PCR which analyses the RNA found directly from the SARS-CoV-2 virus, GeNose C19 analyses VOCs which are the products of metabolic processes and could also be found in other various respiratory diseases [7,13,14]. Despite that these VOCs produced in COVID-19 patients were analyzed using AI to discriminate their unique patterns, it should be known that AI presents with its own limitations. One of the limitations of AI is that generally it only attempts to match the output and input variables which it had learned from training datasets, thus

implying that it needs enormous numbers of datasets for more accurate interpretations [15].

CONCLUSION

GeNose C19 offers a good sensitivity and specificity level. It offers a relatively inexpensive and non-invasive diagnostic method. This means that it can be applied to a wider range of situations, such as on pediatric patients or in resource-limited areas. While it does not reach a level comparable to gold standard diagnostic methods such as RT-PCR, it may function as a cost-effective screening modality. However, volatile organic compounds might vary based on race or other environmental factors on the testing site as they tend to be very prone to the slightest of change. Further study is required to validate this diagnostic method externally on different environment conditions and multiple different races.

FUNDING

This research did not receive any external funding

ACKNOWLEDGEMENT

The authors would like to acknowledge the director of Udayana University Academic Hospital Dr. dr. Dewa Putu Gede Purwa Samatra, Sp. N (K) and the dean of Medical Faculty of Udayana University Prof. Dr. dr. Komang Januartha Putra Pinatih, M.Kes.

REFERENCES

1. WHO. Indonesia Situation [Internet]. World Health Organization. 2022 [cited 2022 Dec 14]. Available from: https://covid19.who.int/region/searo/country/id
2. Wirawan GBS, Januraga PP. Correlation of Demographics, Healthcare Availability, and COVID-19 Outcome: Indonesian Ecological Study. Front Public Heal. 2021;9(February):1–8.
3. WHO. State of health inequality: Indonesia [Internet]. Geneva: World Health Organization; 2019. Available from: http://apps.who.int/iris/handle/10665/259685
4. Sucahya PK. Barriers to Covid-19 RT-PCR Testing in Indonesia: A Health Policy Perspective. J Indones Heal Policy Adm. 2020;5(2):36–42.
5. Allard T, Lamb K. Exclusive: More than 2,200 Indonesians have died with coronavirus symptoms, data shows [Internet]. Reuters. 2020 [cited 2023 Nov 17]. Available from: https://www.reuters.com/article/us-health-coronavirus-indonesia-casualti/exclusive-more-than-2200-indonesians-have-died-with-coronavirus-symptoms-data-shows-idINKCN22A04N/
6. Purnamasidhi CAW, Suteja RC, Adiputra IKH, Purnama GV, Mulyantari NK, Somia IKA. A comparison of antigen-based rapid test and RT-PCR test to diagnose COVID-19 and its infectivity. Rom Med J. 2021;68(3):399–405.
7. Nurputra DK, Kusumaatmaja A, Hakim MS, Hidayat SN, Julian T, Sumanto B, et al. Fast and noninvasive electronic nose for sniffing out COVID-19 based on exhaled breath-print recognition. npj Digit Med. 2022;5(1).
8. Scohy A, Anantharajah A, Bodéus M, Kabamba-mukadi B, Verroken A, Rodriguez-Villalobos H. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. J Clin Virol [Internet]. 2020;129:104455. Available from: https://pubmed.ncbi.nlm.nih.gov/32485618/
9. Mak GC, Cheng PK, Lau SS, Wong KK, Lau CS, Lam ET, et al. Evaluation of rapid antigen test for detection of SARS-CoV-2 virus. J Clin Virol [Internet]. 2020;129:104500. Available from: https://pubmed.ncbi.nlm.nih.gov/32585619/
10. Direktorat Pengembangan Usaha dan Inkubasi Universitas Gadjah Mada. Akurat Deteksi Covid-19 Lewat Hembusan Nafas, GeNose Mampu Mendunia [Internet]. Universitas Gadjah Mada. 2020 [cited 2022 Dec 14]. Available from: https://ditpui.ugm.ac.id/akurat-deteksi-covid-19-lewat-hembusan-nafas-genose-mampu-mendunia/
11. Direktorat Pengembangan Usaha dan Inkubasi Universitas Gadjah Mada. FAQ GENOSE C19 [Internet]. Universitas Gadjah Mada. 2021 [cited 2022 Dec 14]. Available from: https://ditpui.ugm.ac.id/faq/#:~:text=GeNose

C19 versi screening atau,hembusan nafas pasien COVID-19.

12. Hidayat SN, Julian T, Dharmawan AB, Puspita M, Chandra L, Rohman A, et al. Hybrid learning method based on feature clustering and scoring for enhanced COVID-19 breath analysis by an electronic nose. Artif Intell Med [Internet]. 2022;129(December 2021):102323. Available from: https://doi.org/10.1016/j.artmed.2022.102323
13. Gupta A, Madhavan M V., Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med [Internet]. 2020;26(7):1017–32. Available from: http://dx.doi.org/10.1038/s41591-020-0968-3
14. Capuano R, Khomenko I, Grasso F, Messina V, Olivieri A, Cappellin L, et al. Simultaneous Proton Transfer Reaction-Mass Spectrometry and electronic nose study of the volatile compounds released by Plasmodium falciparum infected red blood cells in vitro. Sci Rep [Internet]. 2019;9:12360. Available from: http://dx.doi.org/10.1038/s41598-019-48732-x
15. Chowdhury M, Sadek AW. Advantages and Limitations of Artificial Intelligence. In: Artificial Intelligence Applications to Critical Transportation Issues. Washington D. C.: Transportation Research Board's Artificial Intelligence and Advanced Computing Committee; 2012. p. 6–8.