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Original Article

Analytical performance of the rapid qualitative antigen kit for the detection of SARS-CoV-2 during widespread circulation of the Omicron variant

Hiromichi Suzuki [a,b,c,*], Yusaku Akashi [b,c,d], Daisuke Kato [e], Yuto Takeuchi [a,b], Yoshihiko Kiyasu [a,b,c], Norihiko Terada [b,c], Yoko Kurihara [a], Miwa Kuwahara [e], Shino Muramatsu [e], Atsuo Ueda [f], Shigeyuki Notake [f], Koji Nakamura [f]

[a] *Department of Infectious Diseases, University of Tsukuba Hospital, 2-1-1 Amakubo, Tsukuba, Ibaraki, 305-8576, Japan*
[b] *Division of Infectious Diseases, Department of Medicine, Tsukuba Medical Center Hospital, 1-3-1 Amakubo Tsukuba, Ibaraki, 305-8558, Japan*
[c] *Department of Infectious Diseases, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, 305-8575, Japan*
[d] *Akashi Internal Medicine Clinic, 3-1-63 Asahigaoka, Kashiwara, Osaka, 582-0026, Japan*
[e] *Denka Co., Ltd. Gosen Site, Research & Development Division, Reagent R&D Department, 1-2-2 Minami-hon-cho, Gosen-shi, Niigata, 959-1695, Japan*
[f] *Department of Clinical Laboratory, Tsukuba Medical Center Hospital, 1-3-1 Amakubo, Tsukuba, Ibaraki, 305-8558, Japan*

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ABSTRACT

Introduction: Rapid qualitative antigen testing is essential in the clinical management of COVID-19. However, most evaluations of antigen tests have been performed before the emergence of the Omicron variant.
Methods: This prospective observational study evaluated QuickNavi-COVID19 Ag, a rapid antigen detection test between December 2021 and February 2022 in Japan, using real-time reverse transcription (RT)-PCR as a reference. Two nasopharyngeal samples were simultaneously collected for antigen testing and for RT-PCR. Variant analysis of the SARS-CoV-2 genomic sequencing was also performed.
Results: In total, nasopharyngeal samples were collected from 1073 participants (417 positive; 919 symptomatic; 154 asymptomatic) for analysis. Compared with those of RT-PCR, the sensitivity, specificity, positive predictive value, and negative predictive value were 94.2% (95% CI: 91.6%–96.3%), 99.5% (95% CI: 98.7%–99.9%), 99.2% (95% CI: 97.8%–99.8%), and 96.5% (95% CI: 94.8%–97.7%), respectively. The sensitivity among symptomatic individuals was 94.3% (95% CI: 91.5%–96.4%). Overall, 85.9% of sequences were classified as Omicron sublineage BA.1, 12.4% were Omicron sublineage BA.2, and 1.6% were Delta B.1.617.2. (Delta variant). Most of the samples (87.1%) had Ct values of <25, and the sensitivity was 47.4% for low viral load samples (Ct $\geq$ 30); a similar trend has been observed in both symptomatic and asymptomatic groups.
Conclusions: The QuickNavi-COVID19 Ag test showed sufficient diagnostic performance for the detection of the SARS-CoV-2 Omicron sublineages BA.1 and BA.2 from nasopharyngeal samples. However, the current study was mainly performed in symptomatic patients and the results are not sufficiently applicable for asymptomatic patients.

1. Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.529, i.e., the Omicron variant, dramatically increased the clinical cases of coronavirus disease 2019 (COVID-19). Owing to its high transmissibility, short incubation period [1–4] and reduced vaccine efficacy [5,6], the Omicron variant sublineages BA.1 and BA.2 became predominant worldwide by early 2022 [7]. Compared with previously dominant variants, COVID-19 caused by the Omicron variant is less likely to damage the lung [8] and more frequently causes sore throat and a hoarse voice [9].

Qualitative antigen tests that use immunochromatography are a useful point-of-care diagnostic testing method for infectious diseases because of their low cost, simple procedure, high availability of the test

* Corresponding author. Department of Infectious Diseases, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, 305-8575, Japan.
E-mail addresses: hsuzuki@md.tsukuba.ac.jp (H. Suzuki), yusaku-akashi@umin.ac.jp (Y. Akashi), daisuke-kato@denka.co.jp (D. Kato), yuto-takeuchi@umin.ac.jp (Y. Takeuchi), ykiyasu@md.tsukuba.ac.jp (Y. Kiyasu), terada.norihiko.ck@ms.hosp.tsukuba.ac.jp (N. Terada), kurihara.yoko.fu@un.tsukuba.ac.jp (Y. Kurihara), miwa-kuwahara@denka.co.jp (M. Kuwahara), shino-muramatsu@denka.co.jp (S. Muramatsu), atsuo.ueda06090727@outlook.jp (A. Ueda), notake@tmch.or.jp (S. Notake), koji-nakamura@tmch.or.jp (K. Nakamura).

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device, and short analytical time. For the laboratory diagnosis of COVID-19, antigen testing has been recommended for both symptomatic and asymptomatic individuals who are at high risk of infection, especially in situations where the prevalence of SARS-CoV-2 is ≥ 5% or where nucleic acid amplification test capacity is limited [10]. The diagnostic performance of antigen testing had been presumed to be preserved for the Omicron variant [7]. However, a significant impairment of sensitivity to the Omicron variant has been reported for nine antigen tests [11,12].

Herein, we prospectively evaluated the diagnostic performance of a qualitative antigen test (QuickNavi-COVID19 Ag, Denka Co., Ltd., Tokyo, Japan) using nasopharyngeal swab samples. We also conducted a genomic sequencing analysis to identify SARS-CoV-2 variants.

1.1. Patients and methods

This study was conducted between December 28, 2021 and February 16, 2022. Sample collection and antigen testing were performed at a drive-through sample collection point at Tsukuba Medical Center Hospital (TMCH), and PCR was performed in the TMCH microbiology department. TMCH provides SARS-CoV-2 testing for the Tsukuba district in Japan. People with and without symptoms were referred from 65 clinics and a local public health center. All asymptomatic individuals had a history of contact with a confirmed or suspected COVID-19 cases.

Informed consent was verbally obtained from all participants and was documented in their electronic medical record to prevent infection transmission, written informed consent was not obtained. The ethics board of the University of Tsukuba Hospital approved the study (approval number: R03-042), including the method of obtaining informed consent.

1.2. Study process

Two nasopharyngeal samples were separately collected by medical professionals one for RT-PCR and the other for antigen testing, as previously described [13–20]. A nasopharyngeal sample was obtained from each nasal cavity. All antigen tests were immediately performed on site after sample collection. A swab was inserted into a specimen buffer tube, and three drops of the prepared specimen were added on the test device. The sample processing time was 8 min, and the result was analyzed visually by the personnel who collected the sample.

For RT-PCR, a swab was diluted in 3 mL of Universal Transport Medium (Copan Italia S.p.A., Brescia, Italy) on site, and the sample was transferred to the TMCH microbiology department for in-house RT-PCR testing [13,21]. A 200 μL aliquot of each nasopharyngeal sample was extracted with a magLEAD 6gC (Precision System Science Co., Ltd., Chiba, Japan), and 100 μL of purified sample was eluted. The eluted samples were transferred to Denka Co., Ltd. For reference real-time RT-PCR testing to identify SARS-CoV-2, we used a method developed by the National Institute of Infectious Diseases (NIID), Japan. This method used an Applied Biosystems QuantStudio 3 (Thermo Fisher Scientific Inc., Waltham, MA, USA) with a QuantiTect probe RT-PCR kit (Qiagen Inc., Germantown, MD, USA) and a primer/probe N and N2 set [22]. Until the evaluation, all samples were preserved at −80 °C.

In case of discrepancy between the in-house PCR and the NIID method results for the presence or absence of SARS-CoV-2, additional examinations with the Xpert Xpress SARS-CoV-2 and GeneXpert system (Cepheid, Sunnyvale, CA, USA) [23] were performed, and those results were used as the final judgment.

1.3. SARS-CoV-2 variant analysis

Of the 393 RT-PCR and QuickNavi-COVID19 Ag positive samples, 185 samples with high viral load (Ct ≤ 21) were subjected to genomic sequencing analysis. RNAs of 185 samples were extracted using QIAGEN Viral RNA mini kit and sent to Denka Co., Ltd. Denka Co., Ltd. then sent the RNA to iLAC Inc. (Ibaraki, Japan) requesting to perform Next-Generation Sequencing (NGS) and the SARS-CoV-2 variant analysis. NGS was performed using Illumina's COVIDSeq test and IDT for Illumina-PCR indexes Sets 1–4 (Illumina, San Diego, CA, USA) to prepare sequencing libraries. Sequencing runs were performed on the prepared libraries using Illumina NovaSeq 6000 sequencer and NovaSeq 6000 SP Reagent Kit ver1.5. Sequencing results were then analyzed for SARS-CoV-2 variants using Illumina's DRAGEN COVIDSeq Test Pipeline.

1.4. Statistical analyses of the rapid antigen test

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the antigen tests were calculated with 95% confidence intervals (CIs).

The sensitivity stratified by the cycle threshold (Ct) value based on the N2 set of the NIID method was also evaluated. All statistical analyses were conducted using R 4.1.2 software (R Foundation, Vienna, Austria) with the "readxl," "tidyverse," and "epiR" packages.

2. Results

Nasopharyngeal samples were collected from 1073 participants during the study period; 919 were from symptomatic individuals and 154 were from asymptomatic individuals. For symptomatic participants, the median duration from symptom onset to sample collection was 2 days (interquartile range: 1–3 days).

Of the 1073 samples, 411 were SARS-CoV-2 positive by RT-PCR with the NIID method. There were six discordances between the NIID and in-house RT-PCR results. Of the six discordant samples, all were SARS-CoV-2 positive when analyzed by the GeneXpert® system. Consequently, 417 samples (38.9%) were considered to be positive. The positive rate was similar to that of Ibaraki prefecture during the study period, which is available at the prefecture's web site [24].

The QuickNavi-COVID19 Ag results are shown in Table 1. The sensitivity, specificity, PPV, and NPV were 94.2% (95% CI: 91.6%–96.3%), 99.5% (95% CI: 98.7%–99.9%), 99.2% (95% CI: 97.8%–99.8%), and 96.5% (95% CI: 94.8%–97.7%), respectively. For symptomatic individuals (Table 2a), the sensitivity was 94.3% (95% CI:91.5%–96.4%) and the specificity was 99.8% (95% CI: 99.0%–100%). For asymptomatic individuals (Table 2b), the sensitivity was 93.1% (95% CI: 77.2%–99.2%) and the specificity was 98.4% (95% CI: 94.3%–99.8%).

The antigen test sensitivities stratified by Ct value (N2) are shown in Table 3–a (all samples), Table 3–b (samples in symptomatic individuals) and Table 3–c (samples in asymptomatic individuals). The percentages of samples with Ct values of <25 were 88.6% for overall individuals, 88.8% for symptomatic individuals and 85.7% for asymptomatic individuals, respectively. For all samples (Table 3–a), the sensitivities of Ct values of <20, 20–24, 25–29, and ≥30 were 98.9% (95% CI: 96.1%–99.9%), 97.8% (95% CI: 94.4%–99.4%), 85.7% (95% CI: 67.3%–96.0%), and 47.4% (95% CI: 24.4%–71.1%), respectively. For samples in symptomatic individuals (Table 3–b), the sensitivities of Ct values of <20, 20–24, 25–29, and ≥30 were 98.9% (95% CI: 95.9%–99.9%), 97.6% (95% CI: 93.9%–99.3%), 84.0% (95% CI: 63.9%–95.5%), and 50.0% (95% CI: 26.0%–74.0%), respectively. For samples in

Table 1
Sensitivity and specificity of the QuickNavi-COVID19 Ag test among all samples.

		real-time RT-PCR	
		Positive	Negative
Antigen test	Positive	393	3
	Negative	24	653
Sensitivity (%)		94.2 (91.6–96.3)	
Specificity (%)		99.5 (98.7–99.9)	

RT-PCR, reverse transcription-polymerase chain reaction.
Data in parentheses indicate 95% confidence intervals.

Table 2a
Sensitivity and specificity of the QuickNavi-COVID19 Ag test among symptomatic individuals.

		real-time RT-PCR	
		Positive	Negative
Antigen test	Positive	366	1
	Negative	22	530
Sensitivity (%)		94.3 (91.5–96.4)	
Specificity (%)		99.8 (99.0–100)	

RT-PCR, reverse transcription-polymerase chain reaction.
Data in parentheses indicate 95% confidence intervals.

Table 2b
Sensitivity and specificity of the QuickNavi-COVID19 Ag test among asymptomatic individuals.

		real-time RT-PCR	
		Positive	Negative
Antigen test	Positive	27	2
	Negative	2	123
Sensitivity (%)		93.1(77.2–99.2)	
Specificity (%)		98.4(94.3–99.8)	

RT-PCR, reverse transcription-polymerase chain reaction.
Data in parentheses indicate 95% confidence intervals.

Table 3-a
Sensitivity of QuickNavi-COVID19 Ag test stratified by Ct values among all samples.

Ct values (N2)	Sensitivity (%)	Positive	Negative
<20	98.9 (96.1–99.9)	181	2
20–24	97.8 (94.4–99.4)	177	4
25–29	85.7 (67.3–96.0)	24	4
≥30	47.4 (24.4–71.1)	9	10

Ct, cycle threshold.
Data in parentheses indicate 95% confidence intervals.

Table 3-b
Sensitivity of QuickNavi-COVID19 Ag test stratified by Ct values among samples in symptomatic individuals.

Ct values (N2)	Sensitivity (%)	Positive	Negative
<20	98.9 (95.9–99.9)	173	2
20–24	97.6 (93.9–99.3)	161	4
25–29	84.0 (63.9–95.5)	21	4
≥30	50.0 (26.0–74.0)	9	9

Ct, cycle threshold.
Data in parentheses indicate 95% confidence intervals.

Table 3-c
Sensitivity of QuickNavi-COVID19 Ag test stratified by Ct values among samples in asymptomatic individuals.

Ct values (N2)	Sensitivity (%)	Positive	Negative
<20	100 (63.1–100)	8	0
20–24	100 (79.4–100)	16	0
25–29	100 (29.2–100)	3	0
≥30	0 (0–97.5)	0	1

Ct, cycle threshold.
Data in parentheses indicate 95% confidence intervals.

asymptomatic individuals (Table 3–c), the sensitivities of Ct values of <20, 20–24, 25–29, and ≥30 were 100.0% (95% CI: 63.1%–100%), 100% (95% CI: 79.4%–100%), 100% (95% CI: 29.2%–100%), and 0% (95% CI: 0%–97.5%), respectively. Detailed information regarding the 24 patients with in which false-negative results were obtained with the QuickNavi-COVID19 Ag test are summarized in Table 4. Low viral load samples (Ct ≥ 30) were observed in 14 out of 24 samples (58.3%). 4 samples that were negative by the NIID method were positive only by the GeneXpert system.

The positive rate of the QuickNavi-COVID19 Ag test stratified by the days from the onset of symptoms to sample collection is summarized in Fig. 1. The positive rates were 93.8% (day 0), 93.1% (day 1), 97.6% (day 2), 95.1% (day 3), 93.2% (day 4–6), 71.4% (day 7–9) and 66.7% (day >10).

The SARS-CoV-2 genome analysis results are shown in Fig. 2. Of the 185 samples, 140 (75.7%) were determined to be BA.1.1.2, 21 (11.4%) were BA.2.3, 13 (7.0%) were BA.1.1, 3 (1.6%) were BA.1., 3 (1.6%) were AY.29, 2 (1.1%) were BA.1.1.1, 2 (1.1%) were BA.2 and 1(0.5%) was BA.1.15. Overall, 85.9% of the samples were classified as Omicron variant sublineage BA.1, 12.4% were Omicron variant sublineage BA.2, and 1.6% were Delta variant B.1.617.2.

3. Discussion

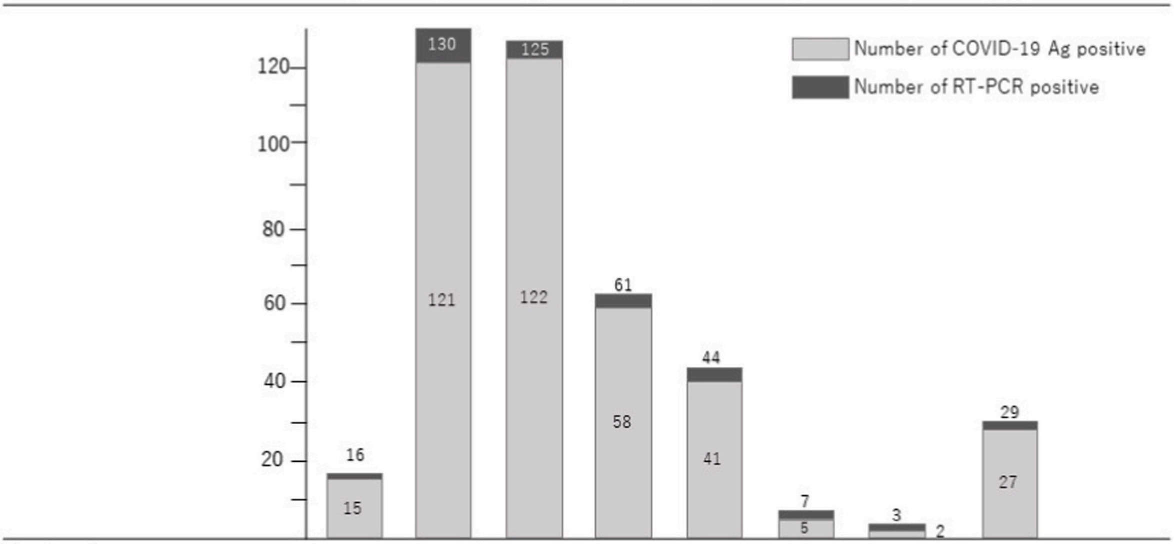
In this study, more than 90% of individuals who were PCR positive for SARS-CoV-2 were correctly identified by rapid antigen testing. The current investigation showed that the QuickNavi-COVID19 Ag test has sufficient sensitivity for the detection of Omicron BA.1 and BA.2 from nasopharyngeal samples. However, the current study was mainly performed in symptomatic patients and the results are not sufficiently applicable for asymptomatic patients.

There has been insufficient investigation into the diagnostic performance of antigen testing for the Omicron variant. Osterman et al. demonstrated that nine SARS-CoV-2 antigen tests commercially available in Europe showed decreased sensitivities for the Omicron variant

Table 4
Detailed information of 24 patients with QuickNavi-COVID19 Ag-negative and RT-PCR-positive results in the current study.

No.	Age	Sex	Symptoms	Days from symptom onset to sample collection	Ct values of RT-PCR with the NIID method	
					N gene	N2 gene
1	28	F	No	N/A	37	38
2	74	M	Yes	8	28	24
3	39	M	Yes	4	27	22
4	19	M	Yes	0	33	30
5	40	F	No	N/A	–	–
6	55	M	Yes	3	28	24
7	10	F	Yes	1	34	29
8	39	M	Yes	2	34	31
9	53	M	Yes	2	–	–
10	30	F	Yes	4	23	18
11	44	M	Yes	2	25	21
12	50	M	Yes	1	–	36
13	22	F	Yes	12	–	34
14	43	M	Yes	3	33	28
15	1	M	Yes	1	30	29
16	2	F	Yes	6	30	26
17	26	M	Yes	1	–	–
18	29	M	Yes	1	–	36
19	58	F	Yes	1	20	16
20	6	M	Yes	3	–	–
21	6	F	Yes	1	33	30
22	17	M	Yes	9	36	30
23	37	F	Yes	1	37	33
24	30	F	Yes	1	35	31

RT-PCR, reverse transcription-polymerase chain reaction; NIID, National Institute of Infectious Diseases.
Four patients showed negative results by RT-PCR using the NIID method and a positive result was confirmed with Xpert Xpress SARS-CoV-2 and the GeneXpert System.
Symptoms included fever, rhinorrhea, cough, sputum, rhinorrhea, malaise, sore throat, headache, diarrhea, vomiting.



	Day 0	Day 1	Day 2	Day 3	Day 4-6	Day 7-9	> Day 10	No symptoms	Total
Number of test	38	302	288	130	100	21	7	154	1040
Number of COVID-19 Ag positive	15	121	122	58	41	5	2	27	391
Number of RT-PCR positive	16	130	125	61	44	7	3	29	415
Median Ct (N2) value	20	20	20	20	21	24	21[a]	21.5	
Sensitivity of COVID-19 Ag	93.8%	93.1%	97.6%	95.1%	93.2%	71.4%	66.7%	93.1%	94.2%

We excluded 33 patients of the 1073 patients for the analysis for the missing data of the onset day of symptoms

a Each Ct value of the 3 positive patients were 20, 21 and 34, respectively.

Fig. 1. The sensitivities of QuickNavi-COVID19 Ag test stratified by days from symptom onset to sample collection.

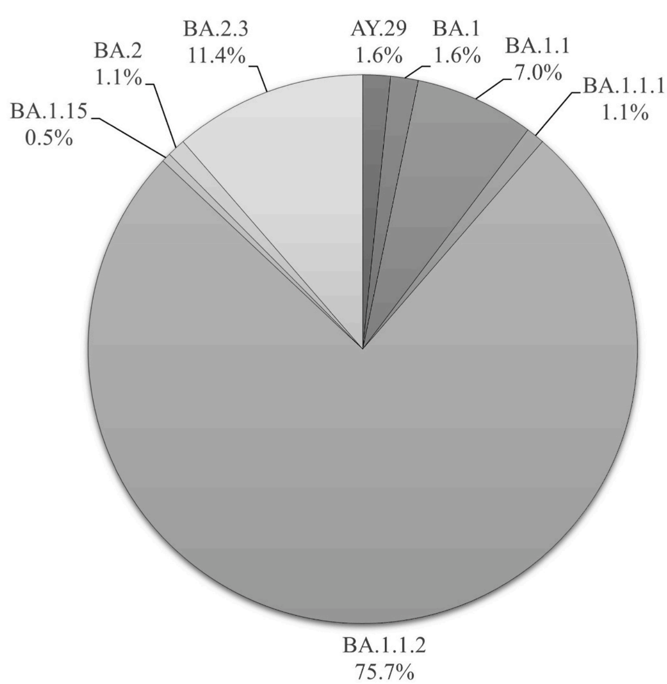


Fig. 2. Proportions of SARS-CoV-2 variants by genomic sequencing analysis.

[12]. Bayart also showed that six antigen tests had significantly decreased sensitivities for samples with low viral loads of Omicron variant [11]. Meanwhile, the BinaxNOW (Abbott Diagnostics Scarborough Inc., ME, USA) rapid antigen test was shown to detect 95.2% (95% CI: 91%–98%) of samples with RT-PCR Ct values <30 and 82.1% (95% CI: 77%–87%) of those with Ct values <35 during an Omicron surge period [25].

In a 2020–2021 clinical study, we evaluated the QuickNavi-COVID19 Ag test using 1934 samples. The test sensitivity was 89.3% (95% CI: 82%–94%) for symptomatic individuals and 67.1% (95% CI: 55%–78%) for asymptomatic individuals, and no false positives were observed [15]. A re-evaluation of the QuickNavi-COVID19 Ag test was performed in 1510 cases during the Delta variant dominantly circulating period in 2021, and the test sensitivity was 88.3% (95% CI: 83%–93%) for symptomatic individuals and 69.4% (95% CI: 60%–78%) for asymptomatic individuals, and three false-positive tests (0.2%) were identified [20].

The current study found a slightly better clinical performance for the QuickNavi-COVID19 Ag test during the widespread Omicron circulating period. This observed improvement could be due to the higher proportions of people with high viral loads. Meanwhile, the sensitivity of the QuickNavi-COVID19 Ag stratified by Ct values for the Omicron variant was similar to that evaluated in previous examinations [15,20]. While the sensitivity of the QuickNavi-COVID19 Ag was higher than 90% for moderate to high viral load samples (Ct $<$ 30), the sensitivity was lower than 50% for low viral load samples (Ct $\geq$ 30), which was observed in both the symptomatic individuals and asymptomatic individuals. Similarly, most of false negative results were observed in low viral load samples (Ct $\geq$ 30). The Ct values of people who are infected with the Omicron variant are considered to be nearly the same as for previous variants; thus, it is unclear why a high proportion of participants had a high viral load [26]. In this study, the median duration from symptom onset to sample collection was 2 days and most of patients took evaluation soon after the onset of COVID-19. While the sensitivities of QuickNavi-COVID19 Ag test stratified by days from symptom onset to sample collection were higher than 90% in day 0, day1, day2, day3 and day 4–6 groups, the sensitivities were approximately 70% in day 7–9 and day >10 groups. We considered that the early evaluations after the onset of COVID-19 attributed to the current good performance of the QuickNavi-COVID19 Ag test. Similarly, the total sensitivity of the QuickNavi-COVID19 Ag test is better than that of BinaxNow, which was performed with anterior nasal samples [25]. However, the Ct stratified sensitivity of the QuickNavi-COVID19 Ag is almost equal to that of BinaxNOW for the Omicron variant. In the analytical evaluation of BinaxNOW, anterior nasal samples were used for the evaluation and the viral load of anterior nasal samples has been reported to be much lower than that of nasopharyngeal samples [27,28], which is considered to be the gold standard and which was used in this study. We consider that the difference of the samples caused the difference in sensitivity. In this study, there are some false-negative cases among the high viral load samples (Ct < 25), which have been observed in previous antigen testing evaluations [15,16,18–20]. We considered that the results are mainly due to the differences of the viral loads of the obtained samples because the swabs for antigen testing and RT-PCR were obtained separately from different nares.

This study has some limitations. First, the samples were collected at one site in Japan, and most samples were collected soon after symptom onset. The sample size for asymptomatic individuals might have been insufficient and we did not gather detailed information on asymptomatic patients, such as the subsequent onset of COVID-19 or the number of days after close contact with an individual with COVID-19. Second, the assessment of lateral flow device results can vary among examiners [29]. Third, the reference RT-PCR examinations were performed with frozen samples, and the storage and transportation processes may have affected the test results. In addition, study samples were collected from the nasopharyngeal tract, and anterior nasal samples were not analyzed. Fourth, we performed the current evaluation only with the QuickNavi-COVID19 Ag test and we did not perform different rapid qualitative antigen tests. Additional evaluation of other rapid qualitative antigen tests is required to evaluate their sensitivity in the detection of the Omicron variant.

In conclusion, the current study showed that the QuickNavi-COVID19 Ag test had sufficient diagnostic performance for the detection of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in nasopharyngeal samples in symptomatic patients with Ct values of less than 30.

Authorship statement

All authors meet the ICMJE authorship criteria. Hiromichi Suzuki drafted the manuscript, designed the study, and supervised the project. Shigeyuki Notake, Atsuo Ueda, and Koji Nakamura collected samples and operated the equipment. Daisuke Kato, Miwa Kuwahara and Shino Muramatsu interpreted the results. Yusaku Akashi drafted the manuscript and performed the statistical analysis. Yuto Takeuchi, Yoshihiko Kiyasu, Norihiko Terada, and Yoko Kurihara revised the manuscript. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

Denka Co., Ltd. provided funds for research expenses the QuickNavi-COVID19 Ag tests without charge. Hiromichi Suzuki received a lecture fee from Otsuka Pharmaceutical Co., Ltd. Daisuke Kato, Miwa Kuwahara and Shino Muramatsu work for Denka Co., Ltd., the developer of the QuickNavi-COVID19 Ag tests.

The Ct values for RT-PCR were determined using the NIID (N2 gene), Japan method [22], 6 positive samples were excluded because the samples were found to be negative by the NIID method, and positive results were determined by Xpert Xpress SARS-CoV-2 and the GeneXpert System.

The Ct values for RT-PCR were determined using the NIID (N2 gene), Japan method [22], 5 positive samples were excluded because the samples were found to be negative by the NIID method, and positive results were determined by Xpert Xpress SARS-CoV-2 and the GeneXpert System.

The Ct values for RT-PCR were determined using the NIID (N2 gene), Japan method [22], 1 positive sample was excluded because the samples were found to be negative by the NIID method, and positive results were determined by Xpert Xpress SARS-CoV-2 and the GeneXpert System.

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