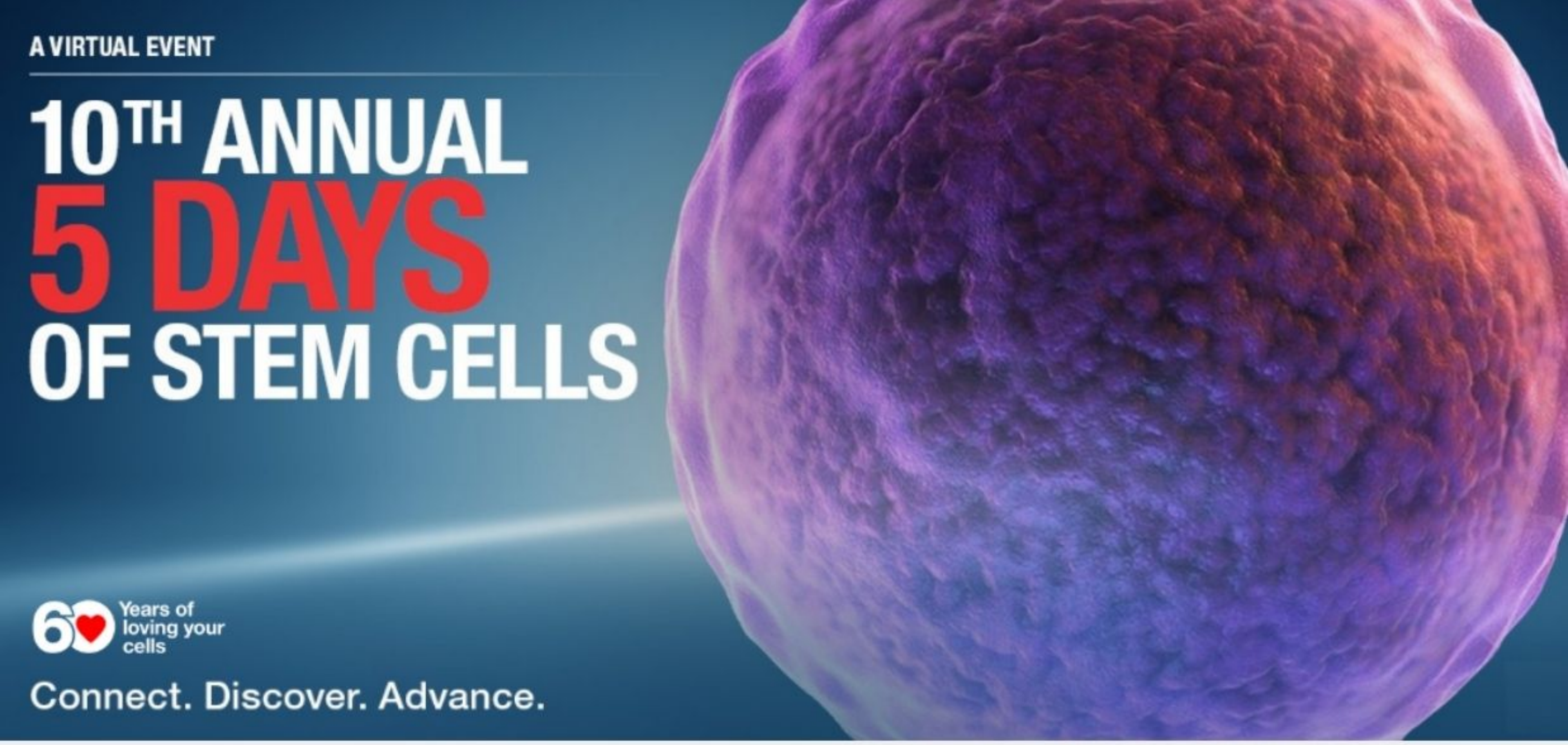

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RESEARCH ARTICLE

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Clinical evaluation of an automated, rapid mariPOC antigen test in screening of symptomatics and asymptomatics for SARS-CoV-2 infection

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Abstract

A novel automated mariPOC SARS-CoV-2 antigen test was evaluated in a Health Care Center Laboratory among symptomatic and asymptomatic individuals seeking SARS-CoV-2 testing. According to the national testing strategy, reverse transcription polymerase chain reaction (RT-PCR) was used as a reference method. A total of 962 subjects were included in this study, 4.8% (46/962) of their samples were SARS-CoV-2 RT-PCR-positive, and 87% (40/46) of these were from symptomatics. Among the symptomatics, the overall sensitivity of the mariPOC SARS-CoV-2 test was 82.5% (33/40), though the sensitivity increased to 97.1% (33/34) in samples with a $C_t < 30$. The mariPOC SARS-CoV-2 test detected two of six PCR-positive samples among the asymptomatics, four cases that remained antigen test negative had C_t values between 28 and 36. The specificity of the mariPOC SARS-CoV-2 test was 100% (916/916). The evaluation showed that the mariPOC SARS-CoV-2 rapid antigen test is very sensitive and specific for the detection of individuals who most probably are contagious.

KEYWORDS

antigen detection, mariPOC, RT-PCR, SARS-CoV-2, screening

1 | INTRODUCTION

The global COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a significant burden for both society and the carrying capacity of health care since late 2019 when this emerging virus was initially recognized in Wuhan, China.[1] SARS-CoV-2 can mutate into the new emerging variants escaping immunity, and it can in addition to symptomatic infections, manifest as both asymptomatic and presymptomatic infections, which has enabled the virus to spread efficiently all over the world. According to a simulation model made by US CDC, transmission from asymptomatic individuals, including presymptomatic individuals and those who never develop symptoms, is estimated to account for more than half of all SARS-CoV-2 infections.[2] To prevent the spread of infection, rapid and accurate diagnostic tests are needed, which detect contagious individuals irrespective of their presence or absence of COVID-19 symptoms.

Polymerase chain reaction (PCR)-based methods, especially reverse transcription polymerase chain reaction (RT-PCR) are widely used in SARS-CoV-2 diagnostics.[3,4] However, large-scale RT-PCR testing, although with excellent sensitivity and analytical specificity, also has some major disadvantages such as long turnaround time as well as the requirement for sophisticated equipment and highly trained personnel. Furthermore, it has been proposed that a positive PCR result may not correlate with infectivity,[5] as viral nucleic acids can be detected for a long time after the acute infection, without the presence of infectious and actively replicating SARS-CoV-2 virus.[6–12] As COVID-19 continues of being a worldwide threat, there is a constant demand for rapid SARS-CoV-2 testing. Several inexpensive and easy-to-use rapid antigen tests have been developed.[13] Rapid antigen tests have been shown to correlate more accurately with SARS-CoV-2 viral culture than RT-PCR,[12] thus also controversial results have been reported.[5,14] Currently, rapid antigen testing of SARS-CoV-2 as a complementary diagnostic method alongside RT-PCR testing has been accepted,[3,4,15] and ECDC has recommended the use of antigen tests for SARS-CoV-2 diagnostics with a sensitivity of at least 80% and specificity of at least 97%.[16]

The technique of the mariPOC SARS-CoV-2 rapid antigen test (ArcDia International Ltd.) is based on the detection of the conserved epitope of SARS-CoV-2 nucleocapsid (N) protein with specific monoclonal antibodies.[17] Majority of positive test results are reported after 20 min and final results within 55 min.[17–19] The mariPOC platform is an automated and random access test system that enables simple and quick workflow, high capacity testing, as well as objective result readout. The mariPOC test system can be used in decentralized testing in on-call laboratories or outside of a laboratory, for POC usability.[18,20] On the platform, the SARS-CoV-2 test is also available as part of syndromic multianalyte tests Quick Flu+ (20 min results only) and Respi+ (final results in 2 h).

In the present study, the clinical performance of the mariPOC SARS-CoV-2 rapid antigen test was prospectively evaluated in samples collected in the city of Kaarina, Southwest Finland during spring 2021, when most of the population was not vaccinated or infected with SARS-CoV-2. Results of on-site rapid antigen testing were compared with central laboratory RT-PCR results to estimate the clinical sensitivity and specificity of the mariPOC SARS-CoV-2 antigen test.

2 | MATERIALS AND METHODS

2.1 | Study population and specimen collection

An automated mariPOC SARS-CoV-2 antigen test system was verified for use in the Kaarina City Health Care Center laboratory for SARS-CoV-2 diagnostics. Verification was conducted between February and May 2021, when the prevalence of SARS-CoV-2 positivity among the tested samples in South–West Finland was approximately 4%. The main circulating SARS-CoV-2 variant in the geographical area during the study period was the Alpha variant (B.1.1.7). At the time, according to the Finnish national COVID-19 hybrid strategy, all individuals having respiratory symptoms as well as those exposed to SARS-CoV-2 were tested and screened, respectively, for SARS-CoV-2.

Two consecutive nasopharyngeal swab (NPS) specimens were obtained from a total of 939 subjects after collecting oral consent. Age, gender, symptoms, and time from the symptom onset were collected from each subject. Of the subjects, 881 had COVID-19-like symptoms and 58 were asymptomatic. The first collected NPS specimen was placed into a viral transport medium (VTM; Bioer sample preservative fluid; BSC82X1-A1) and transported to Turku University Hospital for SARS-CoV-2 RT-PCR testing (Cohort 1). The Clinical Microbiology Laboratory at Turku University Hospital is the primary laboratory responsible for SARS-CoV-2 testing in the Hospital District of Southwest Finland. The second NPS specimen was stored, if needed before mariPOC analysis, at +4°C in the Health Care Center Laboratory.

During the study period, the prevalence of SARS-CoV-2 in the target population was very low. It became soon obvious that based on national verification guidelines of microbiological CE marketed tests,[21] a sufficient amount of positive samples to assess test accuracy before introduction in clinical diagnostics, could not be collected in a reasonable time. Therefore, the protocol for sample collection and analysis was altered. Thereafter, together with the strategy implemented in Cohort 1, the primary screening of SARS-CoV-2 positive samples was performed with RT-PCR in the Clinical Microbiology Laboratory. PCR-positive samples were stored at −20°C and later analyzed by mariPOC antigen test in the Health Care Center laboratory (Cohort 2). Two samples in Cohort 2, were omitted from the analysis due to improper handling of the samples before being aliquotted for mariPOC testing and thus 23 consecutive SARS-CoV-2 positive samples of which 6 were taken from asymptomatic subjects, were included. For this cohort, NPS specimens were suspended into 2 ml VTM (VACUETTE Virus Stabilization tube; 456162) for the primary screening of SARS-CoV-2 by RT-PCR. In contrast to the Bioer tube, VACUETTE VTM was found to be applicable also in mariPOC antigen analysis.

2.2 | In-house SARS-CoV-2 RT-PCR

SARS-CoV-2 RT-PCR from NPS specimens was performed in the Clinical Microbiology Laboratory at Turku University Hospital. Nucleic acid extraction was performed with Chemagic 360 extractor with Viral DNA/RNA 300 Kit H96 (PerkinElmer). The in-house RT-PCR test used for SARS-CoV-2 E gene detection was based on the Charité protocol by Corman et al.[22] The human β-actin gene was used as an internal control in the test. Final primer concentrations were 400 nM for E gene primers and 200 nM for E gene probe, 40 nM for β-actin primers bA-F926 5′-TTGCCGACAGGATGCAGAA-3′ and bA-R1001 5′-TCAGGAGGAGCAATGATCTTGAT-3′ and 80 nM for probe bA-P954 5′-HEX-TGCCCTGGCACCCAGCACAA-BHQ-1-3′. SensiFAST Probe No-ROX One-Step Kit (Meridian Bioscience) was used for RT-PCR. Each 25 µl reaction consisted of

12.5 µl of 2X SensiFAST Probe One-Step mix, 1 µl of E gene primers and 0.5 µl of E gene probe, 0.1 µl of β-actin primers, and 0.2 µl β-actin probe, 0.2 µl reverse transcriptase, 0.4 µl RiboSafe RNase inhibitor, and 9 µl of extracted RNA template. Cycling conditions were 55°C (10 min), 95°C (3 min) followed by 45 cycles of 95°C (15 s) and 58°C (30 s) performed with BMS MIC analyzers (BMS Australia).

2.3 | mariPOC SARS-CoV-2 antigen test

The mariPOC SARS-CoV-2 testing was performed in the on-site laboratory of Kaarina City Health Care Center. NPS specimens from Cohort 1 were suspended into 1.3 ml mariPOC RTI sample buffer in sample tubes and analyzed with the mariPOC test system according to the manufacturer's instructions as soon as possible. The samples in Cohort 2 were collected in VACUETTE VTM and stored at −20°C after the primary SARS-CoV-2 RT-PCR test and were further diluted 1:1 (0.65 ml + 0.65 ml) with mariPOC RTI sample buffer to gain the required sample volume for mariPOC analysis. The VTM samples were diluted approximately three times more than in the dry swab procedure recommended by the mariPOC manufacturer.

2.4 | Statistical analysis

The mariPOC SARS-CoV-2 rapid antigen test sensitivity, including 95% confidence intervals, was determined using MedCalc Software.[23]

3 | RESULTS

3.1 | Study population

Demographic data of the population included in the mariPOC rapid antigen test evaluation is presented in Table 1. Of the whole study population, 6.7% (64) were asymptomatic and 93.3% (898) had symptoms linked to COVID-19, such as sore throat, headache, fever, shortness of breath, and diarrhea. Cohort 1 included 58 and Cohort 2 included six samples from asymptomatic subjects.

TABLE 1 Demographic data on the population included in the mariPOC SARS-CoV-2 rapid antigen test evaluation study.

Demographic data	Female	Male
Sex distribution (%)	575 (59.8)	387 (40.2)
Median age	40.9 years	39.2 years
Age distribution	4–81 years	2–81 years
<18 year of age (%)	9 (0.9)	20 (2.1)
>65 years of age (%)	30 (3.1)	20 (2.1)
SARS-CoV-2 positive (%)	22 (2.3)	24 (2.5)

3.2 | SARS-CoV-2 RT-PCR test results

Totally, 962 samples were analyzed with RT-PCR. Of the tested samples, 46 (4.8%) were SARS-CoV-2 positive with the RT-PCR method. C_t values for E gene amplification varied from 14.66 (high RNA load) to 38.13 (low RNA load). C_t values <40 cycles for the E gene were interpreted as SARS-CoV-2 positive. In cohort 1, all 23 subjects with positive RT-PCR results had COVID-19 symptoms, whereas, in Cohort 2, 6 of the 23 PCR-positive samples were from asymptomatic subjects (Figure 1).

3.3 | Comparison of mariPOC SARS-CoV-2 antigen test and RT-PCR test results

The correlation of C_t values and mariPOC SARS-CoV-2 rapid antigen test results among asymptomatic and symptomatic subjects are presented in Figure 2. Totally, 35 out of 46 of the SARS-CoV-2 RT-PCR-positive samples were positive in the mariPOC test (overall sensitivity 76.1%, specificity 100%, PPV 100%, NPV 98.8%). The test sensitivity for symptomatic patients including both Cohorts 1 and 2 was 97.1% (33/34) and 82.5% (33/40) when C_t values <30 and <40 were used, respectively (Table 2). The mariPOC test was positive for up to 10 days from the onset of symptoms.

In Cohort 1, 18 PCR-positive samples were positive in the mariPOC SARS-CoV-2 rapid antigen test and five samples remained negative. C_t values for 18 true positive samples in the antigen detection varied from 14.80 to 29.01 (Figure 2) and the mean duration of symptoms was 2.5 days (range 1–10 days). Of the five false-negative samples in the antigen detection, C_t values varied from 30.24 to 38.13, and the mean duration of symptoms was 2 days (range 0–5 days). The mariPOC test sensitivity for Cohort 1 was 78.3% (18/23, specificity 100%, PPV 100%, NPV 98.9%). When only samples with C_t values <30 were considered, the mariPOC sensitivity in Cohort 1 within symptomatic subjects was 100.0% (18/18) (Table 2).

In Cohort 2, all 23 samples were PCR-positive and 17 of these were mariPOC SARS-CoV-2 test positive and six samples remained negative. Four samples in Cohort 2 were taken from patients whose second NPS specimen was also included in Cohort 1. Of the six false negative samples in the antigen detection, four were taken from asymptomatic patients and two had only mild COVID-19 symptoms for 1 or 2 days (Figure 1). C_t values for 17 true positive samples in the antigen detection varied from 14.66 to 27.25 (Figure 2) and the mean duration of symptoms was 2.5 days (range 0–7 days). C_t values for the false negative samples in the antigen detection varied from 27.91 to 36.06, only two samples had C_t value <30 (Figure 2), and the mean duration of symptoms was 0.5 days (range 0–2 days). The sensitivity of the mariPOC antigen test for Cohort 2 was 73.9% (17/23, PPV 100%, and NPV not determined), but when only symptomatic subjects were considered, the sensitivity was 88.2% (Table 2).

The results of the mariPOC SARS-CoV-2 test reported after 20 min correlated well with the final results. Only three samples (one

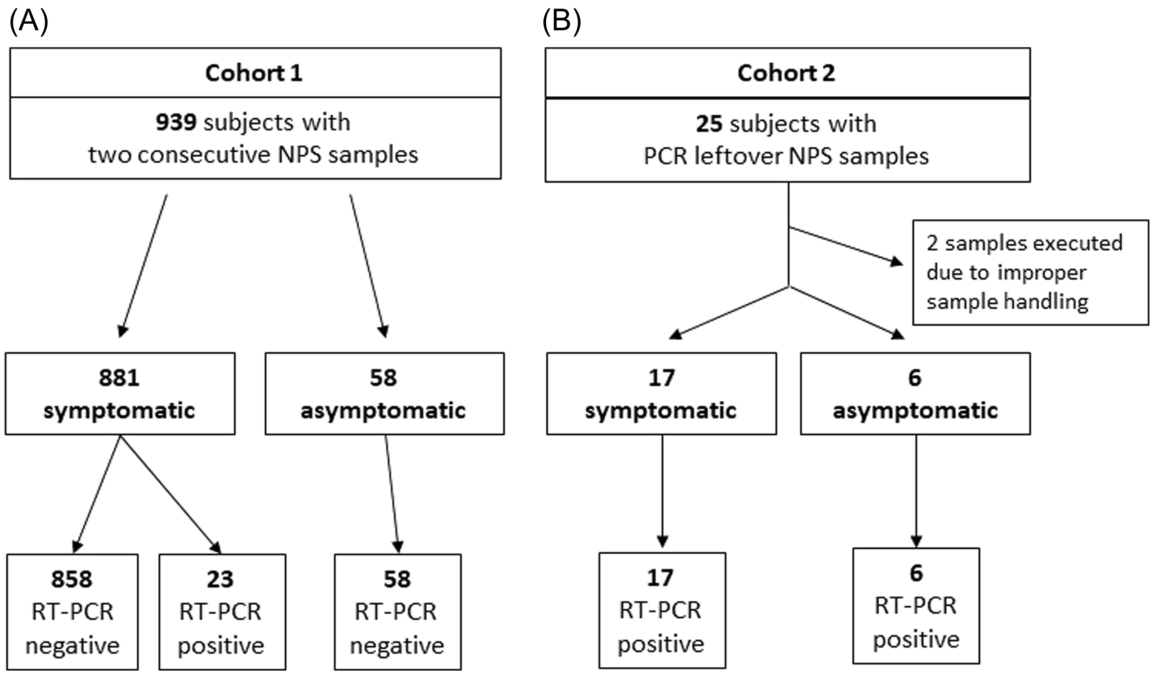

FIGURE 1 Sample flow chart showing the samples collected from symptomatic and asymptomatic subjects in Cohort 1 (A) and Cohort 2 (B).

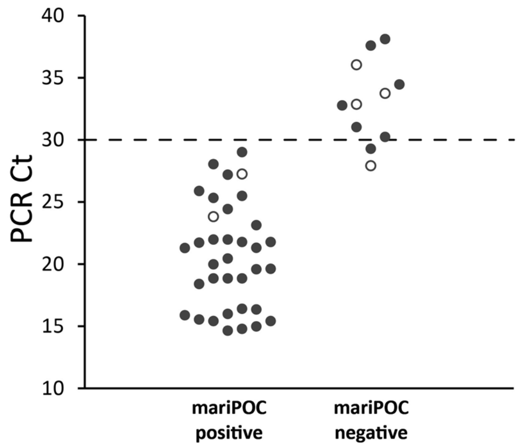

FIGURE 2 Correlation of C_t values of RT-PCR method and mariPOC SARS-CoV-2 rapid antigen test among symptomatic (black dots) and asymptomatic (empty dots) subjects.

sample in Cohort 1 and two samples in Cohort 2, totally 3/35) were negative after 20 min and turned positive in the final results at a 55-min outcome (Table 2). The C_t values for these positive samples varied from 24.43 to 28.04, and the duration of symptoms was 1–5 days.

4 | DISCUSSION

Early and accurate detection of SARS-CoV-2 infection is crucial for reducing virus transmission in the community. During the COVID-19 pandemic, the need for rapid testing has raised significantly and numerous antigen tests have been introduced in the market. mariPOC is a fully automated test system that enables the testing of up to 100 samples within a work shift at the sampling site. Over 90% of SARS-CoV-2 positive results are obtained in 20 min and low positive and negative results are reported after 55 min. Hands-on time is less than a minute and analysis, as well as result reading, is automated. These properties make mariPOC test systems suitable for use in medium and small-size volume laboratories and decentralized testing.[17–19]

The evaluation of the mariPOC SARS-CoV-2 rapid antigen test to be used in a health care center laboratory was performed in a medium-sized Finnish city representing adequate variation in social, ethnic, and age distribution of the population seeking COVID-19 testing in Finland. The SARS-CoV-2 positivity rate among the study population was 4.8%, determined by the RT-PCR method, which was well in correlation to the SARS-CoV-2 prevalence in the Hospital District of Southwest Finland during spring 2021. According to the National testing strategy in Finland, asymptomatic subjects were not tested unless they have had close contact with subjects with laboratory-confirmed SARS-CoV-2. Therefore, the number of asymptomatic subjects in this study was significantly lower compared to symptomatic subjects. It is of note that at the time of the study, only a small number of the population was vaccinated or infected with SARS-CoV-2.

According to the published studies, the sensitivity of antigen tests varies depending on test products, study protocols, and patient cohorts.[24,25] The overall sensitivity of the mariPOC antigen test in our evaluation was 76.1% which is in correlation with a recent meta-analysis showing the overall pooled sensitivity of 72.1% of the antigen tests in publications fulfilling the criteria to be included in the

TABLE 2 Clinical sensitivity (including 95% confidence intervals) of mariPOC SARS-CoV-2 rapid antigen test among symptomatic subjects at 20-min (preliminary) and 55-min (final) outcomes in correlation to C_t values of the reference RT-PCR method.

			mariPOC positives		mariPOC Sensitivity (95% CI)	
	C_t value	RT-PCR positives	20 min outcome	55 min outcome	20 min outcome	55 min outcome
Cohort 1	$C_t < 30$	18	17	18	94.4% (72.7%–99.9%)	100.0% (81.5%–100%)
	$C_t < 33$	20	17	18	85.0% (62.1%–96.8%)	90.0% (68.3%–98.8%)
	$C_t < 40$	23	17	18	73.9% (51.6%–89.8%)	78.3% (56.3%–92.5%)
Cohort 2	$C_t < 30$	16	13	15	81.3% (54.4%–96.0%)	93.8% (69.8%–99.8%)
	$C_t < 33$	17	13	15	76.5% (50.1%–93.2%)	88.2% (63.6%–98.5%)
	$C_t < 40$	17	13	15	76.5% (50.1%–93.2%)	88.2% (63.6%–98.5%)
Cohort 1 and 2	$C_t < 30$	34	30	33	88.2% (72.6%–96.7%)	97.1% (84.7%–99.9%)
	$C_t < 33$	37	30	33	81.1% (64.8%–92.0%)	89.2% (74.6%–97.0%)
	$C_t < 40$	40	30	33	75.0% (58.8%–87.3%)	82.5% (67.2%–92.7%)

meta-analysis.[26] When the results of Cohorts 1 and 2 were assessed separately, the sensitivity in Cohort 2 was lower (73.9%) than that in Cohort 1 (78.3%). This could be explained by the fact that in Cohort 2, four out of six false-negative samples were from asymptomatic subjects who most probably carry less SARS-CoV-2 virus than the subjects with symptoms. Threshold cycle (C_t) data from our RT-PCR was in line with this proposition. Furthermore, in Cohort 2, the samples in VACUETTE tubes were diluted three times more for mariPOC analysis compared to the recommended procedure of the manufacturer (NPS collected directly in mariPOC RTI sample buffer). No false-positive findings were reported in this study.

The performance of antigen tests to detect SARS-CoV-2 is known to be highest during the first 7 days from the onset of symptoms[25,26] and most guidelines advise using rapid tests accordingly and for symptomatic subjects.[4,16] Our results show, that the overall sensitivity of 82.5% was reached when the sensitivity for samples obtained only from symptomatic individuals was assessed. Thus mariPOC SARS-CoV-2 rapid antigen test shows good performance in diagnostic testing. While the number of positive samples among asymptomatic individuals was low ($n = 6$), definitive conclusions about the use of the mariPOC antigen test in detecting SARS-CoV-2 in asymptomatics cannot be drawn based on this study.

Infectivity of SARS-CoV-2 is associated with viral load, and the lower C_t values in RT-PCR indicate a higher viral load.[27] In the present study, we have shown that asymptomatic RT-PCR-positive subjects had on average higher C_t values compared to subjects with symptoms and that antigen test sensitivity increases when C_t values decrease. When C_t <30 was used as a threshold, the sensitivity of the antigen test was 97.1% and even up to 100% when only symptomatic patients were included. Thus, the sensitivity of the mariPOC rapid antigen test correlates better to RT-PCR C_t value than the patient symptom status or the intensity of symptoms, indicating that the mariPOC SARS-CoV-2 rapid antigen test recognizes well the subjects with contagious SARS-CoV-2 infection.[28–30]

Results for the SARS-CoV-2 test of the mariPOC test system are reported in two phases. At a 20-min outcome, most positive results are reported and due to the high specificity (here 100%) of the test, preliminary results are reliable. At a 55-min outcome also low positives and negatives are reported. In our study, 32 of 35 of all mariPOC antigen test positive samples were positive already in a 20-min outcome. Our prospective evaluation results of the mariPOC test are well in line with those reported earlier from a retrospective study.[17]

Although antigen tests have lower sensitivity compared to RT-PCR methods,[27,31] to fight against COVID-19 pandemics both PCR and antigen tests are needed.[5,14,15] Especially, in places where central hospital laboratory facilities are not available, shorter turnaround time and ease of use make antigen tests a powerful tool to prevent the spread of COVID-19. In addition, rapid antigen tests, such as automated mariPOC SARS-CoV-2, could be a good alternative for large-scale screening of individuals at schools and workplaces and, therefore, help to prevent the spread of COVID-19 in the community.[30,32]

5 | CONCLUSION

We conclude that the mariPOC SARS-CoV-2 antigen test detected the majority of the samples with RT-PCR cycle threshold below 30 among symptomatic and asymptomatic subjects justifying its use for rapid detection of individuals who most probably are contagious. In addition, the mariPOC test system is practicable in small and medium-sized laboratories as well as Health Care Centers to be used for rapid SARS-CoV-2 detection in symptomatics.

AUTHOR CONTRIBUTIONS

Tytti Vuorinen, Antti Sandén, and Rita Arjonen contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Marianne Gunell and Kaisa Rantasärkkä. The first draft of the manuscript was written by Marianne Gunell and revised by Kaisa Rantasärkkä. All authors have commented on previous versions of the manuscript and have read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

This study was approved by the Hospital District of Southwest Finland, research approval number T12/009/21. The Institutional Review Board from the Hospital District of Southwest Finland determined that the use of information, including information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects and thus is exempt from the Ethical committee review. All experiments were performed in compliance with relevant laws and institutional guidelines and in accordance with the ethical standards of the Declaration of Helsinki.

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