

The potential of rapid molecular RT-PCR for SARS-CoV-2 detection: implementation of the Cobas Liat system with urgent patients during a high-incidence season in Thailand

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KEYWORDS

Cepheid GeneXpert;
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Urgency.

ABSTRACT

There had been a high incidence of COVID-19 in Thailand between May 2021 and February 2022. Urgent cases in the emergency department (ED) or labor room (LR) should be immediately tested. We aim to implement a rapid molecular point-of-care tests (POCTs) using Cobas Liat for SARS-CoV-2 identification. A total of 32 random leftover-samples represented 100% overall concordance among the 2 POCTs and standard RT-PCR assays. A total of 3,188 nasopharyngeal swabs from an ED and LR were investigated with Cobas Liat system. The incidence of SARS-CoV-2 infection was observed to be 7.53% (164/2,179) in ED and 2.87% (29/1,009) in LR. Furthermore, symptomatic cases were noted in 69.51% (114/164) of ED patients, whereas only one case was recorded from the LR. Finally, this potential strategy could reduce turnaround time and the risk of infection in medical staff during the management of patients or medical procedures in the ED and LR.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19) was first reported in Wuhan, in the Hubei province of China, in December 2019. The infected case by the novel coronavirus was presented with an atypical pneumonia⁽¹⁻³⁾. The phylogenetic analysis represented SARS-CoV-2 was classified as a new strain with enveloped, positive sense, and single-stranded RNA virus. The bioinformatics analysis showed that the genetic sequence of SARS-CoV-2 is 80% identical to SARS-CoV and 50% to MERS-CoV⁽⁴⁾. Patients with a SARS-CoV-2 infection mostly presented with fever, cough, sputum production, upper airway congestion, and shortness of breath whereas headache, diarrhea, or hemoptysis was rarely found⁽¹⁾. The SARS-CoV-2 infection could transmit between person to another person via respiratory droplets by coughing or sneezing. Furthermore, environmental contamination is another way to spread the SARS-CoV-2, through contact objects that have been contaminated with droplets^(1,5). The median incubation period of COVID-19 was estimated to be 5.1 days and the symptoms developed within 11.5 days of infection⁽⁶⁾. In 2021, COVID-19 was a pandemic disease worldwide. The numbers of confirmed and fatal cases were increasing during 2021 and 2022. A novel variants of SARS-CoV-2 has been found recently⁽¹⁾.

Thailand has had a high-incidence season of COVID-19 since April 2021. The number of confirmed cases in Thailand promptly doubled to one million infected persons in August 2021⁽⁷⁾. During the high-season period, all urgent cases at the emergency department or pregnant women in the labor room should be examined for SARS-CoV-2 before any medical procedure. However, these patients may come to the hospital at any time. Furthermore, preventing nosocomial COVID-19 infection and maintaining the efficiency and quality of the health care service during the pandemic are essential⁽⁸⁾. Confirmation testing for SARS-CoV-2 infection was recommended and performed using the reverse transcription polymerase chain reaction (RT-PCR) method⁽⁹⁾. In laboratory practice, RT-PCR methods could be

accomplished with analysis of a batch conducted at the same time. Issues arisen with patients under investigation for SARS-CoV-2 infection in the emergency department (ED) or labor room (LR) that could not be tested as soon as possible. Several management methods for resolving the problem have been suggested, such as a screening test, i.e., Ag screening or IgM antibody detection. These assays mostly represented a lower sensitivity and specificity which was not suitable for the situation and increased the risk of nosocomial infection in the medical staff⁽¹⁰⁻¹¹⁾. However, Chaimayo et al⁽¹²⁾ reported the rapid assay for SARS-CoV-2 antigen detection and showed comparable sensitivity and specificity with the real-time RT-PCR assay. Recently, rapid molecular point-of-care tests (POCTs) were developed for SARS-CoV-2 identification based on RT-PCR, including at least two platforms: the Cobas Liat and Cepheid GeneXpert systems⁽¹³⁻¹⁷⁾. It seems that these assays could resolve the problem more effectively than a screening test because the rapid molecular testing could be performed within a short time (20-50 minutes), in an individual run without batch analysis, and based on the standard RT-PCR method. The high sensitivity and specificity of the two systems have been reported in a previous work⁽¹³⁻¹⁷⁾. In this study, we aim to demonstrate the success of the implementation of rapid molecular testing for SARS-CoV-2 using the Cobas Liat system in patients from the ED and LR.

Materials and methods

Study design and clinical samples

Ethical approval for this study was obtained and got exceptions for informed consent from the Institutional Review Board of Srinakharinwirot University, Thailand (SWUEC/E/M-024/2564). A total of 32 leftover-samples were selected and validated with three methods, including the Cobas Liat and Cepheid GeneXpert systems, as well as RT-PCR (Sansure Biotech Inc., P.R. China). Sample size was selected based on method validation in guidebook of Department of Medical Sciences Ministry of Public Health, Thailand. Furthermore, a retrospective study was investigated by routine

MSMC protocol. A total of 3,188 nasopharyngeal swab specimens were recorded from urgent patients at the ED and LR, Maha Chakri Sirindhorn Medical Center (MSMC), Faculty of Medicine, Srinakharinwirot University, who were suspected of having a SARS-CoV-2 infection, and were investigated with rapid molecular RT-PCR (Cobas Liat system) between May 2021 and February 2022 by routine MSMC protocol.

Validation of RT-PCR for SARS-CoV-2 detection with three methods (Pilot study)

A total of 32 leftover specimens were recruited from routine laboratory for SARS-CoV-2 detection based on RT-PCR (Sansure Biotech Inc., P.R. China) including 10 undetected samples and 22 detected samples. All the samples were also validated for SARS-CoV-2 infection with two POCTs using the Cobas Liat and Cepheid GeneXpert systems.

Routine RT-PCR for SARS-CoV-2 was performed on a real-time PCR machine ABI7500 (Thermo Fisher, Waltham, USA) using a commercial kit (Sansure Biotech Inc., P.R. China). Two specific regions of SARS-CoV-2, including the ORF1ab and N genes, are targeted in the assay. Furthermore, an endogenous human gene (RNase P gene) was monitored as an internal control (IC) for the appropriate specimen collection in the RT-PCR. The LOD assay is 200 copies/ μ L. The assay was executed in 96 minutes on a real-time PCR machine. However, this assay included the pre-PCR process, i.e., RNA extraction, and the preparation of the reagent, which consumed two to four hours per batch.

The Cobas Liat system is a multiplex RT-PCR for the rapid in vitro detection and discrimination of RNA targets for three viruses: SARS-CoV-2, and the influenza A and B viruses. Two regions (ORF1a/b and nucleocapsid (N)) of the SARS-CoV-2 genome are targeted for the assay. The lower limit of detection (LOD) of the Cobas Liat SARS-CoV-2 and influenza A/B nucleic acid test is 12 copies/ μ L. For specimen collection, nasopharyngeal swabs were collected and preserved in viral transport media (VTM). The assay was performed according to the manufacturer's instructions. Briefly, 200 μ L of specimen was added to the assay tube

and inserted into the tube slot of the Cobas Liat system. Internal control checks were also analyzed. The total processing time is about 20 minutes per specimen.

The Xpert Xpress SARS-CoV-2 assay of the Cepheid GeneXpert system is a rapid RT-PCR for SARS-CoV-2 detection. The two region gene sequences of the envelope (E) and nucleocapsid (N2) proteins of SARS-CoV-2 are targeted. The LOD of the Xpert Xpress SARS-CoV-2 is 250 copies/ μ L. Each cartridge includes a sample processing control and a probe check control to ensure that the sample was processed correctly. For specimen collection, nasopharyngeal swabs were assembled and preserved in VTM. The test was performed on the GeneXpert instrument using the Xpert Xpress SARS-CoV-2 cartridge. Briefly, 300 μ L of each specimen was added to a separate Xpert Xpress SARS-CoV-2 cartridge and loaded into an instrument. The results were interpreted automatically by the GeneXpert system with a RT-PCR curve. The total processing time is about 50 minutes per sample.

The implementation of the Cobas Liat system for SARS-CoV-2 detection in urgency

According to recommendation, the Cobas Liat system has been launched for rapid molecular testing for SARS-CoV-2 infection, which is 20 minutes, whereas the Xpert Xpress SARS-CoV-2 takes 50 minutes. Thus, in this study, we aim to assess only the Cobas Liat system. Laboratory molecular testing for SARS-CoV-2 was undertaken in our routine setting at the Department of Pathology, Faculty of Medicine, Maha Chakri Sirindhorn Medical Center (MSMC), Srinakharinwirot University. Urgent cases at the ED and pregnant women at the LR under investigation for infection who had to be examined before an operation or medical procedure were enrolled in rapid RT-PCR for SARS-CoV-2 detection between May 2021 and February 2022 using Cobas Liat system. The positive cases were recorded, along with basic patient characteristics, including age, sex, vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature (BT), pulse rate (PR), respiratory rate (RR)), and clinical symptoms.

Statistical analysis

The data collection was recruited via EMR software and data analysis was prepared in Microsoft excel. Furthermore, the statistical analysis and graphic were performed by MINITAB release 14.12.0 statistical software. A p -value < 0.05 was considered statistically significant. The Mann-Whitney test was tested for the difference between the Ct values of the ORF1ab/N genes in the symptomatic and asymptomatic groups. The percent agreement, including the overall (OPA), positive (PPA), and negative percent agreement (NPA), were calculated in comparative assays by Microsoft excel.

Results

Validation of RT-PCR for SARS-CoV-2 detection with three methods (Pilot study)

A total of 32 random leftover-samples were recruited from two groups (10 undetected samples and 22 detected samples) in routine RT-PCR for SARS-CoV-2 detection. All the samples were also investigated for SARS-CoV-2 infection with two

POCTs using the Cobas Liat and Cepheid GeneXpert systems. Based on this interpretation, a total of 22 detected samples and 10 undetected samples (32/32) represented 100% overall concordance among the three assays. Figure 1 demonstrates the comparison of the linear regression of the Ct values of the 22 detected cases in each assay. The comparison of the Ct value between RT-PCR (ORF1ab and N genes) and the rapid molecular Cobas Liat system (ORF1ab/N genes) showed the correlation in each of the Ct values of the genes (Figure 1A). Finally, the comparison of Ct values between the rapid molecular Cobas Liat and Cepheid GeneXpert systems displayed a good correlation in all samples, as depicted in figure 1B. Furthermore, the percentage of agreement, including positive (PPA), negative (NPA) and overall percentage agreement (OPA), was calculated between RT-PCR and the rapid molecular POCTs and found to be 100% in all parameters for the Cobas Liat and Cepheid GeneXpert systems, as displayed in table 1.

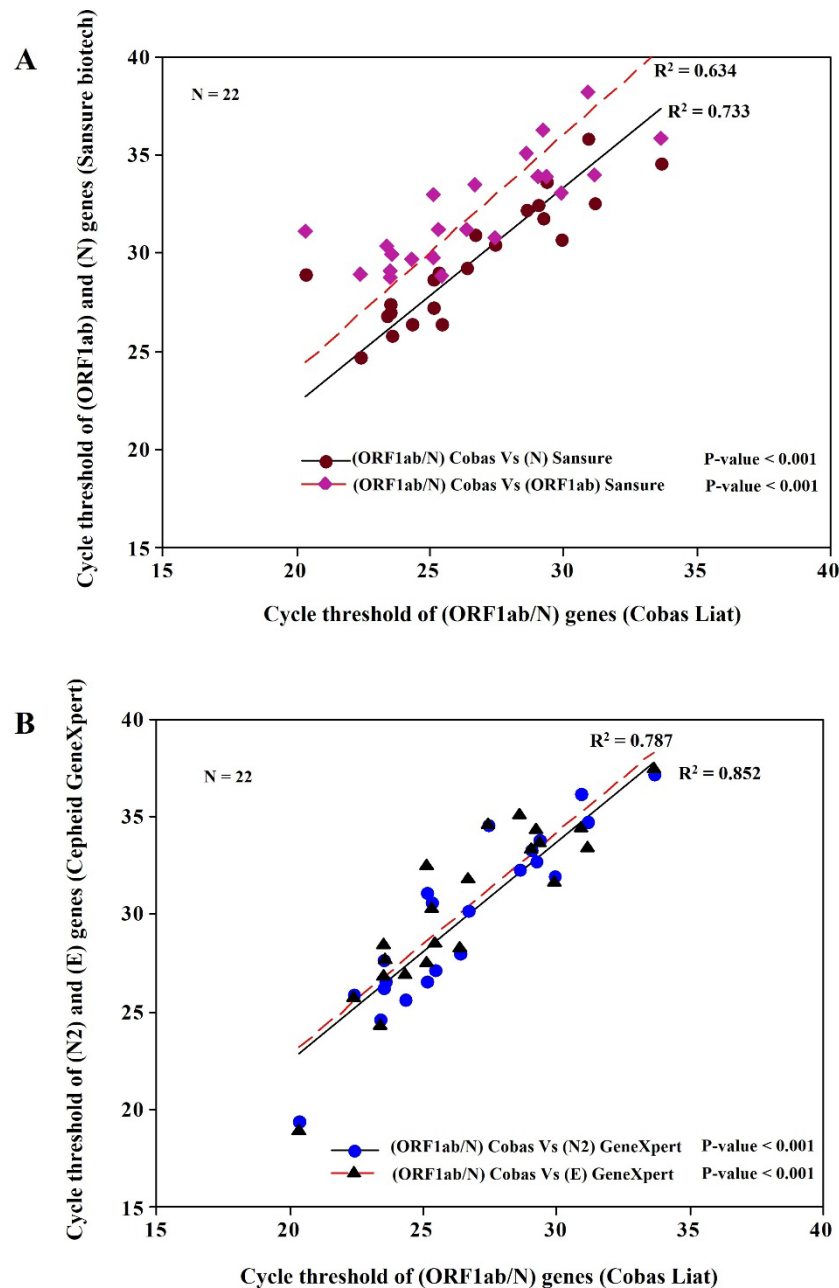


Figure 1 Ct values comparison between 3 platforms including RT-PCR (Sansure biotech), rapid molecular POCT (Cobas Liat), and rapid molecular POCT (Cepheid GeneXpert systems). Linear regression analyses (reporting the R^2 and P -value) between Ct values. (A) Linear regression of Ct value by RT-PCR (ORF1ab, and N genes) and Cobas Liat system (ORF1ab/N genes). (B) Linear regression of Ct value by Cobas Liat system (ORF1ab/N genes) and Cepheid GeneXpert system (N2 and E genes).

Table 1 The percentage of agreement was calculated between RT-PCR and rapid molecular POCTs including Cobas Liat system and Cepheid GeneXpert system

		RT-PCR (Sansure Biotech)	
		Positive	Negative
Cobas Liat system	Positive	22	0
	Negative	0	10
Cepheid GeneXpert system	Positive	22	0
	Negative	0	10

Cobas Liat system vs RT-PCR

Positive percentage agreement = 100% (22/22; kappa = 1.0)

Negative percentage agreement = 100% (10/10; kappa = 1.0)

Overall percentage agreement = 100% (32/32; kappa = 1.0)

Cepheid GeneXpert system vs RT-PCR

Positive percentage agreement = 100% (22/22; kappa = 1.0)

Negative percentage agreement = 100% (10/10; kappa = 1.0)

Overall percentage agreement = 100% (32/32; kappa = 1.0)

The potential of the Cobas Liat system for SARS-CoV-2 detection in urgency

A total of 3,188 nasopharyngeal swabs were recorded between May 2021 and February 2022 from the ED and LR according to suspected urgent cases. Figure 2 demonstrates the flowchart for SARS-CoV-2 detection in urgency. At the ED, the patients under investigation for infection accounted for 2,179 specimens, while pregnant women in the LR provided 1,009 specimens. All of these

were tested with rapid molecular POCTs using the Cobas Liat system. The positive cases were found in 164 samples (7.53%) and 29 samples (2.87%) from the ED and LR, respectively. Table 2 shows the patient characteristics of the detected cases in the two groups from the ED and LR. However, of the detected cases in pregnant women (LR), only one person had symptoms, which were febrile with a productive cough and sore throat.

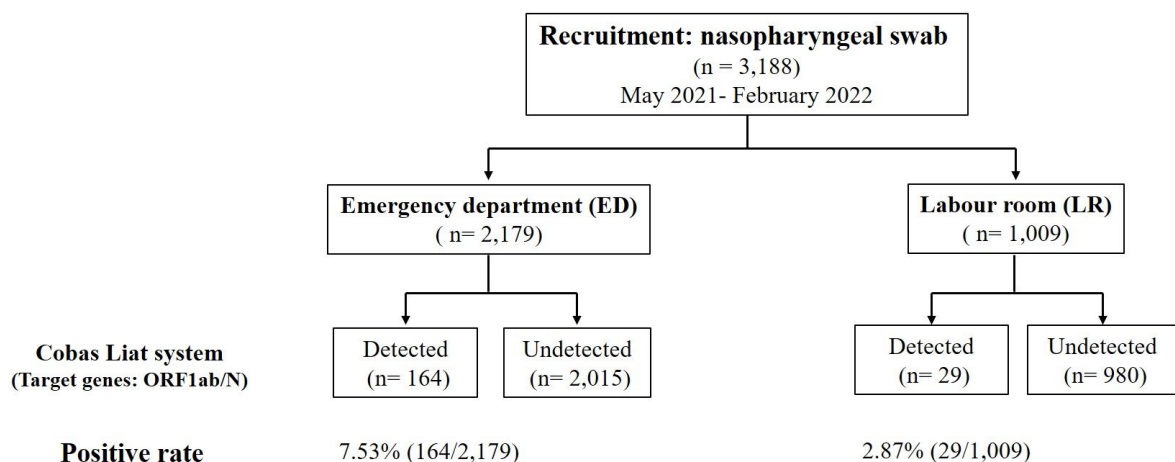
**Figure 2** Flowchart of SARS-CoV-2 detection using Cobas Liat system was demonstrated in urgency at emergency department and labour room. A total of 3,188 nasopharyngeal swabs were recruited during May 2021- February 2022.

Table 2 The patient characteristics in 193 urgent cases who were positive for SARS-CoV-2 infection

	Emergency department (n = 164)	Labor room (n = 29)
Age: median (range): years	58 (1-102)	27 (18-40)
Sex (number)		
Female	78	29
Male	86	-
Vital sign: median (range)		
Systolic blood pressure (mmHg)	131 (117-149)	128 (120.0-132.5)
Diastolic blood pressure (mmHg)	79 (69-89)	80 (72.5-85.0)
Body temperature (°C)	36.8 (36.6-37.6)	36.7 (36.5-36.9)
Pulse rate (times)	94 (80-112)	90 (20-100)
Respiratory rate (times)	24 (20-28)	20 (20-22)
Symptomatic: n (percent)		
Febrile or fever	82 (50.0)	1 (3.5)
Cough	29 (17.7)	-
Dry cough	6 (3.7)	-
Productive cough	48 (29.3)	1 (3.5)
Anosmia	5 (3.1)	-
Sore throat	21 (12.8)	1 (3.5)
Stuffy nose or runny nose	14 (8.5)	-
Headache or dizziness	16 (9.8)	-
Myalgia	9 (5.5)	-
Fatigue	75 (45.7)	-
Nausea or vomiting	14 (8.5)	-
Diarrhea	18 (11.0)	-

Rapid molecular POCTs for SARS-CoV-2 detection were performed on the Cobas Liat in urgent cases (from the ED and LR). A total of 193 detected cases exhibited a Ct value range of 9.84 - 36.60 of ORF1ab/N genes on the Cobas Liat system. A total of 142 positive cases (73.58%) that presented with symptoms are included in table 2, but the remaining 51 (26.42%) were asymptomatic. The Ct values of the ORF1ab/N genes on the

Cobas Liat system were compared between the symptomatic and asymptomatic groups, as shown on the boxplot (Figure 3). The Mann-Whitney test revealed highly significant differences (p -value < 0.001) for the Ct values of the ORF1ab/N genes in the symptomatic (median 18.28 with interquartile range (IQR) = 7.79) and asymptomatic groups (median 31.90 with IQR = 8.40).

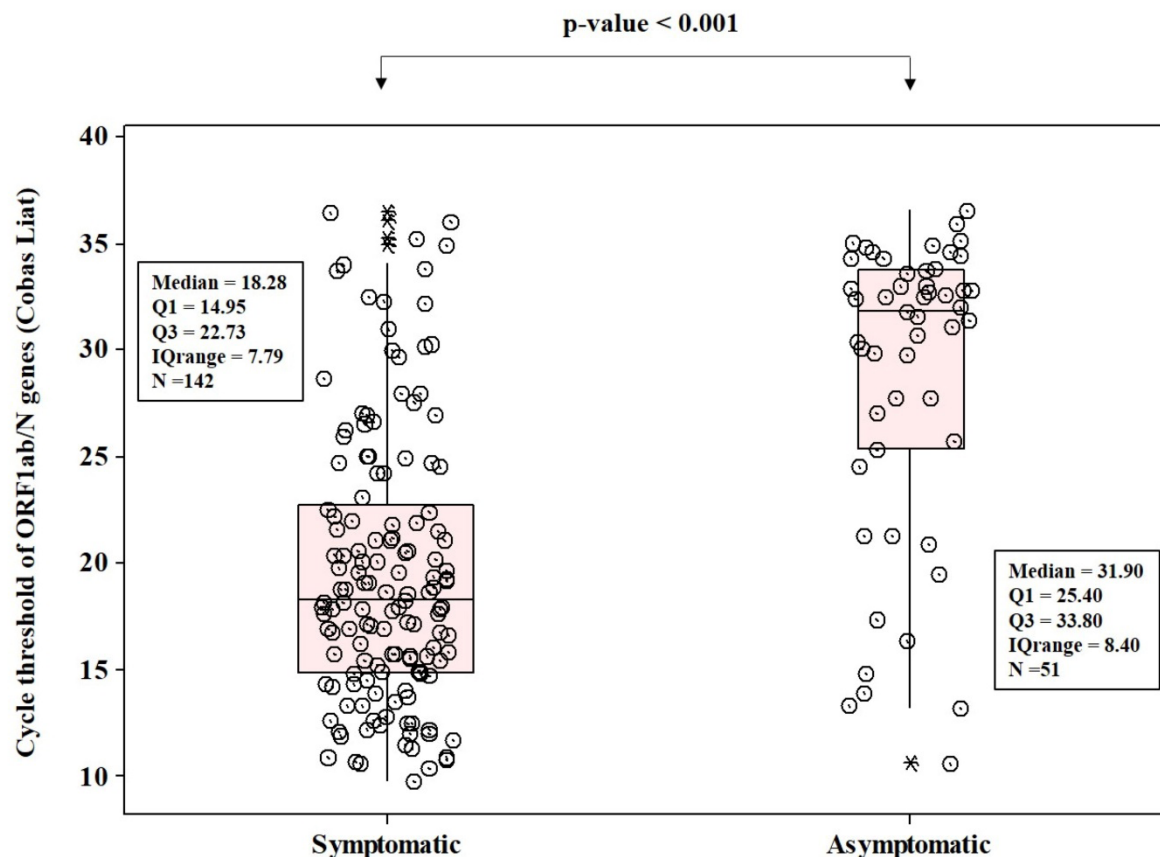


Figure 3 Distribution of Ct values of ORF1ab/N genes from positive cases grouped by symptom status and detected on the Cobas Liat system. The boxplot shows the median and interquartile range (box) of data and the box size represent sample number in each group.

Discussion

The COVID-19 pandemic has been investigated since February 2020. In Thailand, a high-incidence season has occurred since April 2021⁽⁷⁾. The detection of SARS-CoV-2 infection has been performed using RT-PCR as the standard method worldwide⁽⁹⁾. However, RT-PCR is not suitable for use in urgent cases because they should be immediately tested before management of the underlying emergency. Furthermore, identification of an infected case could lower the risk of nosocomial infection in medical staff during a procedure. This study demonstrated the rapid molecular POCTs based on the RT-PCR assay in ED and LR cases. We firstly report the proposed strategy for using rapid molecular POCTs in urgent cases.

The validation method between RT-PCR and rapid molecular POCTs demonstrated 100% overall concordance in this study. A total of 22 positive cases showed a correlation of Ct values in each assay. However, we found one sample in RT-PCR, as illustrated in figure 1A, that had a high Ct value and represents an outlier when analyzed with the two rapid molecular POCTs. This may have resulted from a random error in the sample preparation or RNA extraction process. Furthermore, the factors that led to poor analytical performance, such as the presence of inhibitors, genomic mutations, or samples with very low viral concentrations. The rapid molecular POCTs, the Cobas Liat and Cepheid GeneXpert systems, exhibit a good correlation, as depicted in the linear regression line (Figure 1C). The calculation of the percentage agreement of

results was discovered to have 100% concordance overall in three assays, including RT-PCR (Sansure Biotech), POCT 1 (Cobas Liat system) and POCT 2 (Cepheid GeneXpert system). A previous work has also noted an excellent overall 100% test concordance between the Cepheid Xpress SARS-CoV-2 assay and Cobas Liat SARS-CoV-2 and Influenza A/B assay in nasopharyngeal swabs and posterior oropharyngeal saliva⁽¹⁸⁾. Hansen et al⁽¹⁵⁾ reported the overall agreement between the Cobas Liat and 68/8800 systems for SARS-CoV-2 detection and values of 100% and 97.4% for PPA and NPA, respectively. Thus, the high accuracy of rapid POCTs has been established and is suitable for applying in an emergency.

The potential of rapid molecular POCTs for SARS-CoV-2 in urgency has been evaluated in this study. The Cobas Liat system has been launched for rapid molecular testing for SARS-CoV-2 infection. This research demonstrated the successful application of the rapid molecular assays in urgent cases from the ED and LR. In the high-incidence season in Thailand that began in April 2021, SARS-CoV-2 detection has resulted in a bottleneck in laboratory investigation using RT-PCR. The proposed strategy of using rapid molecular POCT for detecting SARS-CoV-2 infection at the ED and LR started in May 2021. The patients in both departments could be immediately tested and unnecessary resources significantly reduced, i.e., wearing full personal protective equipment (PPE) in undetected cases, as this equipment is limited in the health care environment during the COVID-19 pandemic^(19, 20). This research represented the urgent cases who came to the ED or LR during the period May 2021-February 2022. As shown in figure 2, a total of 3,188 nasopharyngeal swabs were analyzed by the Cobas Liat system, which has been reported to have a short operation time of 20 minutes and the lowest LOD (12 copies/uL). However, the limitation of the Cobas Liat system is

a higher cost when compared with antigen test kit. The rapid assay for SARS-CoV-2 antigen detection also showed comparable sensitivity and specificity with the real-time RT-PCR assay. Thus, there is optional use of this rapid and simple SARS-CoV-2 antigen detection test as a screening assay⁽¹²⁾.

In this study, we compared the symptomatic and asymptomatic groups by using the Ct values of the ORF1ab/N genes. The symptomatic group shows a significant difference from the asymptomatic one (p -value < 0.001). Previous studies have also reported significantly lower Ct values in the symptomatic group when compared with asymptomatic cases. Nearly 60% of specimens from asymptomatic individuals had a PCR Ct value >30 as measured using the Cobas 6800 assay E gene⁽²¹⁾. The active cases who demonstrated clinical symptoms may have an early stage of infection and there is a high growth of the replication of the virus in this period. During a late infection, the virus may be eliminated in the nasopharynx and a lower copy number of the virus (representing a high Ct value) might be found, meaning that asymptomatic cases are present in this group. Moreover, a previous work has reported that the viral load may be low (a high Ct value) in patients who were IgG-positive at discharge and high in those who were IgG-negative⁽²²⁾.

Conclusion

The implementation of rapid molecular point-of-care tests for SARS-CoV-2 detection using the Cobas Liat system in urgent patients from an emergency department and labor room could be promising and highly effective. This proposed strategy could reduce turnaround time and the risk of infection in medical staff during the management of patients or medical procedures in the ED and LR.

Clinical implication

- The validation method between RT-PCR and rapid molecular POCTs demonstrated 100% overall concordance in this study.
- During the high-season period, all urgent cases could be examined for SARS-CoV-2 infection before any medical procedure in our setting.
- The implementation of Cobas Liat system for SARS-CoV-2 detection in urgent case could be promising and highly effective.
- The preventing nosocomial COVID-19 infection and maintaining the efficiency and quality of the health care service during the pandemic are demonstrated.

Conflicts of interest

The authors declare no conflict of interest.

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