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The value of anal swab RT-PCR for COVID-19 diagnosis in adult Indonesian patients

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ABSTRACT

Objective This study will test the performance of the anal swab PCR test when compared with the nasopharyngeal swab PCR test as a diagnostic tool for COVID-19.

Design An observational descriptive study which included hospitalised suspected, or probable cases of hopitalised COVID-19 patients, conducted in Dr. Cipto Mangunkusumo National Hospital, Ciputra Hospital, Mitra Keluarga Depok Hospital and Mitra Keluarga Kelapa Gading Hospital, Indonesia. Epidemiological, clinical, laboratory and radiology data were obtained. Nasopharyngeal and anal swabs specimens were collected for SARS-CoV-2 RNA detection.

Results We analysed 136 subjects as part of this study. The clinical spectrum of COVID-19 manifesation in this study was typical of hospitalised patients, with 25% classified as mild cases, 14.7% in severe condition and 12.5% of subjects classified as having acute respiratory distress syndrome. When compared with nasopharyngeal swab as the standard specimen for reverse transcription polymerase chain reaction (RT-PCR) detection of SARS-CoV-2 antigen, the sensitivity and specificity of the anal swab was 36.7% and 93.8%, respectively. The positive and negative predictive value were 97.8% and 16.5 %, respectively. The performance of the anal swab remained similar when only the subgroup of patients with gastrointestinal symptoms (n=92, 67.6%) was analysed (sensitivity 40% and specificity 91.7%). Out of all the subjects included in analysis, 67.6% had gastrointestinal symptoms. Similarly, 73.3% of patients in the anal swab-positive group had gastrointestinal symptoms. The two most common gastrointestinal symptoms in the subjects' population were nausea and anorexia.

Conclusion Anal swab specimen has low sensitivity (36.7%) but high specificity (93.8%) for detecting SARS-CoV-2 antigen by RT-PCR. Only one additional positive result was found by anal swab among the nasopharyngeal swab-negative group. Anal swab may not be needed as an additional test at the beginning of a patient's diagnostic investigation and nasopharyngeal swab RT-PCR remains as the standard diagnostic test for COVID-19.

Summary box

What is already known about this subject?

- Positive RT-PCR results of SARS-COV-2 RNA were found not only in the respiratory tract but also in other specimens including faeces and biopsy specimens from the stomach, duodenum, ileum and rectum.

What are the new findings?

- This study found that anal swab RT-PCR have low sensitivity (36.7%) compared with nasopharyngeal swab as the standard specimen. Specificity is 93.8%. Similar sensitivity and specificity was found when only the subgroup of subjects who had gastrointestinal symptoms are analysed (40% and 97%, respectively).

How might it impact on clinical practice in the foreseeable future?

- Anal swab may not be needed as an additional test at the beginning of a patient's diagnostic investigation. Only one additional positive case was found using anal swab when nasopharyngeal swab was negative for SARS-CoV-2.

INTRODUCTION

Since the authorities in Wuhan, China, announced a cluster of pneumonia cases on 31 December 2019, to date (January 2021), the SARS COV-2 virus has infected more than 100 million people with a mortality rate of 2.2%.[1]

In Indonesia, there were more than one million confirmed cases with 2.8% mortality rate. Until January 2021, 25% of the confirmed case in Indonesia came from the country's capital, Jakarta.[2]

Gastrointestinal (GI) symptoms are a common feature in COVID-19 patients presenting to hospital. In Indonesia alone, data from the COVID-19 Handling Task Force showed nausea (17.9%), abdominal pain (7.4%), and diarrhoea (7.2%), were found in patients with confirmed COVID-19.[3] Meanwhile, positive RT-PCR results were found not only in the respiratory tract but also in GI

tract specimens including faeces (29%–53.42% positivity rate),[4 5] anal swabs[6] and endoscopic biopsy specimens from stomach, duodenum, ileum and rectum.[7] Stool viral RNA was detected in 38.5% of those with diarrhoea, and 8.7% in the non-diarrhoea group,[8] meaning that even in the absence of diarrhoea, faecal specimen RT-PCR may still be diagnostic for COVID-19. One study reports 55% of patients with positive faecal SARS-CoV-2 RNA had a prolonged positive result (mean 11.2 days) after the respiratory specimens became negative. The authors suggest that fecal-oral transmission is possible even after respiratory specimens become negative.[9]

There are also reports of positive SARS-CoV-2 RT-PCR of anal swab specimens in the absence of positive nasopharyngeal swab results.[10 11] These findings certainly need further investigation because it raises the possibility of COVID-19 cases undetected by nasopharyngeal swab but detected by anal swab. An anal swab specimen is expected to be an alternative to specimens from the nasopharynx for SARS-CoV-2 RT-PCR.

AIM

This study will test the performance of the anal PCR swab test when compared with the nasopharyngeal swab PCR test as a diagnostic tool for COVID-19.

METHODS

Study design

This study is an observational descriptive study by detection of viral particles by RT-PCR on anal swabs from patients with suspected or probable COVID-19 infection. To estimate the sample size for this diagnostic study, an estimated prevalence of 52.6% positive anal swab specimen[6] were used. The minimum requirement is to include 66 subjects. Consecutive sampling were conducted and patients meeting the inclusion criteria were recruited to the study on consent.

Participants

This study was conducted in Dr. Cipto Mangunkusumo National Hospital, Ciputra Hospital Citra Garden City, Mitra Keluarga Depok Hospital and Mitra Keluarga Kelapa Gading Hospital, Indonesia, between July 2020 and November 2020. Informed consent was obtained from each subject. The inclusion criteria were in-hospital suspected or probable COVID-19 patients based on Indonesia's National COVID-19 Prevention and Control Guidelines,[12] who had undergone nasopharyngeal swab to obtain specimen for the detection of viral particles by RT-PCR. The exclusion criteria were profuse diarrhoea, massive haematochezia or melena and anal wound.

Indonesia's national COVID-19 criteria

The operational definition of COVID-19 case in Indonesia uses several terminology: suspected, probable and confirmed cases.

A patient falls into the category of suspected case when (1) acute respiratory infection is present with history of travelling or living in area with local transmission within the past 14 days, (2) acute respiratory infection is present with COVID-19 contact within the past 14 days and (3) severe pneumonia/acute respiratory infection that requires hospitalisation without any other possible aetiology other than COVID-19.

A patient is classified as a probable case when severe acute respiratory infection/acute respiratory distress syndrome (ARDS)/death occurs, with high clinical probability of COVID-19 but the RT-PCR results is not yet confirmed, while confirmed cases are people with confirmed SARS-CoV-2 infection by RT-PCR.[12]

Specimen collection and processing

Nasopharyngeal swab was done by entering the swab straight along the floor of the nose until resistance was met, indicating that the swab had reached the posterior nasopharynx. The swab was then rotated several times and withdrawed. Anal swab specimen was collected by inserting the swab into the anus with a length of 3–5 cm from the end of the swab, followed by turning the stick 360° and leaving it for about 20 s. In order to make it easier for the swab stick to enter the anus, the wand can be dipped in saline solution first.

After collection, swab sticks were inserted into viral transport medium tube. Each specimens were extracted using Total RNA Extation Miniprep extraction kit from Viogene. Extraction was performed based on manufacturer's protocol. PCR amplification used kit from MiRXES Fortitude V.2.1 Singapore, and machine used was Roche Light Cycler 480 (Roche, Basel Switzerland). Cut-off cycle threshold (CT) value of the kit was 40, which means if CT value below 40 and amplification curve was present, the sample was valued as positive, and if otherwise, negative.

Participants were asked about GI and non-GI symptoms using a standardised case report form approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, and data were recorded using Microsoft Excel.

Statistical analysis

Data were expressed as counts and percentages for categorical variables and as mean and SD or median and IQR for continuous variables. The sensitivity, specificity, positive predictive value and negative predictive value were then counted. All analyses were performed with SPSS software, V.26.0 (IBM).

RESULTS

We analysed 136 subjects in this study. Sixty-six (48.5%) are male, and 70 (51.5%) are female. The mean age of the participants was 44.4 years old. Majority (52.5%) are between 40 and 60 years old. Most of these patients reported one or more comorbidities: type 2 diabetes mellitus (n=20), hypertension (n=20), pulmonary diseases (n=1), heart diseases (n=7), malignancies (n=4)

Table 1 Demographics and baseline characteristics of COVID-19 patients according to SARS-CoV-2 RNA detection in anal swab

Characteristics	All Patients (136) n (%)	Patients with positive nasopharyngeal swab SARS-CoV-2 (120) n (%)	Patients with positive anal swab SARS-CoV-2 (45) n (%)
Age, year (mean±SD)	44.41±12.72	44.17 ± (12.35)	45.31 ±(13.26)
<40 n (%)	48 (35.3)	47 (39.2)	16 (35.6)
40–60 n (%)	71 (52.2)	56 (46.7)	24 (53.3)
>60 n (%)	17 (12.5)	17 (14.2)	5 (11.1)
Sex			
Male, n (%)	66 (48.5)	59 (49.2)	24 (53.3)
Female, n (%)	70 (51.5)	61 (50.8)	21 (46.7)
Comorbidity			
No comorbid	53 (39)	48 (40)	22 (48.9)
<2	63 (46.3)	57 (47.5)	18 (40)
≥2	20 (14.7)	15 (12.5)	5 (11.1)
Habits			
Exercise, n (%) almost never	64 (47.1)	52 (43.3)	23 (51.1)
Lack of exercise (<3x/ week,<30 min/ session)	72 (52.9)	68 (56.7)	22 (48.9)
Smoking, n (%)			
Never	115 (84.6)	101 (84.2)	38 (84.4)
Active smokers	15 (11)	14 (11.7)	4 (8.9)
Former smokers	6 (4.4)	5 (4.2)	3 (6.7)
Body mass index			
<18.5	5 (3.7)	3 (2.5)	0 (0)
18.5–24.9	69 (50.7)	61 (50.8)	30 (66.7)
≥25	62 (45.6)	56 (46.7)	15 (33.3)
Radiologic findings			
Pneumonia, n(%)	100 (73.5)	90 (75)	38 (84.4)
Clinical outcome			
ARDS, n (%)	17 (12.5)	14 (11.7)	7 (15.6)
ICU referral, n (%)	20 (14.7)	18 (15)	8 (17.8)
HFNO, n (%)	14 (10.3)	12 (10)	4 (8.9)

ARDS, acute respiratory distress syndrome; HFNO, high-flow nasal oxygen; ICU, intensive care unit.

and obesity (according to Asia-Pacific classification: body mass index >25 kg/m^2, n=62). Characteristics of the subjects are described in table 1.

Out of all the subjects included in analysis, 67.6% had GI symptoms. Similarly, 73.3% of patients in the anal swab-positive group had GI symptoms. The frequencies of GI symptoms reported by our patients are presented in table 2.

Table 3 shows that 44 out of all patients confirmed positive with nasopharyngeal swab were also found positive with anal swab. When compared with nasopharyngeal swab as the standard specimen for RT-PCR detection of SARS-CoV-2 antigen, the sensitivity and specificity of the anal swab was 36.7% (95% CI 28% to 45.3%) and 93.8% (95% CI 81.9% to 100%), respectively. The positive and negative predictive value were 97.8% (95% CI 93.5% to 100%) and 16.48% (8.9% to 24.1%), respectively. The performance of the anal swab remained similar when only the subgroup of patients with GI symptoms (n=92, 67.6%) was analysed (sensitivity 40% (95% CI 29.2% to 50.7%) and specificity 91.7% (95% CI 91.1% to 100%).

The clinical spectrum of COVID-19 manifesation in this study was typical of hospitalised patients, with 25% classified as mild cases according to national guidelines (had non-specific symptoms such as fever, cough, sore throat, stuffed nose, malaise, headache and muscle aches), 14.7% in severe condition (one or more criteria are met: respiratory rate >30/min, presence of respiratory distress

Table 2 Gastrointestinal symptoms among study subjects

	All Patients (136) n (%)	Patients with positive nasopharyngeal swab SARS-CoV-2 (120) n (%)	Patients with positive anal swab SARS-CoV-2 (45) n (%)
Gastrointestinal symptoms, n (%)	92 (67.6)	81 (67.5)	33 (73.3)
Anorexia	63 (46.3)	56 (46.7)	24 (53.3)
Bloated stomach	26 (19.1)	24 (20)	11 (24.4)
Diarrhoea	17 (12.5)	15 (12.5)	8 (17.8)
Constipation	4 (2.9)	3 (2.5)	0 (0)
Nausea	64 (47)	58 (48.3)	25 (55.6)
Vomiting	21 (15.4)	19 (15.8)	8 (17.8)
Abdominal pain	28 (20.6)	25 (20.8)	9 (20)

or oxygen saturation <90% at room air) and 12.5% of subjects classified as having ARDS according of the fifth version of Indonesia's National COVID-19 Prevention and Control Guidelines.

DISCUSSION

RT-PCR from nasopharyngeal specimen is still the gold standard for the diagnosis of SARS CoV-2. However, the sensitivity varies, depending on the timing of the test relative to exposure.[13 1415] Our study found 45 (37.8%) anal swab-positive patients out of 136 subjects. Fifteen (11.03%) of the patients that were suspected to have COVID-19 clinically were found to be negative both by nasopharyngeal and anal swab RT-PCR.

There is not much research that provides data on RT-PCR anal swabs for the diagnosis of COVID-19. More reports, however, were found on faecal RT-PCR. Yuan *et al* found 52.6% positive results on anal swab examination in children.[16] Another study reports anal swab positivity rate of 24.32%, and found two subjects with positive anal swab but negative nasopharyngeal swab.[17] This is similar to our finding, where one patient had positive anal swab result with negative nasopharyngeal swab RT-PCR. This particular patient had two negative nasopharyngeal swab 2 days apart, both negative, but CT scan showed multifocal ground glass opacities and the patient is considered a COVID-19 probable case. These findings suggests that anal swab may find additional COVID-19 case when respiratory specimens are negative. A study by Wang *et al* reports that anal swab had higher positivity rate (20%) than pharyngeal swab (12%) in detecting SARS-CoV-2 nucleid acid among convalescent COVID-19 patients. In 10 patients with positive anal swab, nine cases had negative respiratory tract specimens.[18]

Table 3 Correlation of nasopharyngeal swab and anal swab of the study population

	Positive nasopharyngeal swab (n)	Negative nasopharyngeal swab (n)	
Positive anal swab (n)	44	1	45
Negative anal swab anal (n)	76	15	91

The sensitivity of the anal swab in this study is indeed low, so it is not ideal if it is used as a diagnostic tool for COVID-19 screening. However, with a specificity of 93.8%, it can be said that it is good enough for a confirmation test for COVID-19. We also found that anal swab's sensitivity and specificity remain similar regardless of the presence of GI symptoms.

In this study, we found that 67.6% (n=92) of the subjects complained of GI symptoms. The most common GI symptoms in the subject's population is nausea (47%), followed by anorexia (46.3%).

Pan *et al* reported 50% of patients present with digestive symptoms, and a small proportion of patients (3%) presented solely with GI symptoms[19] GI involvement is also often found in infections of related viruses from the Coronaviridae family, namely SARS-CoV and MERS-CoV. During the SARS outbreak, more than 76% of patients had diarrhoea, generally in the first 1 week of illness. Intestinal biopsy shows active replication of SARS-CoV in both small and large intestine.[20] It is known that SARS-CoV-2 binds to ACE-2 as its main receptor for cell entry. The tissues of GI tract express high level of ACE-2 on cell surfaces and data suggests that the small intestine express the highest level of ACE-2 among all tissues in human body.[21] This high expression of ACE-2 is a potential site of SARS-CoV-2 binding, and potentially contributes to subsequent GI tract infection and digestive symptoms.

During the study, there were no complications or complaints from patients about the anal swab procedure.

CONCLUSION

RT-PCR anal swabs is a good confirmatory test for COVID-19 cases (specificity 93.8%). However, this study found only one additional COVID-19 case by anal swab when respiratory specimens were negative, which may imply that RT-PCR from respiratory specimens should still be used as a primary diagnostic test, and anal swab may not be needed as additional test at the beginning of a patient's investigation. We consider anal swab as a safe procedure for patients, but although there were no complaints from patients during or after the

procedure, the comfort and acceptability aspects of anal swab were not included in this study and further research may be needed.

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Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. The authors confirm that the data supporting the findings of this study are available within the article and its online supplemental materials.

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