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Follow-up COVID-19 PCR result up to day 5 with clinical features predicts positivity for inconclusive results

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ABSTRACT

Introduction: False-positive inconclusive polymerase chain reaction (PCR) results against severe acute respiratory syndrome coronavirus 2 were not low and have potentially harmful effects. We aimed to find parameters to differentiate positive cases from false-positive ones, and suggest an optimal scheme and follow-up period for inconclusive results.

Methods: Cases with inconclusive PCR tests among healthcare personnel from February 2020 to June 2021 were classified as confirmed positive, clinically positive, and clinically negative groups, which were compared. The diagnostic accuracy of follow-up tests and composites of clinical and laboratory data were analyzed.

Results: Symptoms, contact history, and lower cycle threshold of the N gene were more common in the COVID-19 positive group. The scoring schemes combining symptom and contact history with follow-up PCR results had higher sensitivities than the PCR tests only modality. Follow-up tests up to 5 days combined with symptoms and contact history could discriminate between positive and negative cases.

Conclusion: A follow-up PCR test up to day 5 with clinical features might predict positivity and shorten the quarantine period in most healthcare personnel.

1. Introduction

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 [1], real-time reverse transcription PCR (RT-PCR) has been an essential tool in diagnosing coronavirus disease 2019 (COVID-19) [2]. Most SARS-CoV-2 RT-PCR assays target two or more distinct genes. When not all targets are detected, or targets are detected at a high cycle threshold (C_t) close to cutoff, the test result is reported as "inconclusive" [3]. A systemic review [4] found a correlation between low Ct values and progression to severe disease, severe disease, and positive viral culture. However, viral load determined via Ct value does not always correlate with infectivity, as the virus was rarely cultured after 9 days despite persistently high viral loads [5]. Non-amplification of some genes may be attributed to low viral loads in samples and/or different amplification efficiencies of individual target during PCR [6].

In practice, inconclusive results are initially treated as presumably positive cases, which can carry substantial infection risks to patients, carers, and healthcare workers [7]. However, RT-PCR assays cannot distinguish between a viable live virus or a dead virus which can persist after infectious period. Furthermore, one study reported that the false-positive rate among inconclusive PCR test results was not low, ranging from 14% to 39% [3]. False-positive results may lead to an over-diagnosis of COVID-19, which has potential detrimental effects, including unnecessary isolation, anxiety, and additional tests [8]. These effects are especially problematic in healthcare setting, causing workforce depletion, delayed management of emergent non-COVID-19 health issues, and ineffective utilization of healthcare resources [9]. In contrast, if inconclusive test results are misinterpreted as false-negative, they may spread the virus in communities and hospitals, causing SARS-CoV-2 tests distrust and hesitancy. Nevertheless, there have been scarce data on the interpretation and management of inconclusive results.

We hypothesized that healthcare personnel (HCP) with inconclusive PCR results could be evaluated more accurately if combined with clinical, epidemiological, and follow-up laboratory data. The research aimed to find parameters to differentiate positive cases from false-positive

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Table 1
Classification criteria of cases with inconclusive PCR results.

	Ct value of each gene
Negative	Ct of E gene > 40 and Ct of RdRp/S gene > 40 and Ct of N gene > 40 and Cactt of IC ≤ 40
Positive	Ct of E gene ≤ 40 and Ct of RdRp/S gene ≤ 40 and Ct of N gene ≤ 40
Inconclusive	Ct of E gene > 40 or Ct of RdRp/S gene > 40 or Ct of N gene > 40except negative cases.

Ct: cycle threshold; RdRp/S: RNA-dependent RNA polymerase/Spike; IC: internal control

ones, and suggest an optimal scheme and follow-up period for inconclusive results.

2. Methods

2.1. Study population

This retrospective study analyzed inconclusive SARS-CoV-2 PCR tests among HCP from 17th February 2020 to 25th June 2021. COVID-19 recovery cases within three months of PCR test and staff without follow-up tests within seven days were excluded to minimize cases with newly acquired infection [10] and maximize the likelihood of detecting infections [11]. Once identified as cases with inconclusive results, data about demographic information, symptoms, close contact history, and laboratory findings were collected. Assessed symptoms consistent with COVID-19 included fever, cough, runny nose, sneezing, sore throat, shortness of breath, anosmia, loss of taste, headache, fatigue, muscle aches, diarrhea, nausea, and vomiting.

2.2. Sampling, RT-PCR testing, & reporting

All staff visited drive-thru pod during the study period, and a physician performed a nasopharyngeal swab. Specimens were transported in a suitable outer container immediately after sampling. All samples were nasopharyngeal swabs. If there is still suspicion of COVID-19, resampling and/or retesting were conducted.

The presence of SARS-CoV-2 was confirmed by RT-PCR. Ribonucleic acid (RNA) was extracted from the nasopharyngeal swab samples using MICROLAB Nimbus IVD (in vitro diagnostics) system (Hamilton, Reno, NV, USA) with STARMag96 Virus kit (Seegene, Seoul, Korea). Reverse transcription was performed at 50°C for 20 minutes, followed by inactivation of the reverse transcriptase at 95°C for 15 minutes. PCR amplification was performed with 45 cycles at 94°C for 15 seconds at 58°C for 30 seconds using CFX96 real-time PCR detection system (Bio-rad, Hercules, CA, USA) with Allplex 2019-nCoV assay real-time PCR kit (Seegene, Seoul, Korea), which targeted the envelope (E), RNA-dependent RNA polymerase (RdRp) (Spike (S) gene co-detected in the upgraded PCR kit version), and nucleocapsid (N) genes of SARS-CoV-2. Internal control (RP-V IC) was also included in each PCR mixture, and its cycle threshold over 40 with no positive signal among other target genes was regarded as invalid result. The PCR data were analyzed using Seegene Viewer Software. The manufacturer's claimed detection limit of Allplex 2019-nCoV assay was 100 RNA copies/reaction.

The sample was defined as negative if the C_t value of all three target genes exceeded 40 cycles and internal control was amplified, according to the manufacturer's interpretative criteria. Samples were reported positive for SARS-CoV-2 when three target signals were detected at $C_t \leq 40$. The inconclusive result indicated detection of only 1 or 2 PCR target amplification not more than 40 of C_t value (Table 1). Once inconclusive results were recognized, PCR tests were repeated on day 3, day 7, and day 14 unless additional tests were positive.

Table 2
New scoring scheme to predict positive cases.

Parameter	Results	Score
Symptoms consistent with COVID-19	Yes	1
	No or unclear	0
Contact history	Yes	1
	No or unclear	0
Follow-up PCR test results	Positive	5
	inconclusive	3
	Negative or NA	0

COVID-19: coronavirus disease 2019; NA: not applicable

2.3. Classification of cases with inconclusive PCR results

Yang et al. [3] showed that a scoring scheme using symptoms, contact history, and additional labs effectively interpreted inconclusive COVID-19 PCR results. Yang's scheme was tailored to overcome rare specific symptoms and few cases that underwent antibody tests in our cohort (Table 2). Confirmed positive cases were defined as those with follow-up PCR results that turned positive within two weeks [12]. Staff in the clinically positive group had subsequent inconclusive or negative test results, but COVID-19 could not be excluded, given symptoms and contact history. The clinically negative group had negative follow-up test results without suspicion of COVID-19. Based on these definitions, a total score was interpreted as "confirmed positive", "clinically positive", or "clinically negative" when the score is more than 4, 2 to 4, or less than 2, respectively.

A case in the "confirmed positive" group has at least one positive PCR result or follow-up inconclusive PCR result plus having symptoms and contact history. The "clinically positive" group should have at least one additional inconclusive PCR result and either symptoms or contact history, or symptoms plus contact history without any follow-up inconclusive results. A case with either symptoms or contact history but a negative PCR result was deemed "clinically negative". When classification was unclear, the nurse (Gatchalian) and two physicians (Park and Oh) reviewed cases and finalized the case grouping.

2.4. Data analysis

First, the positive rate for inconclusive tests was calculated during the study period. The confirmed positive, clinically positive, and clinically negative groups were compared to find significant factors related to positivity. As support staff usually share a small room with a dozen of their colleagues [13], which increases the risk of close contact with COVID-19 patients, subgroup analysis was done for support staff and non-support staff, respectively. The diagnostic accuracy of follow-up tests and composites of clinical and laboratory data were analyzed using areas under the receiver operating characteristic curve (AUCs).

The Chi-square (χ^2) and Mann–Whitey tests were used to compare nominal and continuous data, respectively. A two-sided alpha level of 0.05 defined statistical significance. Analyses were conducted using SPSS version 18.0 (SPSS Inc., Chicago, IL). The institutional review board and Research Ethical Committee of the Ministry of Health granted

Table 3
Characteristics of included cases.

	Total(N=128)	Non-support staff(N=66)	Support staff(N=62)	P value
Age, median (IQR), years	34.0(29.0, 40.0)	37.0(32.0, 42.5)	31.0(26.8, 36.2)	< 0.001
Female	57 (44.5%)	37 (56.1%)	20 (32.3%)	0.007
Symptoms	12 (9.4%)	9 (13.6%)	3 (4.8%)	0.088
Close contact	57 (44.5%)	8 (12.1%)	49 (79.0%)	< 0.001
Number of positive genes				0.067
1 gene	103 (80.5%)	49 (74.2%)	54 (87.1%)	
2 genes	25 (19.5%)	17 (25.8%)	8 (12.9%)	
C_t				
E gene, median (IQR)	37.9(37.4, 38.1)(N=22)	37.8(36.8, 38.2)(N=11)	37.9(37.8, 38.0)(N=11)	
RdRp/S gene, median (IQR)	38.2(37.2, 38.7)(N=23)	38.2(37.3, 38.6)(N=17)	38.2(36.7, 38.8)(N=6)	
N gene, median (IQR)	37.2(35.4, 38.3)(N=108)	37.7(36.4, 37.7)(N=55)	36.4(34.8, 37.5)(N=53)	< 0.001
Follow-up PCR results				0.088
Detected	16 (12.5%)	8 (12.1%)	8 (12.9%)	
Inconclusive	13 (10.2%)	3 (4.5%)	10 (16.1%)	
Non-detected	99 (77.3%)	55 (83.3%)	44 (71.0%)	
Final discretion				0.030
Confirmed positive	16 (12.5%)	8 (12.1%)	8 (12.9%)	
Clinically positive	15 (11.7%)	3 (4.5%)	12 (19.4%)	
Clinically negative	97 (75.8%)	55 (83.3%)	42 (67.7%)	

IQR: interquartile range; C_t: cycle threshold; RdRp/S: RNA-dependent RNA polymerase/Spike

ethical and regulatory approval. Informed consent was waived owing to the retrospective nature of the study.

3. Results

3.1. Identification of cases with inconclusive PCR results

A total of 11,212 PCR tests was performed on 1,474 HCP from 17th February 2020 to 25th June 2021. Positive results for COVID-19 accounted for 3.1% (351/11,212 tests). Support staff had a higher positive rate than non-support staff (7.2% vs. 1.6%, $P < 0.001$).

Inconclusive PCR results of 160 tests were identified, resulting in a rate of 1.4% (160/11,212 tests). The rate was higher in support staff (3.0% vs. 0.8%, $P < 0.001$). Finally, a total of 128 inconclusive results, which was 1.1% of all tests (128/11,212), was analyzed after excluding cases with delayed (more than 7 days) follow-up PCR tests.

3.2. Characteristics of the study population

Of 128 inconclusive results, the median age (interquartile range, IQR) was 34.0 (29.0, 40.0) years, and 57 (44.5%) were female. Twelve (9.4%) had symptoms consistent with COVID-19, and 57 (44.5%) were close contacts with COVID-19 patients (Table 3). No one was admitted to hospital with infection-related symptoms. Only one gene was detected in 80.5% (103/128). N gene was the most commonly detected among three genes in 84.4% of cases (108/128). Support staff had more contact history and a lower C_t value of the N gene.

3.3. Comparison of confirmed positive, clinically positive, and clinically negative groups

The modified Yang's scheme classified a total of 31 cases into 16 confirmed positive cases and 15 clinically positive cases, respectively (Table 4). The first classifications of 3 cases by modified Yang's scheme were changed after reviewing cases. The false-positive rate was 75.8% (97/128). Most of the clinically positive group belonged to support staff (12/15, 80%). Compared with the clinically negative group, the other two groups had more symptoms, close contact history, and a lower C_t value of the N gene. There was no significant difference in the first and sequential Ct values of E, RdRp/S, and N genes in the confirmed positive group.

3.4. An optimal timing of additional PCR tests and scheme

Of 16 confirmed positive cases, the average number of days to test positive was 5.5 days (IQR 1, 7). Except for two cases that tested positive on day 12 and 15, follow-up tests of 14 cases in the confirmed positive group turned positive within 7 days. Two cases tested positive on day 12 and 15 have close contact with members of their households.

The scoring schemes combining symptom and contact history with PCR results (Table 2) had higher sensitivities than follow-up PCR tests only modality, though differences were insignificant (Table 5). AUC of composites of follow-up test results and clinical data on day 5 was comparable to that of day 7 in predicting positivity (difference 0.005; 95% CI: -0.005 to 0.108, P=0.07).

4. Discussion

Up to now, few studies have investigated the positive rate of inconclusive SARS-CoV-2 PCR results. In our study, inconclusive cases (1.4%) were almost half of COVID-19 positive cases (3.1%). Recent studies found that the rate of inconclusive tests ranged from 0.34% to 1.0% [3,14], which was lower than our result. It needs to be taken into consideration that our study included support staff who had a more frequent contact history (79.0%), leading to a higher rate. The false-positive rate in inconclusive results was high (75.8%). Given more inconclusive cases during screenings and extensive contact tracing in the institution, the high false-positive rate might be associated with asymptomatic screening rather than the test procedure itself [3]. Sampling-related issues are one of the causes of inconclusive PCR results [6]. However, the institution's standardized sampling and transportation process may minimize sampling-related inconclusive results.

One unanticipated finding was that symptom and contact history did not add much benefit to the differentiation of inconclusive cases compared with follow-up tests. It may be related to the high prevalence of contact history in support staff and relatively rare symptoms. Boeckmans et al. [15] also found that COVID-19-like symptoms were not good predicting factors for positive follow-up tests in borderline SARS-CoV-2 patients. In contrast, another study demonstrated no presumptive positive case in screening asymptomatic cases [14]. More research needs to be undertaken to understand this discrepancy.

Interestingly, lower C_t values of the N gene in positive groups were noted only in support staff, not in non-support staff. Several studies demonstrated a relatively low Ct value associated with infectivity in COVID-19 patients [16,17]. Given that a higher proportion of support

Table 4
Comparison among three groups.

	Confirmed positive(N=16)	Clinically positive(N=15)	Clinically negative(N=97)	P value
Age, median (IQR), years	35.0(29.0, 37.75)	32.0(30.0, 39.0)	34.0(29.0, 40.5)	0.914
Female	8 (50.0%)	5 (33.3%)	44 (45.4%)	0.612
Support staff	8 (50.0%)	12 (80.0%)	42 (43.3%)	0.030
Symptoms	4 (25.0%)	3 (20.0%)	5 (5.2%)	0.013
Close contact	10 (62.5%)	11 (73.3%)	36 (37.1%)	0.010
Number of positive genes				1.000
1 gene	13 (81.3%)	12 (80.0%)	78 (80.4%)	
2 genes	3 (18.8%)	3 (20.0%)	19 (19.6%)	
C_t				
E gene, median (IQR)	37.9(37.3, 38.3)(N=5)	38.0(N=2)	37.8(36.8, 37.9)(N=15)	
RdRp/S gene, median (IQR)	38.7(38.1, 39.1)(N=4)	36.7(N=3)	38.2(37.3, 38.6)(N=16)	
N gene, median (IQR)	35.9(33.0, 37.2)(N=10)	35.2(33.3, 36.6)(N=13)	37.4(36.3, 38.4)(N=85)	< 0.001
Follow-up PCR results				<0.001
Non-detected	0 (0%)	2 (13.3%)	97 (100%)	
Inconclusive	0 (0%)	13 (86.7%)	0 (0%)	
Detected	16 (100%)	0 (0%)	0 (0%)	

IQR: interquartile range; C_t: cycle threshold; RdRp/S: RNA-dependent RNA polymerase/Spike

Table 5
Test characteristics of PCR results on different follow-up days with or without clinical data.

Used variable	Sensitivity (%)	Specificity (%)	PPV(%)	NPV(%)	AUC	95% CI
PCR tests onlyon day 5 (N=121)	75.9	100	100	92.9	0.879	0.808-0.931
Clinical data withtests up to day 5	82.8	98.9	96.0	94.8	0.908	0.842-0.953
PCR tests onlyon day 7	87.1	100	100	96.0	0.931	0.870-0.969
Clinical data withtests up to day 7	93.5	99.0	96.7	98.0	0.960	0.908-0.987
PCR tests onlyon day15	93.5	100	100	98.0	0.966	0.916-0.990
Clinical data withtests up to day 15	96.8	99.0	96.8	99.0	0.977	0.932-0.996

PPV: positive predictive value; NPV: negative predictive value; AUC: area under the ROC curve; ROC: receiver operating characteristic; CI: confidence interval

staff was in the positive group, their low C_t values may be associated with positivity. However, as there was a significant overlap in C_t value, it could not be used to differentiate positive cases from negative ones.

The present study showed that additional PCR testing up to day 5 and clinical information could help differentiate most positive cases from false-positive ones, which could shorten the quarantine period. Our findings appear to be linked to 3-5 days of window period between exposure and detectability of SARS-CoV-2 RNA [18]. The finding also supports the idea that quarantine for close contact can end after Day 5 if tests are negative and no symptoms are reported [19].

Exceptional cases with longer window periods than five days all had close contact with members of their households. New infection cannot be excluded for these cases, especially those who tested positive on day 12 and day 15. Nie et al. [12] indicated that 97.5% of exposed cases will develop symptoms within 11 days and 99% within 14 days. However, an individual case may show longer delays in developing symptoms and detecting SARS-CoV-2 RNA, up to 24 days. Future research might explore if a more extended follow-up period is required when inconclusive cases have confirmed COVID-19 members in their households.

The strength of this research lies in that it evaluated the clinical implications of inconclusive PCR results among healthcare personnel over more than a one-year period. A detailed survey for symptoms and contact history was conducted as well. However, it is difficult to generalize the findings of one specific PCR assay in a single center. Two cases

In conclusion, inconclusive PCR results, including the false-positive cases, were common in our cohort, especially in support staff in a high-risk congregate setting. Follow-up PCR test results up to day 5, combined with symptoms and contact history, generally aligned with medical professionals' final discretion, which may shorten the quarantine period. Further studies are needed on whether this finding applies to the general population.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Sung-Soo Park: Methodology, Formal analysis, Writing – original draft. **Duck-Jin Hong:** Conceptualization, Writing – review & editing. **Katrine K Gatchalian:** Investigation, Resources, Project administration. **Hye-Young Oh:** Validation, Supervision.

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