

Title: Positive ratio of polymerase chain reaction (PCR) and validity of pre-screening criteria at an outpatient screening center during the early phase of the COVID-19 epidemic in Japan

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Summary

Despite the increase in COVID-19 cases worldwide, the number of cases in Japan has been relatively low, and an explosive surge in the prevalence has not occurred. Since March 2020, the Ministry of Health, Labour and Welfare (MHLW) in Japan recommended original criteria for considering polymerase chain reaction (PCR) testing, although there was a lack of clear evidence for appropriate targets for COVID-19 testing. This study aimed to evaluate COVID-19 positive ratio and pre-screening criteria in Tokyo immediately after insurance-covered SARS-CoV-2 polymerase chain reaction testing became available in Japan. We tested 277 individuals (positive: 9.0%) from March 9–29, 2020. In total, 277 patients with mild symptoms in metropolitan Tokyo underwent SARS-CoV-2 PCR testing. The results revealed that 25 (9.0%) patients were PCR positive. The sensitivity and specificity of the MHLW criteria were 100% and 10.7%, respectively. When the criteria excluded nonspecific symptoms, fatigue, and dyspnea, sensitivity slightly decreased to 92%, and specificity increased to 22.2%. Specificity was highest when the fever criterion was $\geq 37.5^{\circ}\text{C}$ for ≥ 4 days, and exposure/travel history, including age and underlying comorbidities, was considered. Our findings suggest that MHLW criteria, including symptoms and exposure/travel history, could support COVID-19 pre-screening.

The number of COVID-19 cases has increased in Japan, with 14,281 cases confirmed on May 1, 2020 (1). Despite Japan's high population density, the prevalence of COVID-19 has been relatively low; an explosive surge in its prevalence has not occurred. It is also reported that 2.2 polymerase chain reaction (PCR) tests per 1,000 population were performed in Japan between April 26 and May 3, 2020, ranking 35th among the 36 Organisation for Economic Co-operation and Development countries, suggesting relatively few tests were performed (2).

From March 2020, the Ministry of Health, Labour and Welfare (MHLW) in Japan recommended that individuals consider PCR testing if any of the three following criteria ("MHLW criteria") were met: (i) prolonged symptoms of a cold (nasal discharge, sore throat, cough, sputum) or fever ($\geq 37.5^{\circ}\text{C}$) for ≥ 4 days; (ii) fatigue or dyspnea; (iii) old age, underlying disease (e.g., diabetes, heart failure, respiratory disease [e.g. chronic obstructive pulmonary disease: COPD]), or end-stage renal failure or immunosuppressive or anticancer therapy and symptoms of a cold or fever ($\geq 37.5^{\circ}\text{C}$) persisting for ≥ 2 days (3).

Although identifying positive cases via mass PCR testing is promoted worldwide, a high testing rate may not avert the COVID-19 burden. In fact, the mortality rate of COVID-19 in Japan was 432 (3.4 per million) by May 1, 2020, lower than that in other countries (1). Determining which patients should be tested for COVID-19 is a difficult question during the early phase of the epidemic due to the limited number of tests available.

The current study began on March 9 when the national insurance plan began covering PCR in Japan to evaluate the SARS-CoV-2 positive ratio among mildly ill

patients in Tokyo, Japan, their characteristics, the MHLW criteria, and to identify better criteria.

Patient information and PCR test results were collected via a retrospective chart review of 277 patients who underwent SARS-CoV-2 PCR testing at the National Center for Global Health and Medicine in Tokyo from March 9–29, 2020.

Eligible patients for the outpatient screening center were those who met one or more of the following criteria: [1] Patients who have fever or symptoms (e.g. respiratory, fatigue, headache, myalgia); [2] Patients who had exposure to COVID-19 patient; [3] Patients who did not meet 1) or 2) but referred by another physician due to possible exposure to COVID-19 patient or travel history. Patients were Shinjuku-ku residents or had been referred from a clinic within/outside the city. Patients who were non-ambulatory upon presentation were ineligible for outpatient screening and were referred to the infectious disease clinic for further evaluation.

The questionnaire included items regarding underlying disease, regular medication, history of exposure to COVID-19, history of overseas travel within one month, symptoms, date of symptom onset, and vital signs on that day. The study was approved by the ethics committee from the appropriate institution (approval number: 3534) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived given the retrospective design.

Nasopharyngeal swabs were obtained; real-time reverse transcription PCR for SARS-CoV-2 (rRT-PCR) was conducted as recommended (4). Univariate analyses were performed using two-tailed Fisher's exact tests for categorical variables, and Mann-Whitney U tests for continuous variables with an α level $p < .05$ were considered significant. Pre-screening sensitivity and specificity were examined. Statistical analyses were performed using Microsoft Excel 2013 and IBM SPSS version 25.0.

In total, 277 patients underwent SARS-CoV-2 PCR testing; 25 (9.0%) were PCR positive (Table 1). Age, travel history, residential area, and underlying disease did not differ between PCR-positive and negative groups. The parameters observed significantly more frequently among the PCR-positive group were being male, COVID-19 exposure, cough, sputum, and myalgia/joint pain. Additionally, 250 (90.2%) patients met the MHLW criteria. The parameters observed significantly more frequently among the MHLW criteria-positive group were sore throat, cough, sputum, fatigue and headache.

The MHLW criteria sensitivity and specificity in patients were 100.0% and 10.7%, respectively (Table 2). We established modified criteria excluding nonspecific symptoms (i.e., fatigue, dyspnea) and included history (i.e., exposure to COVID-19 or overseas travel) (Table 2). When history was required, sensitivity decreased, but specificity increased. When the criteria excluded nonspecific symptoms, sensitivity slightly decreased, and specificity increased to 25%. Specificity was highest when the fever was $\geq 37.5^{\circ}\text{C}$ for ≥ 4 days, and exposure/travel history, including age and underlying comorbidities, were considered.

We assessed COVID-19's positive ratio, COVID-19 positive patient characteristics, and validity of criteria based on symptoms and exposure/travel history

among patients from Tokyo during the early epidemic phase. New COVID-19 cases in Japan in March 2020 were likely to reflect the early phase of community-acquired infections following outbreaks related to cruise ships or returning travelers.

By April 1, 2020, the total PCR positivity rate in Japan was 6.6% (2,107 positive results from 32,002 tests) (5). The current study indicates a slightly higher positive rate than previously reported because it was conducted in a densely populated urban area and included high-risk patients referred from airport quarantine and public health centers. The higher positive rate among men is consistent with previous reports (6, 7). The disease's exact prevalence, including asymptomatic cases, is unknown and further clarification via serum antibody testing is warranted (8).

The frequency of the occurrence of each COVID-19 symptom was similar to that of previous reports (9); however, the rate of dyspnea observed in the current study was lower, possibly due to the inclusion of only mild cases.

The sensitivity of the MHLW criteria was 100%, indicating their suitability for use in COVID-19 pre-screening. However, the positive predictive value was too low (10%: 25/250) to identify the true number of positive cases effectively. Specificity increased when a prolonged fever was included, nonspecific symptoms were excluded, or exposure and travel history were considered; however, sensitivity decreased. Therefore, this modification was unsuitable for early diagnosis.

The MHLW criteria were changed on May 8, 2020, and "prolonged fever for ≥ 4 days" was removed (10). The reason for this was perhaps that the number of COVID-19 cases increased in April and PCR testing capacity increased, creating a shift from the early to mid-epidemic phases. The new criteria require further evaluation.

The study has several limitations. Selection bias occurred because the study included only mildly ill and ambulant patients, and because of restricted access to the PCR test center. There are no clear-cut eligibility criteria for this study. Caution must be exercised in the interpretation of this study results, as patients who visited the outpatient screening center and underwent SARS-CoV-2 PCR testing were used as the denominator to calculate sensitivity and specificity. The higher MHLW criteria sensitivity may have resulted from the fact that patients who met the MHLW criteria were often referred for screening. However, patients who did not meet MHLW criteria were also included in this study.

Furthermore, given that most patients visited and were tested only once, false negatives resulting from premature testing and PCR sensitivity are possible. Moreover, the questionnaire excluded characteristic COVID-19 symptoms like dysosmia or dysgeusia, which were identified later. Symptoms and history were based on patients' self-reports and were possibly imprecise.

In conclusion, the COVID-19 positive ratio among patients with mild symptoms in metropolitan Tokyo during the early phase of community-acquired infection was approximately 9%. The original MHLW criteria, based on symptoms and past history, were highly sensitive, which could support COVID-19 pre-screening in the early phase of the epidemic.

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Table 1. Comparison of the characteristics of SARS-CoV-2 PCR positive and negative patients

	PCR Positive (n = 25)	PCR Negative (n = 252)	P-value
Sex/Age			
Sex (male)	22 (88)	131 (52)	.001
Median age, years (IQR)	44.1 (33.2-53.3)	38.9 (29.5-52.3)	
Exposure/travel history			
Overseas travel History	5 (20)	35 (13.9)	.379
Exposure to COVID-19	13 (52)	18 (7.1)	<0.001
Travel or exposure history	18 (72)	50 (19.8)	<0.001
Referral Patient	10 (40)	121 (48)	.531
Resident district			
Shinjuku-ku	14 (56)	134 (53.2)	.836
Other ward Tokyo prefecture	11 (44)	105 (41.7)	.835
Other prefecture	0	13 (5.2)	.615
Underlying disease¹⁾			

Any underlying disease	4 (16)	58 (23)	.615
Diabetes	2 (8)	8 (3.2)	.225
COPD	0	4 (1.6)	1
Asthma	1 (4)	23 (9.1)	.708
Other pulmonary Disease	0	5 (2)	1
Cardiac disease	1 (4)	4 (1.6)	.379
Renal disease	0	7 (2.8)	1
Solid cancer	0	9 (3.6)	1
Hematologic cancer	0	1 (0.4)	1
Autoimmune disease	0	9 (3.6)	1

Travel history

Asia	2 (8)	16 (6.3)	1
Oceania	0	2 (0.8)	1
North America	1 (4)	10 (4)	1
South America	1 (4)	1 (0.4)	.173
Europe	2 (8)	13 (5.2)	.633

Symptoms

Fever (≥ 37.5 °C)	23 (92)	188 (74.6)	.052
Duration of fever, days (median, IQR)	4 (2.5-6)	4 (0-6)	
Nasal discharge	13 (52)	100 (39.7)	.287

Sore throat	10 (40)	113 (44.8)	.679
Cough	22 (88)	123 (48.8)	<0.001
Sputum	16 (64)	79 (31.3)	.002
Dyspnea	2 (8)	49 (19.4)	.276
Fatigue	15 (60)	137 (54.4)	.676
Headache	11 (44)	96 (38.1)	.668
Myalgia/Joint pain	14 (56)	72 (28.6)	0.011
Diarrhea	5 (20)	48 (19)	1
Vomiting	3 (12)	41 (16.3)	.777

MLHW criteria²⁾

(i) Prolonged symptoms/fever ≥ 4 days	23 (92)	187 (74.2)	.391
(ii) Fatigue or dyspnea	15 (60)	154 (61.1)	.509
(iii) Old age or underlying disease and symptoms of a cold or fever ($\geq 37.5^{\circ}\text{C}$) persisting for ≥ 2 days	6 (24)	64 (25.4)	1
Any of (i), (ii), or (iii)	25 (100)	225 (89.3)	.145

Data are presented as n (%) unless indicated otherwise. Each of the percentages displayed represents the “valid percentage,” which indicates the percentage excluding the missing data from the denominator.

¹⁾ Only underlying diseases listed in MHLW criteria: any cardiac disease instead of heart failure, any renal disease instead of end-stage renal failure were included;

respiratory diseases included bronchial asthma, COPD, interstitial pneumonia, and nontuberculous mycobacteriosis; instead of immunosuppressive or anticancer therapy, solid or hematologic cancer and autoimmune disease were included.

²⁾MHLW criteria as follows: (i) prolonged symptoms of a cold or fever ($>37.5\text{ }^{\circ}\text{C}$) for ≥ 4 days; (ii) fatigue or dyspnea; (iii) old age, underlying disease (e.g., diabetes, heart failure, respiratory disease [e.g. chronic obstructive pulmonary disease: COPD]), or end-stage renal failure or immunosuppressive or anticancer therapy and symptoms of a cold or fever ($\geq 37.5^{\circ}\text{C}$) persisting for ≥ 2 days(3).

In this study, cold symptoms were defined as nasal discharge, sore throat, cough, or sputum. Old age was defined as ≥ 65 years, and underlying diseases were defined as above. Some cases were counted multiple times (e.g. both i & iii).

Abbreviations.

COPD = chronic obstructive pulmonary disease, IQR = interquartile range,

MHLW = Ministry of Health, Labour and Welfare, PCR = polymerase chain reaction.

Table 2. Evaluation of the validity of the MLHW criteria ¹⁾ and exploration of improved criteria, n = 277

Criterion number	Fever ²⁾ for ≥ 4 days	Any cold symptom (nasal discharge, sore throat, cough, sputum) for ≥ 4 days	Fatigue and dyspnea	Old age, underlying disease/condition ¹⁾ and symptoms of a cold or fever ²⁾ for ≥ 2 days	Exposure or travel history	Meet the criteria	PCR (+)	PCR (-)	Total	Sensitivity (%)	Specificity (%)
1	○	○	○	○		YES	25	225	250	100	10.7
						NO	0	27	27	(86.3-100)	(7.2-15.2)
2	●	○	○	○		YES	15	129	144	60	48.8
						NO	10	123	133	(38.7-78.9)	(42.5-55.2)
3	○	○		○		YES	23	196	219	92	24
						NO	2	56	58	(74-99)	(17.1-27.9)
4	●	○		○		YES	15	129	144	60	48.8
						NO	10	123	133	(38.7-78.9)	(42.5-55.2)
5	○	○	○	○	●	YES	18	41	59	72	83.7
						NO	7	211	218	(50.6-87.9)	(78.6-88.1)
6	○	○		○	●	YES	16	37	53	64	85.3
						NO	9	215	224	(42.5-82)	(80.3-89.5)
7	●	○	○	○	●	YES	9	24	33	36	90.5
						NO	16	228	244	(18-57.5)	(86.2-93.8)

○: any one of the conditions required, ●: the condition required

- 1) MHLW criteria: (i) prolonged symptoms of a cold (nasal discharge, sore throat, cough, sputum) or fever (≥ 37.5 °C) for ≥ 4 days; (ii) fatigue or dyspnea; (iii) old age, underlying disease (e.g., diabetes, heart failure, respiratory disease [e.g. chronic obstructive pulmonary disease: COPD]), or end-stage renal failure or immunosuppressive or anticancer therapy and symptoms of a cold or fever (>37.5 °C) persisting for ≥ 2 days.
- 2) Fever was defined as ≥ 37.5 °C

Abbreviation.

MHLW = Ministry of Health, Labour and Welfare

Table 3. Comparison of the characteristics of MHLW criteria¹⁾ positive and negative patients

	MHLW Positive (n = 250)	MHLW Negative (n = 27)	P value
Sex/Age			
Sex (male)	139 (55.6)	14 (51.9)	.839
Median age, years (IQR)	39.5 (29.7-53.3)	35.6 (31.5-49.4)	.584
Exposure/travel history			
Overseas travel History	35 (14)	5 (18.5)	.563
Exposure to COVID-19	26 (10.4)	5 (18.5)	.202
Travel or exposure history	59 (23.6)	9 (33.3)	.345
Referral Patient	120 (48)	11 (40.7)	.546
Resident district			
Shinjuku-ku	136 (54.4)	12 (44.4)	.417
Other ward Tokyo prefecture	102 (40.8)	14 (51.9)	.307
Other prefecture	12 (4.8)	1 (3.7)	1
Underlying disease²⁾			

Any underlying disease	60 (24)	4 (14.8)	.344
Diabetes	8 (3.2)	2 (7.4)	.253
COPD	4 (1.6)	0	.145
Asthma	24 (9.6)	0	1
Other pulmonary Disease	5 (2)	0	1
Cardiac disease	5 (2)	0	1
Renal disease	7 (2.8)	0	1
Solid cancer	7 (2.8)	0	1
Hematologic cancer	1 (0.4)	0	1
Autoimmune disease	8 (3.2)	1 (3.7)	1

Travel history

Asia	15 (6)	3 (11.1)	.399
Oceania	2 (0.8)	0	1
North America	11 (4.4)	0	.563
South America	2 (0.8)	0	1
Europe	13 (5.2)	2 (7.4)	.647

Symptoms

Fever (≥ 37.5 °C)	194 (77.6)	17 (63)	.100
Nasal discharge	104 (41.6)	9 (33.3)	.537
Sore throat	119 (47.6)	4 (14.8)	<0.001
Cough	140 (56)	5 (18.5)	<0.001

Sputum	93 (37.2)	2 (7.4)	.001
Dyspnea	51 (20.4)	0	.007
Fatigue	152 (60.8)	0	<0.001
Headache	105 (42)	2 (7.4)	<0.001
Diarrhea	52 (20.8)	1 (3.7)	.037
Vomiting	42 (16.8)	2 (7.4)	.274

Data are presented as n (%) unless indicated otherwise. Each of the percentages displayed represents the “valid percentage,” which indicates the percentage excluding the missing data from the denominator.

¹⁾ MHLW criteria as follows: (i) prolonged symptoms of a cold or fever ($>37.5^{\circ}\text{C}$) for ≥ 4 days; (ii) fatigue or dyspnea; (iii) old age, underlying disease (e.g., diabetes, heart failure, respiratory disease [e.g. chronic obstructive pulmonary disease: COPD]), or end-stage renal failure or immunosuppressive or anticancer therapy and symptoms of a cold or fever ($\geq 37.5^{\circ}\text{C}$) persisting for ≥ 2 days(3).

In this study, cold symptoms were defined as nasal discharge, sore throat, cough, or sputum. Old age was defined as ≥ 65 years, and underlying diseases were defined as above. Some cases were counted multiple times (e.g. both i & iii).

Abbreviations. ¹⁾ Only underlying diseases listed in MHLW criteria: any cardiac disease instead of heart failure, any renal disease instead of end-stage renal failure were included; respiratory diseases included bronchial asthma, COPD, interstitial pneumonia, and nontuberculous mycobacteriosis; instead of immunosuppressive or anticancer therapy, solid or hematologic cancer and autoimmune disease were included.

COPD = chronic obstructive pulmonary disease, IQR = interquartile range,

MHLW = Ministry of Health, Labour and Welfare, PCR = polymerase chain
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