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Characteristics of hospitalized COVID-19 patients with other respiratory pathogens identified by rapid diagnostic test

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ABSTRACT

Rapid diagnostic tests (RDTs) significantly impact disease treatment strategy. In Japan, information on the use of RDTs for patients with COVID-19 is limited. Here, we aimed to investigate the RDT implementation rate, pathogen detection rate, and clinical characteristics of patients positive for other pathogens by using COVIREGI-JP, a national registry of hospitalized patients with COVID-19.

A total of 42,309 COVID-19 patients were included. For immunochromatographic testing, influenza was the most common ($n = 2881$ [6.8%]), followed by *Mycoplasma pneumoniae* ($n = 2129$ [5%]) and group A streptococcus (GAS) ($n = 372$ [0.9%]). Urine antigen testing was performed for 5524 (13.1%) patients for *S. pneumoniae* and for 5326 patients (12.6%) for *L. pneumophila*.

The completion rate of *M. pneumoniae* loop-mediated isothermal amplification (LAMP) testing was low ($n = 97$ [0.2%]). FilmArray RP was performed in 372 (0.9%) patients; 1.2% (36/2881) of patients were positive for influenza, 0.9% (2/223) for the respiratory syncytial virus (RSV), 9.6% (205/2129) for *M. pneumoniae*, and 7.3% (27/372) for GAS. The positivity rate for urine antigen testing was 3.3% (183/5524) for *S. pneumoniae* and 0.2% (13/5326) for *L. pneumophila*. The positivity rate for LAMP test was 5.2% (5/97) for *M. pneumoniae*. Five of 372 patients (1.3%) had positive FilmArray RP, with human enterovirus being the most frequently detected (1.3%, 5/372).

The characteristics of patients with and without RDTs submission and positive and negative results differed for each pathogen. RDTs remain an important diagnostic tool in patients with COVID-19 in whom coinfection with other pathogens needs to be tested based on clinical evaluation.

Although coinfections with other pathogens are rare in patients with coronavirus disease 2019 (COVID-19), there is evidence of a possible association of coinfection with severe COVID-19 [1]. RDTs are considered important in determining treatment strategies in the early stages of the disease. In Japan, information is limited on the use of RDTs in patients with COVID-19 [2]. We aimed to investigate RDT implementation rates, pathogen detection rates, and clinical characteristics of positive

patients with other pathogens using COVIREGI-JP [3], a national registry of hospitalized patients with COVID-19.

Data from patients hospitalized on or before June 30, 2021, were used for the analysis. The results of RDTs, including the rapid immunochromatographic test, loop-mediated isothermal amplification (LAMP), FilmArray Respiratory Panel (FilmArrayRP, BioFire Diagnostics), or the urine antigen test (for *Streptococcus pneumoniae* and

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Legionella pneumophila) conducted within 72 h of admission were evaluated. Each pathogen was counted separately for positive results of multiple pathogens from a single patient. The epidemic waves were defined as follows: first wave (Wave 1): 01/01/2020–05/31/2020, second wave (Wave 2): 06/01/2020–10/31/2020, third wave (Wave 3): 11/01/2020–03/31/2021, and fourth wave (Wave 4): 04/01/2021–06/30/2021. Severity on admission was defined as previously reported [4]. Nominal variables were compared using Fisher's exact or Pearson's chi-square tests. Continuous variables were compared using the Mann–Whitney *U* test. All *p* values were two-tailed, and *p* < 0.05 was considered statistically significant. To compare the characteristics of patients with and without rapid diagnostic test submission, Dunnett's method was used for pairwise comparisons between patients with and without rapid diagnostic test submission (threshold of significant difference was 0.01). All analyses were performed using SPSS version 27 (IBM Corporation, Armonk, NY, USA). This study was approved by the National Center for Global Health and Medicine ethics review committee (NCGM-G-003494-0).

A total of 42,309 COVID-19 patients were included. The number of males was 24,908 (57.0%), with a median age of 59 years (interquartile range [IQR] 41–75). Test for influenza by immunochromatography method was performed most commonly (*n* = 2881 [6.8%]), followed by tests for *Mycoplasma pneumoniae* (*n* = 2129 [5%]) and *Streptococcus pyogenes* [Group A Streptococcus: (GAS)] (*n* = 372 [0.9%]). RSV, adenovirus, and human metapneumovirus (HMPV) test implementation rates were all less than 0.5% (Table 1). Urine antigen testing was performed for *S. pneumoniae* in 5524 (13.1%) patients and for *L. pneumophila* in 5326 patients (12.6%). The completion rate of LAMP testing was low (e.g. *M. pneumoniae*: *n* = 97 [0.2%]). FilmArray RP was performed in 372 (0.9%) patients. Positivity rates of the

immunochromatographic test were 1.2% (36/2881) for influenza, 0.9% (2/223) for RSV, 9.6% (205/2129) for *M. pneumoniae*, and 7.3% (27/372) for GAS. The positivity rate for the urine antigen test was 3.3% (183/5524) for *S. pneumoniae* and 0.2% (13/5326) for *L. pneumophila*. Positivity rate for the LAMP test was 5.2% (5/97) for *M. pneumoniae*. *L. pneumophila* was negative in all 36 patients. FilmArray RP was positive for five of 372 patients (1.3%) and human enterovirus was the most frequently detected (1.3%, 5/372).

We then compared the characteristics of patients with and without RDT presentation (Table 2). Patients with RDT test submission were generally older than patients without, except the GAS and *M. pneumoniae* groups. The use of invasive mechanical ventilation ECMO, or extracorporeal membranous oxygenation on admission was significantly higher in the patient with RDT test submission than patients without.

Fever and fatigue were more frequent symptoms on admission in patients with RDT test submission than patients without.

Cough and shortness of breath were more common in the patients with RDT test groups, except GAS, than patients without, whereas sore throat was more common in the patients with GAS test submission. Prevalence of comorbidity was higher in patients with RDT test submission than patients without, except those in the GAS test group.

Subsequently, the characteristics of patients with positive and negative results for each test were compared (Table 3). Although there was no significant age difference between the influenza-positive and negative groups, the positive group had more symptoms of dysgeusia (27.8% [10/36] versus 11.5% [326/2840], *p* = 0.006) and dysosmia (22.2% [8/36] versus 9.4% [266/2840], *p* = 0.017) than the negative group. Patients with positive influenza test results had a higher rate of obesity than patients with negative test results (22.2% [8/36] versus 6.8% [194/2840], *p* = 0.003). There were no significant differences between positive and negative groups in the test group GAS.

For *M. pneumoniae*, the positive group was significantly younger than the negative group (median age [IQR]: 35 [26–55] vs 57 [43–72], *p* < 0.001), and comorbidity tended to be lower in the positive group than in the negative group. Although the *M. pneumoniae*-positive group had significantly more symptoms on admission than the negative group, including dysgeusia (26.7% [56/210] vs. 14.5% [290/2000], *p* < 0.001) and dysosmia (22.9% [48/210] vs. 12% [241/2000], *p* < 0.001), fever was lower in the positive group than in the negative group (57.6% [121/210] vs. 65.7% [1314/2000], *p* = 0.022). The number of patients who were severely ill on admission was lower in the *M. pneumoniae*-positive group than in the negative group (17.6% [37/210] vs. 37.5% [750/2000], *p* < 0.001). The prevalence of pneumonia identified by radiological testing was also lower in the positive group than in the negative group (75.6% [136/210] vs 87.3% [1621/2000], *p* < 0.001).

For *S. pneumoniae*, the positive group was older (median age [IQR]: 70 [43–83] vs. 59 [45–73], *p* < 0.001) and had a lower proportion of males than did the negative group (47.3% [86/183] vs 62.7% [3344/5341], *p* < 0.001). Positive patients were more likely to have the symptom of wet cough on admission than negative patients (49.5% [46/183] vs 33.2% [913/5341], *p* = 0.002). The prevalence of patients without comorbidity was lower in patients with positive *S. pneumoniae* test results than in patients with negative results (6.0% [11/183] vs 10.7% [569/5341], *p* = 0.049).

In *L. pneumophila*, all patients with positive test results had pneumonia on computed tomography. The prevalence of leukemia and hypertension tended to be higher in the group with positive *L. pneumophila* tests than in the negative group.

We also compared test completion rates and positivity rates between pandemic waves (Supplementary Table 1). Rapid tests for influenza, GAS, *M. pneumoniae*, and urine antigens (*S. pneumoniae* and *L. pneumophila*) were all performed at the highest rates in Wave 1. Positivity for *M. pneumoniae* and *S. pneumoniae* was the highest in Wave 2 and lowest in Wave 4. No apparent difference was observed for *L. pneumophila* between waves.

Table 1

Results of respiratory rapid diagnostic test on admission in hospitalized patients with COVID-19 (*n* = 42,309).

	Positive rate ^A	Test implementation rate ^B
Immunochromatographic test		
Influenza ^C	36 (1.2)	2881 (6.8)
Influenza A	23 (0.8)	
Influenza B	9 (0.3)	
Influenza type unknown	4 (0.1)	
Respiratory syncytial virus	2 (0.9)	223 (0.5)
Adenovirus	0 (0)	206 (0.5)
Human Metapneumovirus	0 (0)	187 (0.4)
<i>Mycoplasma pneumoniae</i>	205 (9.6)	2129 (5.0)
<i>Streptococcus pyogenes</i>	27 (7.3)	372 (0.9)
Urine antigen test		
<i>Streptococcus pneumoniae</i>	183 (3.3)	5524 (13.1)
<i>Legionella pneumophila</i>	13 (0.2)	5326 (12.6)
LAMP test		
<i>Legionella pneumophila</i>	0 (0)	36 (0.09)
<i>Mycoplasma pneumoniae</i>	5 (5.2)	97 (0.2)
<i>Bordetella pertussis</i>	0 (0)	9 (0.02)
FilmArray respiratory panel	5 (1.3) ^D	372 (0.9)
Human enterovirus	5 (1.3)	
Human rhinovirus	4 (1.1)	
Adenovirus	2 (0.5)	
Coronavirus OC43	2 (0.5)	
Human metapneumovirus	1 (0.3)	

For positive results of multiple pathogens from a single patient, each pathogen was counted separately.

A. Number of positive patients (percentage of number of positive results/number of tests performed).

B. Number of tests performed (percentage of number of test performed/total number of patients).

C. Positive for any type of influenza. Five influenza tests were inconclusive results, and thus, counted negative.

D. Positive for any pathogen identified by FilmArray Respiratory Panel. Twenty-five FilmArray tests were inconclusive results and thus, counted negative.

Abbreviations: LAMP, loop-mediated isothermal amplification; COVID-19, coronavirus disease 2019.

Table 2
Comparison of characteristics of patients with and without rapid diagnostic test submission.

	Influenza			<i>Streptococcus pyogenes</i>			<i>Mycoplasma pneumoniae</i> ^C			<i>Streptococcus pneumoniae</i>			<i>Legionella pneumophila</i> ^C		
	Submitted	Not submitted	p value [#]	Submitted	Not submitted	p value	Submitted	Not submitted	p value [#]	Submitted	Not submitted	p value [#]	Submitted	Not submitted	p value [#]
Age [median, IQR]	n = 2881 62 [46–76]	n = 39,428 58 [40–75]	<0.001	n = 372 53 [32–68]	n = 41,937 59 [41–75]	<0.001	n = 2210 56 [40–71]	n = 40,099 59 [41–75]	<0.001	n = 5524 60 [45–74]	n = 36,785 58 [40–75]	<0.001	n = 5343 60 [45–74]	n = 36,966 58 [40–75]	<0.001
Male sex^A	1841 (63.9)	22,257 (56.5)	<0.001	221 (59.4)	23,877 (57.0)	0.371	1375 (62.2)	22,723 (56.7)	<0.001	3430 (62.1)	20,668 (56.2)	<0.001	3369 (63.1)	20,729 (56.1)	<0.001
Onset to admission time [median, IQR] day	5 [2–8]	4 [2–7]	0.034	4 [2–7]	4 [2–7]	0.934	5 [3–8]	4 [2–7]	<0.001	5 [3–8]	4 [2–7]	<0.001	5 [3–8]	4 [2–7]	<0.001
Pneumonia on admission															
Chest radiograph ^B	1649 (68.1)	14,937 (54.2)	<0.001	146 (52.9)	16,440 (55.3)	0.430	1191 (66.3)	15,395 (54.6)	<0.001	3025 (64.4)	13,561 (53.6)	<0.001	2987 (64.7)	13,599 (53.6)	<0.001
Chest CT ^B	2148 (85.0)	20,777 (75.5)	<0.001	226 (71.5)	22,699 (76.4)	0.044	1676 (82.3)	21,249 (75.9)	<0.001	3892 (82.7)	19,033 (75.1)	<0.001	3786 (82.8)	19,139 (75.2)	<0.001
Pneumonia either by radiography or CT	2312 (88.2)	24,089 (84.4)	<0.001	249 (77.8)	26,152 (84.8)	0.001	1757 (86.3)	24,644 (84.6)	0.046	4277 (85.7)	22,124 (84.5)	0.034	4162 (85.7)	22,239 (84.6)	0.038
Severity on admission															
Severe	1286 (44.6)	11,988 (30.4)	<0.001	122 (32.8)	13,152 (31.4)	0.576	787 (35.6)	12,487 (31.1)	<0.001	2225 (40.3)	11,049 (30.0)	<0.001	2198 (41.1)	11,076 (30.0)	<0.001
Oxygen support on admission															
IMV or ECMO	356 (12.4)	1767 (4.5)	<0.001	35 (9.4)	2088 (5.0)	<0.001	175 (7.9)	1948 (4.9)	<0.001	594 (10.8)	1529 (4.2)	<0.001	595 (11.1)	1528 (4.1)	<0.001
NPPV	64 (2.2)	476 (1.2)	<0.001	4 (1.1)	536 (1.3)	>0.999	23 (1.0)	517 (1.3)	0.379	92 (1.7)	448 (1.2)	0.007	90 (1.7)	450 (1.2)	0.005
HFNC	201 (7.0)	1599 (4.1)	<0.001	12 (3.2)	1788 (4.3)	0.368	114 (5.2)	1686 (4.2)	0.032	329 (6.0)	1471 (4.0)	<0.001	322 (6.0)	1478 (4.0)	<0.001
Any oxygen	1429 (49.6)	14,368 (36.4)	<0.001	130 (34.9)	15,667 (37.4)	0.360	859 (38.9)	14,938 (37.3)	0.130	2530 (45.8)	13,267 (36.1)	<0.001	2498 (46.8)	13,299 (36.0)	<0.001
No oxygen	1434 (49.8)	24,907 (63.2)	<0.001	239 (64.2)	26,102 (62.2)	0.452	1344 (60.8)	24,997 (62.3)	0.155	2962 (53.6)	23,379 (63.6)	<0.001	2812 (52.6)	23,529 (63.7)	<0.001
Symptom of admission															
Fever	1926 (66.9)	19,118 (48.5)	<0.001	244 (65.6)	20,800 (49.6)	<0.001	1435 (65.0)	19,609 (48.9)	<0.001	3289 (59.6)	17,755 (48.3)	<0.001	3188 (59.7)	17,856 (48.3)	<0.001
Cough	1637 (56.9)	19,256 (48.9)	<0.001	192 (51.8)	20,701 (49.4)	0.376	1256 (56.9)	19,637 (49.0)	<0.001	2844 (51.5)	18,049 (49.1)	0.001	2743 (51.3)	18,150 (49.1)	0.003
Wet cough	537 (32.9)	6086 (31.7)	0.305	59 (31.4)	6564 (31.8)	0.934	370 (29.6)	6253 (31.9)	0.091	959 (33.7)	5664 (31.4)	0.014	917 (33.5)	5706 (31.5)	0.038
Bloody cough	31 (1.9)	271 (1.4)	0.125	4 (2.1)	298 (1.4)	0.356	25 (2.0)	277 (1.4)	0.106	45 (1.6)	257 (1.4)	0.503	42 (1.5)	260 (1.4)	0.675
Sore throat	503 (17.5)	6389 (16.2)	0.079	97 (26.1)	6795 (16.2)	<0.001	370 (16.7)	6522 (16.3)	0.556	886 (16.0)	6006 (16.3)	0.597	844 (15.8)	6048 (16.4)	0.294
Runny nose	291 (10.1)	3583 (9.1)	0.070	50 (13.4)	3824 (9.1)	0.005	186 (8.4)	3688 (9.2)	0.226	474 (8.6)	3400 (9.2)	0.116	434 (8.1)	3440 (9.3)	0.005
Wheeze	68 (2.4)	622 (1.6)	0.002	7 (1.9)	683 (1.6)	0.677	37 (1.7)	653 (1.6)	0.873	102 (1.8)	588 (1.6)	0.170	99 (1.9)	591 (1.6)	0.164
Short breath	911 (31.7)	8443 (21.4)	<0.001	101 (27.2)	9253 (22.1)	0.019	591 (26.8)	8763 (21.9)	<0.001	1620 (29.3)	7734 (21.0)	<0.001	1551 (29.1)	7803 (21.1)	<0.001
Chest pain	95 (3.3)	1084 (2.8)	0.086	10 (2.7)	1169 (2.8)	>0.999	68 (3.1)	1111 (2.8)	0.390	166 (3.0)	1013 (2.8)	0.293	147 (2.8)	1032 (2.8)	0.890
Myalgia	322 (11.2)	3403 (8.6)	<0.001	39 (10.5)	3686 (8.8)	0.232	198 (9.0)	3527 (8.8)	0.791	529 (9.6)	3196 (8.7)	0.032	478 (8.9)	3247 (8.8)	0.700
Headache	467 (16.2)	5865 (14.9)	0.054	73 (19.7)	6259 (14.9)	0.011	370 (16.7)	5962 (14.9)	0.018	864 (15.6)	5468 (14.9)	0.134	801 (15.0)	5531 (15.0)	0.969
Confusion	67 (2.3)	529 (1.3)	<0.001	7 (1.9)	589 (1.4)	0.375	25 (1.1)	571 (1.4)	0.308	114 (2.1)	482 (1.3)	<0.001	110 (2.1)	486 (1.3)	<0.001
Fatigue	1304 (45.3)	13,728 (34.8)	<0.001	168 (45.2)	14,864 (35.5)	<0.001	986 (44.6)	14,046 (35.0)	<0.001	2344 (42.4)	12,688 (34.5)	<0.001	2248 (42.1)	12,784 (34.6)	<0.001
Abdominal pain	66 (2.3)	708 (1.8)	0.058	8 (2.2)	766 (1.8)	0.558	37 (1.7)	737 (1.8)	0.619	129 (2.3)	645 (1.8)	0.003	114 (2.1)	660 (1.8)	0.078
Vomit	128 (4.4)	1478 (3.8)	0.059	20 (5.4)	1586 (3.8)	0.131	69 (3.1)	1537 (3.8)	0.100	230 (4.2)	1376 (3.7)	0.130	218 (4.1)	1388 (3.8)	0.250
Diarrhea	293 (10.2)	3632 (9.2)	0.088	41 (11.1)	3884 (9.3)	0.241	224 (10.1)	3701 (9.2)	0.151	581 (10.5)	3344 (9.1)	0.001	563 (10.5)	3362 (9.1)	0.001
Dysgeusia	337 (11.7)	5993 (15.2)	<0.001	55 (14.8)	6275 (15.0)	0.993	346 (15.7)	5984 (14.9)	0.343	777 (14.1)	5553 (15.1)	0.046	726 (13.6)	5604 (15.2)	0.003
Dysosmia	275 (9.5)	5348 (13.6)	<0.001	49 (13.2)	5574 (13.3)	0.993	289 (13.1)	5334 (13.3)	0.770	669 (12.1)	4954 (13.5)	0.006	628 (11.8)	4995 (13.5)	<0.001

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Table 2 (continued)

Comorbidity															
No comorbidity	382 (13.3)	8062 (20.4)	<0.001	100 (26.9)	8344 (19.9)	0.001	196 (8.9)	8248 (20.6)	<0.001	580 (10.5)	7864 (21.4)	<0.001	528 (9.9)	7916 (21.4)	<0.001
Myocardial infarction	53 (1.8)	762 (1.9)	0.772	4 (1.1)	811 (1.9)	0.339	26 (1.2)	789 (2.0)	0.009	127 (2.3)	688 (1.9)	0.034	123 (2.3)	692 (1.9)	0.036
Congestive heart failure	83 (2.9)	1287 (3.3)	0.276	6 (1.6)	1364 (3.3)	0.077	41 (1.9)	1329 (3.3)	<0.001	177 (3.2)	1193 (3.2)	0.899	170 (3.2)	1200 (3.2)	0.833
Peripheral vascular disease	44 (1.5)	618 (1.6)	0.929	6 (1.6)	656 (1.6)	0.833	21 (1.0)	641 (1.6)	0.017	96 (1.7)	566 (1.5)	0.269	91 (1.7)	571 (1.5)	0.378
Cerebrovascular disease	211 (7.3)	2620 (6.6)	0.163	17 (4.6)	2814 (6.7)	0.123	120 (5.4)	2711 (6.8)	0.016	350 (6.3)	2481 (6.7)	0.273	343 (6.4)	2488 (6.7)	0.412
Paralysis	42 (1.5)	586 (1.5)	0.991	2 (0.5)	626 (1.5)	0.189	27 (1.2)	601 (1.5)	0.321	74 (1.3)	554 (1.5)	0.370	73 (1.4)	555 (1.5)	0.466
Dementia	224 (7.8)	3306 (8.4)	0.265	5 (1.3)	3525 (8.4)	<0.001	113 (5.1)	3417 (8.5)	<0.001	352 (6.4)	3178 (8.6)	<0.001	342 (6.4)	3188 (8.6)	<0.001
CLD excluding COPD	54 (1.9)	572 (1.5)	0.074	5 (1.3)	621 (1.5)	>0.999	20 (0.9)	606 (1.5)	0.022	93 (1.7)	533 (1.4)	0.187	91 (1.7)	535 (1.4)	0.144
COPD	104 (3.6)	949 (2.4)	<0.001	5 (1.3)	1048 (2.5)	0.181	55 (2.5)	998 (2.5)	0.992	184 (3.3)	869 (2.4)	<0.001	181 (3.4)	872 (2.4)	<0.001
Asthma	143 (5.0)	2063 (5.2)	0.570	14 (3.8)	2192 (5.2)	0.244	106 (4.8)	2100 (5.2)	0.402	282 (5.1)	1924 (5.2)	0.719	254 (4.8)	1952 (5.3)	0.108
Mild liver disease	59 (2.0)	850 (2.2)	0.784	9 (2.4)	900 (2.1)	0.717	46 (2.1)	863 (2.2)	0.872	116 (2.1)	793 (2.2)	0.838	113 (2.1)	796 (2.2)	0.915
Severe liver disease	11 (0.4)	129 (0.3)	0.612	2 (0.5)	138 (0.3)	0.349	5 (0.2)	135 (0.3)	0.565	17 (0.3)	123 (0.3)	0.888	16 (0.3)	124 (0.3)	0.787
Peptic ulcer	28 (1.0)	301 (0.8)	0.224	3 (0.8)	326 (0.8)	0.767	15 (0.7)	314 (0.8)	0.697	53 (1.0)	276 (0.8)	0.097	52 (1.0)	277 (0.7)	0.092
Mild DM	497 (17.3)	5811 (14.7)	<0.001	52 (14.0)	6256 (14.9)	0.656	304 (13.8)	6004 (15.0)	0.126	904 (16.4)	5404 (14.7)	0.001	887 (16.6)	5421 (14.7)	<0.001
Severe DM	78 (2.7)	886 (2.2)	0.117	3 (0.8)	961 (2.3)	0.054	30 (1.4)	934 (2.3)	0.003	120 (2.2)	844 (2.3)	0.592	117 (2.2)	847 (2.3)	0.691
Obesity	203 (7.0)	2288 (5.8)	0.007	19 (5.1)	2472 (5.9)	0.573	187 (8.5)	2304 (5.7)	<0.001	423 (7.7)	2068 (5.6)	<0.001	416 (7.8)	2075 (5.6)	<0.001
Severe renal dysfunction	48 (1.7)	608 (1.5)	0.591	0 (0.0)	656 (1.6)	0.005	10 (0.5)	646 (1.6)	<0.001	64 (1.2)	592 (1.6)	0.012	64 (1.2)	592 (1.6)	0.026
Hemodialysis	33 (1.1)	376 (1.0)	0.324	1 (0.3)	408 (1.0)	0.277	10 (0.5)	399 (1.0)	0.013	26 (0.5)	383 (1.0)	<0.001	26 (0.5)	383 (1.0)	<0.001
Solid tumor	111 (3.9)	1312 (3.3)	0.132	8 (2.2)	1415 (3.4)	0.246	62 (2.8)	1361 (3.4)	0.148	172 (3.1)	1251 (3.4)	0.280	170 (3.2)	1253 (3.4)	0.464
Leukemia	5 (0.2)	90 (0.2)	0.685	1 (0.3)	94 (0.2)	0.568	3 (0.1)	92 (0.2)	0.491	20 (0.4)	75 (0.2)	0.031	20 (0.4)	75 (0.2)	0.019
Lymphoma	15 (0.5)	168 (0.4)	0.460	1 (0.3)	182 (0.4)	>0.999	6 (0.3)	177 (0.4)	0.315	17 (0.3)	166 (0.5)	0.157	15 (0.3)	168 (0.5)	0.080
Metastatic solid tumor	32 (1.1)	321 (0.8)	0.106	2 (0.5)	351 (0.8)	0.774	11 (0.5)	342 (0.9)	0.098	35 (0.6)	318 (0.9)	0.085	35 (0.7)	318 (0.9)	0.150
Collagen disease	52 (1.8)	492 (1.2)	0.011	2 (0.5)	542 (1.3)	0.251	32 (1.4)	512 (1.3)	0.502	81 (1.5)	463 (1.3)	0.199	77 (1.4)	467 (1.3)	0.270
HIV infection	3 (0.1)	67 (0.2)	0.631	0 (0.0)	70 (0.2)	>0.999	2 (0.1)	68 (0.2)	0.587	4 (0.1)	66 (0.2)	0.075	4 (0.1)	66 (0.2)	0.102
Hypertension	971 (33.7)	12,015 (30.5)	<0.001	101 (27.2)	12,885 (30.7)	0.143	613 (27.7)	12,373 (30.9)	0.002	1776 (32.2)	11,210 (30.5)	0.012	1730 (32.4)	11,256 (30.4)	0.004
Dyslipidemia	447 (15.5)	5775 (14.6)	0.209	42 (11.3)	6180 (14.7)	0.069	266 (12.0)	5956 (14.9)	<0.001	853 (15.4)	5369 (14.6)	0.098	833 (15.6)	5389 (14.6)	0.051

Results are presented as number (%) unless otherwise specified. If more than one microbiological test was submitted per person, each test was considered separately. For positive results of multiple pathogens from a single patient, each pathogen was counted separately.

#p values were calculated for the comparison of characteristics of patients with and without rapid diagnostic test submission. Nominal variables were compared using Fisher's exact test. Continuous variables were compared using the Mann–Whitney *U* test. Dunnett's method was used for pairwise comparisons (threshold of significant difference was 0.01).

A. Eight patients were excluded because gender was unknown.

B. Radiograph was not obtained in 12,308 cases; CT scan was not obtained in 12,273 cases.

C. For *Mycoplasma pneumoniae* and *Legionella pneumophila*, Rapid kit test and LAMP test were combined for the analysis. If tests were duplicated (i.e. both Rapid kit test and LAMP tests were submitted), then, one test was counted.

Abbreviations. RDT, rapid diagnostic test; CT, computed tomography; ECMO, extracorporeal membranous oxygenation; IMV, invasive mechanical ventilation; NPPV, non-invasive positive pressure ventilation; HFNC, High-flow nasal cannula; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; IQR, interquartile range.

Table 3

Comparison of Patient characteristics of positive and negative rapid diagnostic test results.

	Influenza ^C			Streptococcus pyogenes			Mycoplasma pneumoniae ^D			Streptococcus pneumoniae			Legionella pneumophila ^D		
	Pos	Neg	p [#]	Pos	Neg	p	Pos	Neg	p	Pos	Neg	P	Pos	Neg	p
Age [median, IQR]	n = 36 67 [54.8–76.8]	n = 2840 62 [46–76]	0.111	n = 27 54 [30–67]	n = 345 53 [32–68]	0.957	n = 210 35 [26–55]	n = 2000 57 [43–72]	<0.001	n = 183 70 [43–83]	n = 5341 59 [45–73]	<0.001	n = 13 73 [58.5–78]	n = 5330 60 [45–74]	0.054
Male sex^A	24 (66.7)	1815 (63.9)	0.862	16 (59.3)	205 (59.4)	>0.99	118 (56.2)	1257 (62.9)	0.062	86 (47.3)	3344 (62.7)	<0.001	9 (69.2)	3360 (63.1)	0.778
Onset to admission time [median, IQR] day	4 [2–8]	5 [2–8]	0.749	4 [3–6]	4 [2–7]	0.957	4 [2.5–7]	5 [3–8]	0.151	3 [1–5]	5 [3–8]	<0.001	6.5 [3–8]	5 [3–8]	0.089
Pneumonia on admission															
Chest radiograph ^B	20 (69.0)	1626 (68.1)	>0.99	4 (40.0)	142 (53.4)	0.524	76 (56.3)	1115 (67.1)	0.014	85 (57.8)	2940 (64.6)	0.097	7 (63.6)	2980 (64.7)	>0.99
Chest CT ^B	25 (80.6)	2120 (85.1)	0.451	15 (62.5)	211 (72.3)	0.348	134 (66.7)	1542 (84.0)	<0.001	121 (76.6)	3771 (82.9)	0.054	13 (100)	3773 (82.8)	0.143
Pneumonia either by radiography or CT	27 (84.4)	2282 (88.3)	0.416	17 (77.3)	232 (77.9)	>0.99	136 (75.6)	1621 (87.3)	<0.001	134 (82.7)	4143 (85.8)	0.255	13 (100)	4149 (85.7)	0.237
Severely ill on admission	17 (47.2)	1266 (44.6)	0.866	4 (14.8)	118 (34.2)	0.053	37 (17.6)	750 (37.5)	<0.001	73 (39.9)	2152 (40.3)	0.939	7 (53.8)	2191 (41.1)	0.404
Oxygen support during admission															
IMV or ECMO	2 (5.6)	352 (12.4)	0.307	2 (7.4)	33 (9.6)	>0.99	6 (2.9)	169 (8.5)	0.003	15 (8.2)	579 (10.8)	0.330	3 (23.1)	592 (11.1)	0.169
NPPV	0 (0.0)	63 (2.2)	>0.99	1 (3.7)	3 (0.9)	0.261	1 (0.5)	22 (1.1)	0.718	1 (0.5)	91 (1.7)	0.373	1 (7.7)	89 (1.7)	0.198
HFNC	2 (5.6)	198 (7.0)	>0.99	2 (7.4)	10 (2.9)	0.214	5 (2.4)	109 (5.5)	0.069	5 (2.7)	324 (6.1)	0.078	2 (15.4)	320 (6.0)	0.183
Any oxygen	16 (44.4)	1410 (49.7)	0.616	7 (25.9)	123 (35.7)	0.403	43 (20.5)	816 (40.8)	<0.001	89 (48.6)	2441 (45.7)	0.451	5 (38.5)	2493 (46.8)	0.591
No oxygen	20 (55.6)	1412 (49.7)	0.507	20 (74.1)	219 (63.5)	0.304	167 (79.5)	1177 (58.9)	<0.001	94 (51.4)	2868 (53.7)	0.547	8 (61.5)	2804 (52.6)	0.588
Symptom of admission															
Fever	23 (63.9)	1899 (66.9)	0.723	17 (63.0)	227 (65.8)	0.834	121 (57.6)	1314 (65.7)	0.022	103 (56.3)	59.7 (3186)	0.359	11 (84.6)	3177 (59.6)	0.089
Cough	21 (58.3)	1614 (56.9)	>0.99	14 (51.9)	178 (51.7)	>0.99	120 (57.1)	1136 (56.8)	0.942	93 (50.8)	2751 (51.5)	0.881	9 (69.2)	2734 (51.3)	0.269
Wet cough	7 (33.3)	528 (32.8)	>0.99	5 (41.7)	54 (30.7)	0.522	39 (32.8)	331 (29.2)	0.460	46 (49.5)	913 (33.2)	0.002	5 (55.6)	912 (33.4)	0.172
Bloody cough	0 (0.0)	31 (1.9)	>0.99	1 (8.3)	3 (1.7)	0.232	0 (0.0)	25 (2.2)	0.160	1 (1.1)	44 (1.6)	>0.99	0 (0.0)	42 (1.5)	>0.99
Sore throat	5 (13.9)	498 (17.5)	0.825	9 (33.3)	88 (25.5)	0.369	38 (18.1)	332 (16.6)	0.561	29 (15.8)	857 (16.0)	>0.99	1 (7.7)	843 (15.8)	0.706
Runny nose	4 (11.1)	286 (10.1)	0.780	5 (18.5)	45 (13.0)	0.386	15 (7.2)	171 (8.6)	0.600	12 (6.6)	462 (8.7)	0.419	1 (7.7)	433 (8.1)	>0.99
Wheeze	0 (0.0)	67 (2.4)	>0.99	0 (0.0)	7 (2.0)	>0.99	5 (2.4)	32 (1.6)	0.392	6 (3.3)	96 (1.8)	0.151	0 (0.0)	99 (1.9)	>0.99
Short breath	12 (33.3)	897 (31.6)	0.857	4 (14.8)	97 (28.2)	0.178	46 (21.9)	545 (27.3)	0.101	42 (23.0)	1578 (29.6)	0.057	7 (53.8)	1544 (29.0)	0.064
Chest pain	2 (5.6)	93 (3.3)	0.335	0 (0.0)	10 (2.9)	>0.99	5 (2.4)	63 (3.2)	0.677	5 (2.7)	161 (3.0)	>0.99	1 (7.7)	146 (2.7)	0.304
Myalgia	4 (11.1)	318 (11.2)	>0.99	3 (11.1)	36 (10.5)	>0.99	13 (6.2)	185 (9.3)	0.162	19 (10.4)	510 (9.6)	0.701	0 (0.0)	478 (9.0)	0.622
Headache	4 (11.1)	461 (16.2)	0.501	5 (18.5)	68 (19.8)	>0.99	32 (15.2)	338 (16.9)	0.627	30 (16.4)	834 (15.6)	0.756	2 (15.4)	799 (15.0)	>0.99
Confusion	0 (0.0)	66 (2.3)	>0.99	0 (0.0)	7 (2.0)	>0.99	1 (0.5)	24 (1.2)	0.505	7 (3.8)	107 (2.0)	0.104	0 (0.0)	110 (2.1)	>0.99
Fatigue	16 (44.4)	1286 (45.3)	>0.99	11 (40.7)	157 (45.5)	0.691	90 (42.9)	896 (44.8)	0.610	72 (39.3)	2272 (42.5)	0.404	9 (69.2)	2239 (42.0)	0.053
Abdominal pain	0 (0.0)	66 (2.3)	>0.99	0 (0.0)	8 (2.3)	>0.99	3 (1.4)	34 (1.7)	>0.99	4 (2.2)	125 (2.3)	>0.99	0 (0.0)	114 (2.1)	>0.99
Vomit	0 (0.0)	128 (4.5)	0.406	1 (3.7)	19 (5.5)	>0.99	2 (1.0)	67 (3.4)	0.059	5 (2.7)	225 (4.2)	0.449	0 (0.0)	218 (4.1)	>0.99
Diarrhea	3 (8.3)	290 (10.2)	>0.99	3 (11.1)	38 (11.0)	>0.99	23 (11.0)	201 (10.1)	0.633	13 (7.1)	568 (10.6)	0.141	0 (0.0)	563 (10.6)	0.385
Dysgeusia	10 (27.8)	326 (11.5)	0.006	3 (11.1)	52 (15.1)	0.780	56 (26.7)	290 (14.5)	<0.001	20 (10.9)	757 (14.2)	0.235	2 (15.4)	724 (13.6)	0.694
Dysosmia	8 (22.2)	266 (9.4)	0.017	5 (18.5)	44 (12.8)	0.378	48 (22.9)	241 (12.0)	<0.001	23 (12.6)	646 (12.1)	0.818	0 (0.0)	628 (11.8)	0.386
Comorbidity															
No comorbidity	5 (13.9)	377 (13.3)	0.807	11 (40.7)	89 (25.8)	0.113	11 (5.2)	185 (9.3)	0.055	11 (6.0)	569 (10.7)	0.049	2 (15.4)	526 (9.9)	0.373
Myocardial infarction	0 (0.0)	53 (1.9)	>0.99	0 (0.0)	4 (1.2)	>0.99	0 (0.0)	26 (1.3)	0.167	6 (3.3)	121 (2.3)	0.316	0 (0.0)	123 (2.3)	>0.99
Congestive heart failure	1 (2.8)	82 (2.9)	>0.99	1 (3.7)	5 (1.4)	0.366	3 (1.4)	38 (1.9)	0.793	13 (7.1)	164 (3.1)	0.008	1 (7.7)	169 (3.2)	0.343
Peripheral vascular disease	1 (2.8)	43 (1.5)	0.428	0 (0.0)	6 (1.7)	>0.99	1 (0.5)	20 (1.0)	0.714	2 (1.1)	94 (1.8)	0.772	0 (0.0)	91 (1.7)	>0.99

(continued on next page)

Table 3 (continued)

	Influenza ^C			Streptococcus pyogenes			Mycoplasma pneumoniae ^D			Streptococcus pneumoniae			Legionella pneumophila ^D		
	Pos	Neg	p [#]	Pos	Neg	p	Pos	Neg	p	Pos	Neg	P	Pos	Neg	p
Cerebrovascular disease	3 (8.3)	207 (7.3)	0.744	1 (3.7)	16 (4.6)	>0.99	5 (2.4)	115 (5.8)	0.037	27 (14.8)	323 (6.0)	<0.001	1 (7.7)	342 (6.4)	0.578
Paralysis	0 (0.0)	42 (1.5)	>0.99	1 (3.7)	1 (0.3)	0.140	0 (0.0)	27 (1.4)	0.103	6 (3.3)	68 (1.3)	0.035	1 (7.7)	72 (1.4)	0.164
Dementia	3 (8.3)	221 (7.8)	0.757	1 (3.7)	4 (1.2)	0.315	2 (1.0)	111 (5.6)	0.001	38 (20.8)	314 (5.9)	<0.001	2 (15.4)	340 (6.4)	0.200
CLD excluding COPD	0 (0.0)	54 (1.9)	>0.99	0 (0.0)	5 (1.4)	>0.99	1 (0.5)	19 (1.0)	0.714	5 (2.7)	88 (1.6)	0.237	1 (7.7)	90 (1.7)	0.200
Asthma	2 (5.6)	140 (4.9)	0.697	2 (7.4)	12 (3.5)	0.270	15 (7.1)	91 (4.6)	0.123	12 (6.6)	5.1 (270)	0.390	1 (7.7)	253 (4.7)	0.469
Mild liver disease	1 (2.8)	58 (2.0)	0.528	0 (0.0)	9 (2.6)	>0.99	1 (0.5)	45 (2.3)	0.122	4 (2.2)	112 (2.1)	0.794	0 (0.0)	113 (2.1)	>0.99
Severe liver disease	0 (0.0)	11 (0.4)	>0.99	0 (0.0)	2 (0.6)	>0.99	0 (0.0)	5 (0.3)	>0.99	1 (0.5)	16 (0.3)	0.436	0 (0.0)	16 (0.3)	>0.99
Peptic ulcer	0 (0.0)	27 (1.0)	>0.99	0 (0.0)	3 (0.9)	>0.99	0 (0.0)	15 (0.8)	0.387	1 (0.5)	52 (1.0)	>0.99	0 (0.0)	52 (1.0)	>0.99
Mild DM	7 (19.4)	490 (17.3)	0.661	3 (11.1)	49 (14.2)	>0.99	11 (5.2)	293 (14.7)	<0.001	30 (16.4)	874 (16.4)	>0.99	3 (23.1)	864 (16.6)	0.464
Severe DM	2 (5.6)	76 (2.7)	0.255	0 (0.0)	3 (0.9)	>0.99	2 (1.0)	28 (1.4)	>0.99	9 (4.9)	111 (2.1)	0.018	0 (0.0)	117 (2.2)	>0.99
Obesity	8 (22.2)	194 (6.8)	0.003	1 (3.7)	18 (5.2)	>0.99	9 (4.3)	178 (8.9)	0.019	10 (5.5)	413 (7.7)	0.321	1 (7.7)	415 (7.8)	>0.99
Severe renal dysfunction	0 (0.0)	48 (1.7)	>0.99	0 (0.0)	0 (0.0)		0 (0.0)	10 (0.5)	0.612	2 (1.1)	62 (1.2)	>0.99	0 (0.0)	64 (1.2)	>0.99
Hemodialysis	0 (0.0)	32 (1.1)	>0.99	0 (0.0)	1 (0.3)	>0.99	0 (0.0)	10 (0.5)	0.612	1 (0.5)	25 (0.5)	0.584	0 (0.0)	26 (0.5)	>0.99
Solid tumor	1 (2.8)	109 (3.8)	>0.99	0 (0.0)	8 (2.3)	>0.99	2 (1.0)	60 (3.0)	0.120	4 (2.2)	168 (3.1)	0.663	0 (0.0)	170 (3.2)	>0.99
Leukemia	0 (0.0)	5 (0.2)	>0.99	0 (0.0)	1 (0.3)	>0.99	0 (0.0)	3 (0.2)	>0.99	1 (0.5)	19 (0.4)	0.491	1 (7.7)	19 (0.4)	0.048
Lymphoma	0 (0.0)	15 (0.5)	>0.99	0 (0.0)	1 (0.3)	>0.99	1 (0.5)	5 (0.3)	0.451	0 (0.0)	17 (0.3)	>0.99	0 (0.0)	15 (0.3)	>0.99
Metastatic solid tumor	1 (2.8)	31 (1.1)	0.333	0 (0.0)	2 (0.6)	>0.99	0 (0.0)	11 (0.5)	0.614	2 (1.1)	33 (0.6)	0.324	1 (7.7)	34 (0.6)	0.082
Collagen disease	0 (0.0)	52 (1.8)	>0.99	1 (3.7)	1 (0.3)	0.140	1 (0.5)	31 (1.6)	0.358	1 (0.5)	80 (1.5)	0.525	0 (0.0)	77 (1.4)	>0.99
HIV infection	0 (0.0)	3 (0.1)	>0.99	0 (0.0)	0 (0.0)		0 (0.0)	2 (0.1)	>0.99	0 (0.0)	4 (0.1)	>0.99	0 (0.0)	4 (0.1)	>0.99
COPD	3 (8.3)	101 (3.6)	0.139	0 (0.0)	5 (1.4)	>0.99	3 (1.4)	52 (2.6)	0.481	10 (5.5)	174 (3.3)	0.136	0 (0.0)	181 (3.4)	>0.99
Hypertension	12 (33.3)	959 (33.8)	>0.99	9 (33.3)	92 (26.7)	0.501	23 (11.0)	590 (29.5)	<0.001	66 (36.1)	1710 (32.0)	0.260	8 (61.5)	1722 (32.3)	0.035
Dyslipidemia	9 (25.0)	438 (15.4)	0.159	3 (11.1)	39 (11.3)	>0.99	7 (3.3)	259 (13.0)	<0.001	24 (13.1)	829 (15.5)	0.407	2 (15.4)	831 (15.6)	>0.99

Results are presented as number (%) unless otherwise specified. If more than one microbiological test was submitted per person, each test was considered separately. For positive results of multiple pathogens from a single patient, each pathogen was counted separately.

#p values were calculated for the comparison of characteristics of patients with positive and negative rapid diagnostic test results. Nominal variables were compared using Fisher's exact test. Continuous variables were compared using the Mann–Whitney *U* test.

A. Eight patients were excluded because gender was unknown.

B. radiograph was not obtained in 12,308 cases; CT was not obtained in 12,273 cases.

C. Five influenza tests were inconclusive results, and thus, counted as negative.

D. For *Mycoplasma pneumoniae* and *Legionella pneumophila*, Rapid kit test and LAMP test results were combined for the analysis. If test results were duplicated (i.e. both Rapid kit test and LAMP tests were positive), then, one test was counted.

Abbreviations. RDT, rapid diagnostic test; CT, computed tomography; ECMO, extracorporeal membranous oxygenation; IMV, invasive mechanical ventilation; NPPV, non-invasive positive pressure ventilation; HFNC, high-flow nasal cannula; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; p, p value; pos, positive; neg, negative; IQR, interquartile range.

In this study, we determined the actual situation of RDT use in COVID-19 hospitalized patients in Japan. Regarding test implementation rates, the immunochromatographic test for influenza (6.8%), *M. pneumoniae* (5.0%), and a urine antigen test (*S. pneumoniae*: 13.1%, *L. pneumophila*: 12.6%) were performed more often than other RDTs. Test completion rates were high in Wave 1 and tended to decline thereafter, although, for influenza, there was a trend toward more testing in Wave 3 than in Waves 2 and 4. This result is likely because Wave 3 occurred in winter. Characteristics, such as symptoms or conditions, of patients undergoing RDT differed. This suggests that physician judgment and individual facility practices influenced the decision to perform the test. During Wave 1, there were many unknowns, such as the frequency of coinfections, which would probably have triggered the high implementation rates of testing. According to the influenza surveillance at designated institutions (excluding pediatric surveillance) in Japan, the positive rate of influenza-like illnesses (ILI) was 13.2% in the 2018/2019 season, 7.9% in the 2019/2020 season, and 0% in the 2020/2021 season (the diagnosis of influenza: 1.7%) [5]. The positive rate of influenza in our cohort in Wave 1 is lower than the ILI rate of influenza surveillance in the 2019/2020 season; contrarily, it was rather higher in our cohort in Wave 3 than it was in the influenza surveillance data from 2020/2021 season. Because our cohort included patients with a confirmed COVID-19 diagnosis, the lower influenza-positive rate in our cohort than in the surveillance data should be considered reasonable. The opposite trend in 2020/2021 and Wave 3 might be influenced by situations such as the change in triage systems for patients with fever, which might have affected the patient population in surveillance institutions [6].

For *M. pneumoniae*, the immunochromatographic test had a higher positivity rate than LAMP. In the previous meta-analysis, *M. pneumoniae* immunochromatographic test showed high specificity (0.92), with modest sensitivity (0.70) for the diagnosis of *M. pneumoniae* infection, suggesting that the false positive rate is low [7]. The discrepancy in *M. pneumoniae*-positive rates between immunochromatographic test and LAMP test can not be fully explained; one possible reason is the selection bias due to the participating facilities and the patients' population. The positive rate of *M. pneumoniae* tests in Wave 2 and the positive rate of GAS in Wave 3 increased in our cohort but did not move in parallel with the number of national reports [8]. The different patient populations may have influenced these differences from national surveillance. National surveillance data were collected from designated sentinel sites regardless of the status of COVID-19 infection, whereas our cohort was comprised of hospitalized COVID-19 patients, who are likely to be older and more comorbid than the general population. There is also a possibility that an asymptomatic carrier was detected in our cohort. Dysgeusia and dysosmia occurred more frequently in patients who tested positive for influenza and *M. pneumoniae*. Patients who tested positive for *M. pneumoniae* were younger than the overall cohort, who were more likely to complain of these symptoms [9]. Therefore, age may have had a confounding influence. However, there was no significant age difference between the positive and negative groups for influenza. Further studies are needed to evaluate the reproducibility of our findings in different cohorts of patients. The *S. pneumoniae*-positive group was characterized by older age, wet cough, and multiple underlying diseases, reflecting the characteristics of pneumococcal pneumonia.

A limitation of this study is that the RDTs were submitted after clinicians' decisions and were not comprehensively performed. Therefore, the interpretation of the positivity rate should be undertaken with caution. This study was based on RDT results recorded by each institution. Therefore, validation of test accuracy at each facility was not performed, and detailed information such as the product name of the kit used was also lacking. An assessment of the impact on inpatient treatment and prognosis based on the identification of pathogens by RDTs is beyond the scope of this study and was not performed.

Although the implementation rate of RDTs in hospitalized patients

with COVID-19 showed a decreasing trend over time, there were still positive cases for other pathogens identified by RDTs. The patients with positive RDT results had different clinicoepidemiological characteristics than the negative patients. In conclusion, RDT remains an important diagnostic tool in patients with COVID-19 whose coinfection with other pathogens must be tested based on clinical evaluation.

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Declaration of competing interest

None.

Author's contributions

All the authors conceived the study and participated in its design and coordination. Y.A. and S.T. reviewed the statistical analyses. M.S. and K.H. drafted the manuscript. All authors contributed to the reviewing and finalization of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jiac.2023.02.006>.

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