Reverse transcription loop-mediated isothermal amplification assay-based infection control strategies for COVID-19 in a hospital under the state of emergency declaration in Tokyo, Japan in spring 2020

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Running title: RT-LAMP assay-based strategies against COVID-19

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Key words: loop-mediated isothermal amplification, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), infection prevention and control.
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Summary

Studies describing reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay-based infection control strategies (LAMP-based ICSs) for COVID-19 are limited. We reviewed the medical records of cases in which RT-LAMP was performed. Standard ICSs and LAMP-based ICSs were implemented during the study period. The strategies were intended to impose longer periods of infection control precautions (ICPs) for specific cases, such as those with a history of exposure to COVID-19 cases and/or bilateral-ground glass opacities (bGGO) on chest CT. Of 212 cases, which included 13 confirmed COVID-19 cases in the diagnostic cohort, exposure to COVID-19 cases \((P<0.0001)\) and chest CT bGGO \((P=0.0022)\) were identified as significant predictors of COVID-19. In the 173 hospitalized cases for whom results of the first RT-LAMP were negative, the durations of ICPs were significantly longer in cases with exposure to COVID-19 cases and/or a high clinical index of suspicion and cases with bGGO than in the remaining cases \((P=0.00046\) and \(P=0.0067\), respectively). Additionally, no confirmed COVID-19 cases indicating nosocomial spread occurred during the study period. Establishing a comprehensive system that combines rational LAMP-based ICSs with standard ICSs might be useful for preventing nosocomial spread.
Introduction

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has rapidly spread worldwide by direct person-to-person transmission. Spread of infection is thought to occur through close-range contact, mainly via respiratory droplets (1). In general, it is difficult to distinguish COVID-19 from other respiratory infections based on clinical symptoms alone because the symptoms of COVID-19 are nonspecific (2). This allows COVID-19 to go unnoticed in the early phase and to spread rapidly. In this context, both an appropriate diagnostic strategy and infection control precautions (ICPs) are indispensable to prevent nosocomial spread. According to guidelines, nucleic acid amplification testing (NAAT) such as reverse-transcription polymerase chain reaction (RT-PCR) is recommended for diagnosing COVID-19 (3-4).

The loop-mediated isothermal amplification (LAMP) assay invented in Japan is a type of NAAT (5). LAMP is simple, easy to perform, and cost effective, and amplifies DNA with high specificity and efficiency under isothermal conditions (60°C-65°C) (5). However, few clinical studies have been reported the utility of reverse transcription LAMP (RT-LAMP) in clinical settings for COVID-19. In previous studies, RT-LAMP showed an accuracy comparable with that of RT-PCR for detecting SARS-CoV-2 in clinical specimens (6-7). However, false negative RT-PCR results were reported in a previous study (8). Thus, COVID-19 should not be ruled out based on RT-PCR (8) or RT-LAMP alone and clinicians should consider the clinical course when deciding whether to discontinue ICPs for the patient whenever COVID-19 is included in the differential diagnosis, even if NAAT is negative (8). Guidance has been issued on when
to discontinue ICPs for confirmed COVID-19 cases (9). Meanwhile, few reports have investigated when to remove ICPs for suspected COVID-19 patients with negative a NAAT result, although strategies to resolve these issues are needed in the real-world setting. Therefore, the aim of this study is to provide real-world data on the RT-LAMP-based infection control strategies implemented during the state of emergency declaration in Tokyo in spring 2020.

Material and methods

A retrospective analysis of patients aged ≥20 years who underwent RT-LAMP assay for detecting SARS-CoV-2 between April 1 and May 25, 2020 at Toranomon Hospital (820 beds; Tokyo, Japan) was performed. Medical and virology records of patients during the study period were reviewed. Also, we observed all the staff and all hospitalized patients of Toranomon hospital during the study period and the subsequent 14-day observational period (until June 9, 2020) to evaluate for nosocomial transmission of SARS-CoV-2.

Definition

A confirmed COVID-19 case was defined as a case with ≥1 positive RT-LAMP and/or RT-PCR results for detecting SARS-CoV-2. A history of exposure was defined as any history of close contact with a confirmed COVID-19 case within the 14 days preceding symptom onset in the case. Close contact was defined as in a previous study (10). ICPs were such that patients were isolated and received medical care provided by health care workers dressed in appropriate personal protective equipment (PPE). ICP duration was
defined as the number of days between the start of ICPs and the day of discontinuation. Health care workers with potential exposure to COVID-19 cases were categorized into low-, intermediate-, or high risk groups based on guidance (11-12). Only data for chest computed tomography (CT) scans taken between 72 h before the first RT-LAMP and on the day of the first RT-LAMP were analyzed in this study.

**Standard infection control strategies against COVID-19 during the study period**

Standard infection control strategies were implemented during the study period. Most implementations were in compliance with international guidelines (1, 13). The details are as follows. During the study period, all staff, inpatients, outpatients and visitors at our institution wore a mask. Also, the infection control team strongly recommended strict hand hygiene that was in line with the WHO guideline (14). Furthermore, standard environmental disinfection and educational programs for healthcare workers were provided (e.g., lectures on how to handle PPE and implement zoning in the ward for confirmed COVID-19 cases).

**Risk assessment system for patients with possible COVID-19 during the study period**

Risk assessment was performed by using specific algorithms (Figures 1 and 2) for all patients admitting to our hospital and for hospitalized patients whose attending doctor suspected they had COVID-19. The algorithms were established at the beginning of April 2020. First, patients were divided into 1 of the 3 risk categories (low, intermediate, or high), before receiving RT-LAMP. Evaluation was performed by the doctor
responsible for the patient’s care. Next, infectious disease experts (ID experts) ordered an RT-LAMP assay for patients categorized as either intermediate or high risk before the test (Figure 1). Nasopharyngeal specimens obtained by well-trained nurses wearing appropriate PPE were used for the assay. Then, confirmed COVID-19 cases (those with positive RT-LAMP results) were isolated in a negative pressure ward for care of only confirmed cases. They were managed by a COVID-19 team. Patients whose RT-LAMP results were negative were divided into 1 of 2 risk categories, either intermediate or high risk according to the algorithm (Figure 2). Patient’s clinical information required to perform the risk assessment and operate the algorithm was obtained mainly from a medical chart review by the ID expert. Furthermore, these patients were each isolated in a private room. If they had at least 1 positive NAAT result, they were moved to the negative-pressure ward. The high-risk patients whose second NAAT result was negative were each isolated in a private room for at least 10 days unless a definite alternative diagnosis was made or the patient died.

Concerning the intermediate-risk patients whose first RT-LAMP results were negative, the ID expert decided when to discontinue the ICPs by referring to the algorithm (Figure 2).

Health care workers who cared for high-risk patients, intermediate-risk patients, and/or confirmed COVID-19 cases wore appropriate PPE, as recommended by the guidelines of our institute (Table 1).

**Other infection control implementation**

Eating and drinking face-to-face with friends and colleagues were prohibited in and
outside the hospital. In addition, spaces for patients to socialize were closed in our institution.

**RT-LAMP assay**

Viral RNA was extracted from nasopharyngeal specimens using an influenza virus extraction reagent (Eiken Chemical, Tokyo, Japan). The method of amplification of SARS-CoV-2 RNA by RT-LAMP in our hospital was as previously described (7). At our institution, RT-LAMP assay was performed twice a day on weekdays only, and once daily during consecutive holidays between May 2 and May 6, 2020.

**RT-PCR assay**

Nasopharyngeal specimens obtained from patients were sent to BML General Laboratory (Tokyo, Japan). RT-PCR was performed as previously described (15). Some patients who underwent RT-LAMP were also tested with RT-PCR as the second NAAT (Figure 2).

**Statistical analysis**

Categorical variables were compared using Fisher’s exact test. The Mann-Whitney U test was performed to test the equality of continuous variables. Variables with P value of <0.20 were entered into logistic regression models with a stepwise selection method for multivariate analysis to identify independent predictors of COVID-19. Significance was set at an α value of 0.05. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R.
Results

Overview of patients who underwent RT-LAMP

RT-LAMP was performed for 228 cases between April 1 and May 25, 2020 for the first time. In total, 13 patients were diagnosed as having COVID-19 (Figure 3). All 13 cases were diagnosed as confirmed COVID-19 cases at the first RT-LAMP testing. There were no cases for whom the first RT-LAMP results were negative and second NAAT results were positive. Of the 228 cases, 212 had at least 1 symptom and/or clinical manifestation (e.g., abnormality of chest CT) indicating the possibility of COVID-19. Therefore, these 212 were included into the diagnostic cohort (Figure 3). The characteristics of cases in the diagnostic cohort are shown in Table 2. The remaining 16 cases were asymptomatic when they were tested and had negative RT-LAMP results. These 16 cases were tested due to post-exposure to COVID-19 cases screening (7 cases), a requirement for transfer to another institution (5 cases), pre-procedure (e.g., pre-surgery) screening (2 cases), and other (2 cases). Additionally, in the diagnostic cohort, 113 cases had pneumonia evident on chest CT and 2 cases had pneumonia evident on chest X ray. Moreover, 184 of the 212 cases in the cohort required admission to our hospital and were included in the infection control cohort (Figure 3) to be evaluated using the algorithm shown in Figure 1.

Analysis of the diagnostic cohort

Both history of prior exposure to COVID-19 cases and bilateral ground-glass
opacities (bGGO) on chest CT were identified as independent predictors of confirmed COVID-19 in the multivariate analysis of the diagnostic cohort (Table 2). In the univariate analysis of the cohort, the ratio of patients who had at least 1 respiratory symptom among confirmed COVID-19 cases tended to be higher than that in non-confirmed COVID-19 cases ($P=0.078$). Other results are shown in Table 2.

**Details of the infection control cohort**

Characteristics of 184 cases in the infection control cohort are shown in Table 3. Eleven cases were included in the high-risk group and the rest of the 173 cases were included in the intermediate-risk group before RT-LAMP (Figure 3). Six (55%) cases in the high-risk group and 5 cases (2.9%) in the intermediate-risk group were diagnosed as confirmed COVID-19 cases. Of the cases for whom results of first RT-LAMP were negative (173 cases), 13 were categorized into the high-risk group by the assessment of ID experts (Figure 3). The remaining 160 cases were categorized into the intermediate-risk group (Figure 3). Although all 13 cases in the high-risk group underwent a second NAAT, none was positive. The duration of ICPs was significantly longer for the high-risk group (median 9 days, range 0-20 days) than for the intermediate-risk group (median 3 days, range 0-14 days) ($P=0.00046$). In addition, the duration of ICPs was significantly longer for the 40 cases with bGGO pneumonia (median 4 days, range 0-14 days) than for the remaining 133 cases (median 3 days, range 0-20 days) ($P=0.0067$).

Furthermore, 33 of the 160 cases included in the intermediate-risk group after the first RT-LAMP had pneumonia with bGGO on chest CT (Figure 3). The duration of ICP was significantly longer for the 33 cases with bGGO pneumonia (median 4 days, range 0-14 days) than for the remaining 127 cases (median 3 days, range 0-14 days) ($P=0.00067$).
days) than for the remaining 127 cases (median 3 days, range 0-13 days) \((P=0.005)\).

No clinical improvement was seen in 9 of these 160 cases. Thus, they underwent the second NAAT and were further assessed by ID experts; the second NAAT was negative in these 9 cases.

**Analysis of possibility of nosocomial spread of SARS-CoV-2**

No confirmed COVID-19 cases occurred in any of the hospitalized patients or staff at our institution during the study period and the subsequent 14-day observation period. Also, there were no clusters of nosocomial respiratory infections, which would indicate possible COVID-19 transmission. However, there were 2 events in which some staff had contact with confirmed COVID-19 cases accidentally at the beginning of April before their definitive diagnosis. In total, 45 staff had low-risk exposure and 5 had intermediate-risk exposure. The 5 staff who had intermediate-risk exposure were individually quarantined in their own homes for at least 14 days. Furthermore, respiratory infection (1 acute bronchitis and 1 pneumonia) developed in 2 of the 50 staff within 14 days after exposure. Although both of them underwent standard microbiological testing and two rounds of NAAT for SARS-CoV-2, the etiologies were uncertain.

**Discussion**

The results of this study provide useful information about COVID-19 as well as insights into new infection control strategies (Figures 1 and 2) based on the results of RT-LAMP, chest CT findings, and the clinical history of patients, which might aid in efforts to
protect all hospital staff and hospitalized patients from COVID-19 in the real-world clinical setting.

In this study, bGGO on chest CT and history of exposure to cases of COVID-19 were identified as independent predictors of confirmed COVID-19 cases in the diagnostic cohort. Furthermore, infection control strategies (Figures 1 and 2) were applied from the beginning of April 2020 with the aim of preventing nosocomial spread of COVID-19 at our institution. Based on previous studies (9, 17-18), history of exposure and bGGO on chest CT were the cornerstones of our algorithms for assessing the risk of COVID-19 (Figures 1 and 2). Indeed, these two factors were also identified as independent predictors of COVID-19 in this study. Thus, the algorithms were reasonable in the real-world clinical setting.

In the algorithm, the requirements to recommend discontinuation of the ICPs are shown in Figure 2. False-negative NAAT results for SARS-CoV-2 have been reported, and thus ICPs should not be removed based on NAAT results alone (8, 19). Accordingly, we continued ICPs even when the results of RT-LAMP were negative until the cases fulfilled the symptom-based requirements and/or were diagnosed as another illness (Figure 2). In particular, the high-risk cases with a history of exposure and intermediate-risk cases with pneumonia, seen as bGGO, required a significantly longer duration of ICPs in accordance with the algorithm (Figure 2). It was thus probably rational to prevent nosocomial spread of COVID-19 from the latent definite COVID-19 cases whose NAAT results were negative. In fact, there were no events that suggested nosocomial spread during the study period and the subsequent 14-day observation period carried out in accordance with the evidence-based standard infection control
strategies (1, 13) and the algorithms, apart from the 2 cases suspected to have contracted the infection at the beginning of April when most staff were unaware of the algorithms. Although some non-emergency procedures were postponed, important medical care, such as allogeneic hematopoietic stem cell transplantation, surgery for cancer patients, and cancer chemotherapy were performed almost as usual even during that time (data not shown).

Furthermore, the algorithms could be utilized by using RT-PCR instead of RT-LAMP because the sensitivity and specificity of RT-LAMP for detecting SARS-CoV-2 were comparable to those of RT-PCR (6-7). Therefore, our strategies may be applied at institutes and facilities globally as long as NAAT modalities, such as RT-PCR, are available. In addition, LAMP is simple, easy to perform, and requires only a laboratory water bath on a heat block for the reactions (5). Thus, RT-LAMP might be useful, particularly in geographical areas with limited medical resources, such as developing countries.

Our study has some limitations. First, this was a small retrospective study, not a randomized controlled trial, conducted to evaluate the utility of RT-LAMP based algorithms and strategies. Thus, it is uncertain whether or not these algorithms and strategies are suitable for other clinical settings, including other hospitals and settings in Japan where COVID-19 might be more prevalent compared with in our setting. Second, the false-negative rate of RT-LAMP was not demonstrated. The other testing, such as serologic test should have been performed to evaluate it. The false negative rate of RT-PCR was estimated to range from 10% to 40% in a previous systematic review (19). During the study period many patients with pneumonia were admitted our hospital,
some of whom probably had pneumonia associated with COVID-19 even though NAAT results were negative. In fact, there were 4 high-risk cases with respiratory infection who had a clear history of exposure to confirmed COVID-19 cases in the infection control cohort, although NAAT results were negative. These 4 cases were strongly suspect for COVID-19. Third, quality control for RT-LAMP was not performed by using reference methods, such as RT-PCR in this study. In addition, the same RNA extraction method for RT-LAMP has not been evaluated in previous studies, although the same amplification method [7] was utilized in the present study. Therefore, the sensitivity of RT-LAMP in this study might be lower than that in the previous studies [6-7]. As a result, the two staff who had respiratory infections within 14 days after exposure might not have been diagnosed as confirmed COVID-19 cases by RT-LAMP in this study.

In conclusion, we reported infection control strategies, based on RT-LAMP. Establishing a strong comprehensive system that combines new strategies based on NAAT modalities with evidence-based standard infection control strategies will potentially be useful to prevent nosocomial spread of SARS-CoV-2 in the era of COVID-19.

Conflict of interest

The authors have no conflict of interests to disclose.

Ethical approval

This study was approved by the Institutional Review Bord of Toranomon Hospital.

Acknowledgements
We thank Ms. Yukiko Fuke, Ms. Hanae Uno, Dr. Sara Ikeda, Dr. Akiko Yoneyama and the staff of the microbiology laboratory at Toranomon Hospital for supporting the infection control strategies.
Reference


13. Infection prevention and control during health care when coronavirus disease


Figure 1. Risk assessment strategy for the patients admitted to the hospital and suspected of having possible nosocomial onset of COVID-19 before the first RT-LAMP

If patients categorized as low risk had a history of exposure to COVID-19, they were individually quarantined in a single room of the hospital for at least 14 days or their admission was postponed for at least 14 days.

Figure 2. Risk assessment strategy and requirements to discontinue the infection control precautions for whom the first RT-LAMP result was negative

If a second NAAT was performed, the ID expert could select RT-LAMP or RT-PCR. The ID expert evaluated patients who were deemed intermediate- and high-risk once per weekday to decide whether they fulfilled the requirements for discontinuation. If the ID expert had a high index of suspicion of possible COVID-19, they could schedule the second NAAT earlier than the time recommended by the algorithm. When an alternative definitive diagnosis was made, the ID expert discontinued the infection control precautions even when the patient did not fulfill the requirements. The infection control precautions required that the patient be isolated and receive medical care from health care workers dressed in appropriate personal protective equipment. Clinical improvement meant that the patients fulfilled all of the following requirements: 1) cough disappears and improves, 2) afebrile state (BT ≤37°C) persists for ≥24 h without use of steroids or antipyretic medicine, 3) chest imaging improves (if the patient has
pneumonia), and 4) oxygen administration is reduced or discontinued.

Figure 3. Flow chart of patient assignment to each cohort and group

bGGO, bilateral-ground glass opacities.
Table 1. Recommended personal protective equipment for each risk category in Toranomon Hospital

<table>
<thead>
<tr>
<th>Risk categories</th>
<th>Medical mask</th>
<th>N95 mask</th>
<th>Eye protection</th>
<th>Gown</th>
<th>Gloves</th>
<th>Medical cap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>High risk</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Algorithms for risk stratification are shown in Figure 1 and Figure 2.

+, Recommended; ±, Recommended only during aerosol-generating procedures; -, Not recommended
Table 2. The characteristics of the 212 cases in the diagnostic cohort and the analysis of predictors of COVID-19

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Result for the following patients</th>
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<th></th>
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</thead>
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<tr>
<td></td>
<td>Total (N=212)</td>
<td>COVID-19 cases (N=13)</td>
<td>None COVID-19 cases (N=199)</td>
<td></td>
<td>P value</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>68 (22 - 97)</td>
<td>78 (22 - 92)</td>
<td>68 (23 - 97)</td>
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<td>0.27</td>
</tr>
<tr>
<td>Gender</td>
<td>Male / Female</td>
<td>109 / 103</td>
<td>4 (31) / 9 (69)</td>
<td>105 (53) / 94 (47)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes Melitus</td>
<td>33</td>
<td>2 (15)</td>
<td>31 (16)</td>
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<td>Hypertension</td>
<td>78</td>
<td>4 (31)</td>
<td>74 (37)</td>
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<td>Chronic Heart Failure</td>
<td>10</td>
<td>0 (0)</td>
<td>10 (5)</td>
<td></td>
<td>1</td>
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<tr>
<td>Chronic Renal Failure</td>
<td>54</td>
<td>1 (7.7)</td>
<td>53 (27)</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Chronic Renal Failure on hemodialysis</td>
<td>8</td>
<td>1 (7.7)</td>
<td>7 (3.5)</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Liver Cirrosis</td>
<td>3</td>
<td>0 (0)</td>
<td>3 (1.5)</td>
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<td>Hematological Malignancy</td>
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<td>1 (7.7)</td>
<td>29 (15)</td>
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<tr>
<td>Solid tumor</td>
<td>47</td>
<td>0 (0)</td>
<td>47 (24)</td>
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<td>0.077</td>
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<tr>
<td>Bronchial athma</td>
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<td>12 (6)</td>
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<td>Chronic Obstructive Pulmonary Disease</td>
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<td>8 (4)</td>
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<td>Medical status</td>
<td>Allogeneic Hematopoietic Stem Cell Transplantation</td>
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<td></td>
<td>Solid Organ Transplantation</td>
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<tr>
<td>Clinical characteristics</td>
<td>Prior exposure to COVID-19</td>
<td>15</td>
<td>7 (54)</td>
<td>8 (4)</td>
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<tr>
<td>Conditions</td>
<td>n</td>
<td>Cases</td>
<td>Total</td>
<td>P</td>
<td></td>
</tr>
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<td>-----------------------------------</td>
<td>-----</td>
<td>-------</td>
<td>-------</td>
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</tr>
<tr>
<td>At least one respiratory symptoms</td>
<td>124</td>
<td>11 (85)</td>
<td>113 (57)</td>
<td>0.078</td>
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<tr>
<td>Chest CT imaging and chest X ray</td>
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<td></td>
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<tr>
<td>Pneumonia</td>
<td>115</td>
<td>10 (77)</td>
<td>105 (53)</td>
<td>0.15</td>
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<td>Any bGGO on CT</td>
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<td>9 (69)</td>
<td>42 (21)</td>
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<tr>
<td>bGGO without consolidation on CT</td>
<td>39</td>
<td>7 (54)</td>
<td>31 (16)</td>
<td>0.0027</td>
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<tr>
<td>bGGO with consolidation(s) on CT</td>
<td>13</td>
<td>2 (15)</td>
<td>11 (5.5)</td>
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<td>Gender</td>
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<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Prior exposure to COVID-19</td>
<td>32</td>
<td>7.1 - 147</td>
<td>&lt; 0.0001</td>
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<tr>
<td>At least one respiratory symptom</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>NR</td>
<td>NR</td>
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</tr>
<tr>
<td>Any bGGO on CT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>bGGO without consolidation on CT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>bGGO with consolidation(s) on CT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

COVID-19, coronavirus disease 2019; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; bGGO, bilateral-ground-glass-opacity; aOR, adjusted odds ratio; NR, not retain final model.
Table 3. The characteristics of the 184 cases in the infection control cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Result for the following patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N=184)</td>
<td>COVID-19 cases (N=11)</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>72 (23-97)</td>
<td>78 (37-91)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male / Female</td>
<td>97 / 87</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Melitus</td>
<td>31</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Chronic Heart Failure</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>52</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Chronic Renal Failure on hemodialysis</td>
<td>8</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Liver Cirrosis</td>
<td>3</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematological Malignancy</td>
<td>29</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>45</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>12</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>7</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Interstitial Lung Disease</td>
<td>12</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Medical status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allgeneic Hematopoietic Stem Cell Transplantation</td>
<td>11</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Solid Organ Transplantation</td>
<td>2</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior exposure to COVID-19</td>
<td>11</td>
<td>6 (55)</td>
</tr>
</tbody>
</table>
At least one respiratory symptom | 104 | 9 (82) | 95 (55) | 0.12
---|---|---|---|---
Chest CT imaging
Any bGGO on CT | 48 | 8 (73) | 40 (23) | 0.0011
bGGO without consolidation on CT | 36 | 6 (55) | 30 (17) | 0.0083
bGGO with consolidation(s) on CT | 12 | 2 (18) | 10 (5.8) | 0.15

COVID-19, coronavirus disease 2019; bGGO, bilateral-ground-glass-opacity.
All the patients admitted to the hospital

Symptom-based screening to determine whether the patient has fever and/or respiratory infection

The patient has fever and/or respiratory infection.

Yes

- Check medical history, including exposure to COVID-19
- Imaging test (chest X ray and/OR chest CT) and/OR
- Blood test

No

Low risk: Standard precaution and mask

Doctor in charge of the patient rules out following two possibilities.
- Etiology of the illness is associated with COVID-19
- Etiology of the illness is associated with respiratory infection

Yes

The patient was exposed to a confirmed or a suspected case of COVID-19 in the 14 days preceding symptom onset

No

Intermediate risk before RT-LAMP: Isolation

Yes

High risk before RT-LAMP: Isolation

Infectious disease expert reviews the patient’s data and orders the RT-LAMP.
RT-LAMP positive: Isolate as a confirmed COVID-19 case
RT-LAMP negative: Isolate as a suspected COVID-19 case and follow the algorithm (See Figure 2).
Patients included in intermediate- or high-risk before RT-LAMP and first RT-LAMP was negative

The ID expert’s screening by using electronic medical chart: the patient fulfill at least one of the followings.

- The patient exposed to a confirmed COVID-19 case within 14 days prior to the onset of symptoms.
- The patient exposed to a suspected COVID-19 case who is waiting for the NAAT result within 14 days prior to the onset of symptoms.
- The ID doctor strongly suspects the patient has COVID-19 because of clinical course and imaging test of the patient.

No

High risk: Isolation and second NAAT

Intermediate risk: Isolation
Chest CT is checked if the ID expert suspects the patient has pneumonia.

There are any possibilities that the patient has any other respiratory infections.
(e.g. bronchitis, sinusitis, and pharyngitis)

No

Remove ICPs

Yes

Continue ICPs for 2-3 days.

ID expert’s additional assessment

Perform NAAT (Second NAAT).
NAAT positive: isolate as confirmed cases.
NAAT negative: Consider three options.
1. ID consultation service
2. Add chest imaging
3. Remove or continue ICPs (requires consensus from multiple ID experts).

The patients possibly has pneumonia.

No

The patient has any one of the following chest CT finding.
- Bilateral GGO
- Consolidation(s) and bilateral GGO

Continues ICPs for 2-3 days.

No

Yes

Clinical improvement

Remove ICPs

The patient fulfills all the 4 requirements.
1. Cough disappears or is improving
2. Afebrile state (BT ≤ 37°C) persists for ≥48 h without steroids or any antifebrile usage.
3. Chest imaging is improving.
4. Oxygen administration is reduced or discontinued.

ID expert’s additional assessment

No

Yes

Remove ICPs
All cases who received RT-LAMP: 228 cases

16 asymptomatic cases were excluded

**Diagnostic cohort** (n=212, including 13 confirmed-COVID-19 cases)

28 were excluded (not admitted to our hospital)

**Infection control cohort** (n=184 cases, comprising 11 high-risk and 173 intermediate cases before RT-LAMP testing)

11 confirmed COVID-19 cases were excluded (6 high-risk cases and 5 intermediate-risk cases before RT-LAMP testing)

Cases with negative first RT-LAMP (n=173, comprising 40 cases with and 133 cases without bGGO-pneumonia)

High-risk after first RT-LAMP (n=13 cases)

Intermediate risk after first RT-LAMP (n=160, including 33 cases with and 127 cases without bGGO-pneumonia)