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A hospital cluster of COVID-19 associated with a SARS-CoV-2 superspreading event

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Abstract Background/purpose: Superspreading events (SSEs) are pivotal in the spread of SARS-CoV-2. This study aimed to investigate an SSE of COVID-19 in a hospital and explore the transmission dynamics and heterogeneity of SSE.

Methods: We performed contact tracing for all close contacts in a cluster. We did nasopharyngeal or throat swabbing for SARS-CoV-2 by real-time RT-PCR. Environmental survey was performed. The epidemiological and clinical characteristics of the SSE were studied.

KEYWORDS SARS-CoV-2; COVID-19; Superspreading event; Outbreak;

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Results: Patient 1 with congestive heart failure and cellulitis, who had onset of COVID-19 two weeks after hospitalization, was the index case. Patient 1 led to 8 confirmed cases, including four health care workers (HCW). Persons tested positive for SARS-CoV-2 were HCW (n = 4), patient 1’s family (n = 2), an accompanying person of an un-infected in-patient (n = 1), and an in-patient admitted before the SSE (n = 1). The attack rate among the HCW was 3.2% (4/127). Environmental survey confirmed contamination at the bed rails, mattresses, and sink in the room patient 1 stayed, suggesting fomite transmission. The index case’s sputum remained positive on illness day 35. Except one asymptomatic patient, at least three patients acquired the infection from the index case at the pre-symptomatic period. The effective reproduction number ($R_t$) was 0.9 (8/9).

Conclusion: The host factor (heart failure, longer viral shedding), transmissibility of SARS-CoV-2 ($R_t$, pre-symptomatic transmission), and possible multiple modes of transmission altogether contributed to the SSE. Rapid response and advance deployment of multi-level protection in hospitals could mitigate COVID-19 transmission to one generation, thereby reducing its impact on the healthcare system.

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number ($R_t$) is defined as the mean number of secondary cases generated by a primary case in a period.11

Environmental survey

We sampled the surfaces of the environment and equipment by the Dacron swab (Copan Diagnostics, Corona, CA). The swabs were put onto 0.8 mL of viral transport medium for subsequent tests. Follow-up survey was performed according to the results of the initial investigation. For swabbing the ground surface of the room, 90 cm squares were delineated and sampled. All samples were processed immediately after the collection.

Collection of respiratory specimens and RT-PCR

Respiratory specimens of the nasopharyngeal or throat swabs were collected where appropriate. All samples were maintained in a transport medium (UTM-RT, Copan Diagnostics, Murrieta, CA) for further analysis. We used reverse transcription polymerase chain reaction (RT-PCR) to detect SARS-CoV-2. RNA was extracted from the specimens using LabTurbo system (Taigen, Taiwan) according to the manufacturer’s instructions, except that the specimen was pretreated with Proteinase K prior to RNA extraction. RT-PCR was performed according to a proposed protocol.12 In brief, the amplification targeted the following genes: RNA-dependent RNA polymerase gene (RdRp), envelope (E) gene, and nucleocapsid (N) gene. We used the E gene and N gene assays as the first-line screening targets, followed by confirmatory testing with the RdRp gene assay.

Results

Contact tracing and investigation

As of March 10, 2020, we performed nasopharyngeal swabbing for HCW ($n = 127$), in-patients ($n = 55$), and visitors who accompanied their family in the hospital ($n = 27$). Those patients who needed in-patient care were transferred to negative pressure isolation rooms or single rooms and quarantined for 14 days after the last day of exposure. HCW considered as close contacts were quarantined at home or a designated dormitory area for 14 days. All in-patients and HCW tested negative were re-assessed and re-tested again before the end of quarantine period. The investigation confirmed eight cases, including four HCW (Table 1 and Fig. 1). The detailed investigation information was available in the Supplementary Methods.

Environmental contamination

On February 28, there were 20 samples collected from the room that patient 1 stayed in the ward 5C. SARS-CoV-2 RNA was found in four samples. The sample area of the floor was 30 × 30cm. There were four samples checked for the floor in the room. Two samples were done for the floor area near the index patient and two were done for the surrounding floor areas. The contaminated sites at the room patient 1 stayed were the bed rails and mattresses of neighboring beds (one bed for another un-infected patient and another for the accompanying person) and the sink (Fig. 2). It is possible that these sites were contaminated by the index case when she approached toilet or closet near the door of the room. On February 29, 104 surface samples were collected from the exposure sites of the emergency room. All were tested negative for SARS-CoV-2.

Complete cleaning of the emergency room and the ward 5C was performed immediately after the identification of patient 1. Follow-up survey of the environment was conducted on March 1. Samples were collected from previously contaminated surfaces of the room. All 25 samples were negative for SARS-CoV-2.

Infection control measures

After Taiwan CDC started the border control in January 2020, the hospital implemented patient traffic control policy, based on risk stratification of the patients and visitors entering the hospital. Universal mask wearing, reinforcement of hand hygiene, and restriction of visitors were also implemented in early February. Ward 5C was closed after cleaning and disinfection. We re-enforced the infection control measures implemented in the hospital to all HCW. Hospital-wide areas including wards and ICUs were allocated and assigned to 20 ID physicians of the hospital. Each ID physician worked with infection control nurses when there were suspected cases of COVID-19 in the responsible region. This workflow and assigned areas were integrated to the computerized antimicrobial stewardship program, which has been deployed since 2004.13 When ID physicians reviewed antibiotic prescriptions, they would review relevant clinical information including vital signs, laboratory data, and chest images simultaneously. Throat or nasopharyngeal swabbing would then be performed for suspected cases in a single room or an isolation room with negative pressure, if deemed necessary. We reduced the workload for HCW by reducing the bed number of the hospital. Beds in emergency room and wards were separated at least 2 m apart. There were no further new cases linked to the cluster after March 10, 2020.

Index case and the event

The index case was admitted due to heart failure and cellulitis. As shown in Table 1, laboratory results reflected leukopenia ($2.1 \times 10^9$/L) and lymphopenia ($0.2 \times 10^9$/L). She developed fever on February 19 (illness day 0) and cough on day 4. She was intubated due to hypoxemic respiratory failure on illness day 9. Extracorporeal membrane oxygenation (ECMO) was applied from day 21 to day 35 due to pulseless ventricular tachycardia. Viral load detected by RT-PCR from throat peaked on day 9 (threshold cycle ($C_t$) value: 16.7). The sputum was still positive on day 35. Eventually the patient died of sepsis, heart failure, ventricular fibrillation, and refractory shock on day 39. The index case did not receive remdesivir treatment since the patient was intubated with mechanical
| Patient | 1     | 2     | 3     | 4     | 5     | 6     | 7     | 8     | 9     |
|---------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| **Description** | Index case | Cleaner | Nurse | Nurse | Nurse practitioner | The index patient’s family | An un-infected patient’s family who stayed in the ward 5C before the cluster was identified | An in-patient admitted to 5C | The index patient’s family |
| **Age (year)** | 57 | Female | Heart failure, coronary artery disease | 56 | Female | Hypertension | 29 | Female | Pregnancy |
| **Sex** | Female | Female | Female | Female | Female | Female | Female | Female | Male |
| **Underlying conditions** | Heart failure, coronary artery disease | | | | Hypertension | Pregnancy | | | |
| **Presenting symptoms** | Fever and cough | Cough | Cough and rhinorrhea | Cough and rhinorrhea | Muscle ache and mild fever (37.5°C) | No symptoms | Fever, cough, and muscle ache | Cough | Cough |
| **Chest radiograph** | Pneumonia | Normal | NA | NA | Normal | Normal | Pneumonia | GGO | GGO |
| **HRCT** | GGO | GGO | NA | NA | GGO | GGO | Pneumonia | GGO | GGO |
| **LOS** | 43 | 14 | 23 | 21 | 31 | 39 | 39 | 28 | 28 |
| **Outcome** | Mortality | Survival | Survival | Survival | Survival | Survival | Survival | Survival | Survival |
| **White blood cell count (10⁹/L)** | 2.1 | 9.1 | 5.3 | 6.4 | 3.6 | 3.0 | 3.1 | 2.8 | 3.0 |
| **Lymphocyte (10⁹/L)** | 0.2 | 2.4 | 1.3 | 2.0 | 1.2 | 1.2 | 1.2 | 2.0 | 2.0 |
| **Platelet count (10⁹/L)** | 158 | 325 | 249 | 273 | 174 | 198 | 198 | 198 | 198 |
| **D-dimer (ng/mL)** | 1902 | 191 | 574 | <170 | <170 | <170 | <170 | 3.4 | 1539 |
| **C-reactive protein (mg/L)** | 73.6 | 2.5 | 1.5 | 2.5 | 3.4 | 2.5 | 2.5 | 3.4 | 2.5 |
| **Lactate dehydrogenase (U/L)** | 690 | 177 | 189 | 212 | 227 | 327 | 265 | 265 | 265 |
| **Creatine (mg/dL)** | 1.4 | 0.6 | 0.4 | 0.7 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| **AST (U/L)** | 45 | 27 | 21 | 21 | 38 | 32 | 41 | 41 | 41 |
| **ALT (U/L)** | 16 | 25 | 18 | 13 | 23 | 29 | 31 | 31 | 31 |
| **Bilirubin (mg/dL)** | 1.3 | 1.2 | 0.2 | 0.3 | 0.7 | 0.5 | 0.3 | 0.3 | 0.3 |
| **Ct value** | 23.9 | 26.6 | 28.8 | 26.4 | 29.9 | 24.1 | 27.5 | 26.6 | 24.95 |
| **E gene** | 29.8 | 26.9 | 25.6 | 24.0 | 37.6 | 25.2 | 29.8 | 28.1 | 27.03 |
| **RdRp-1** | 24.2 | 28.0 | 25.6 | 23.9 | 30.8 | 25.4 | 26.7 | 27.3 | 26.02 |
| **RdRp-2** | 28.5 | 26.6 | 28.8 | 26.4 | 32.3 | 28.1 | 31.7 | 32.0 | 29.73 |

* RT-PCR of the respiratory specimens collected at the time of diagnosis.

Ct = cycles of thresholds; GGO = ground-glass opacities; HRCT = High-resolution computed tomography; LOS = length of stay; NA = not available.
ventilation. Steroids were not used because the evidence for dexamethasone use was limited at that time.

Overall, we performed nasopharyngeal swabbing for HCW ($n = 127$), the in-patients admitted in the ward 5C ($n = 57$) and accompanying persons for their family admitted in the ward 5C ($n = 27$), as of March 5, 2020 in the investigation. Persons tested positive for SARS-CoV-2 were summarized in Fig. 1. In this outbreak, the secondary attack rate for HCW was 3.2% (4/127). The $R_t$ was calculated 8/9 (0.9) as there were 9 infectors (primary cases) and 8 infectees (secondary cases). The pre-symptomatic transmission was observed among the infected in at least patients 2, 3, and 8, and possibly in patient 9, with a wide distribution of the serial intervals (range, 1 to 16) (Fig. 1). All but the index case had mild symptoms only; one case (patient 6) was totally asymptomatic. Half of them had no underlying diseases. The index case and patient 6 had a relatively higher viral shedding (lower $C_t$ values) at the time of diagnosis (Table 1), indicating it is the longer duration of shedding, rather than the higher viral load at diagnosis, that characterized the super-spreader in this superspreading event. Furthermore, we were able to isolate SARS-CoV-2 from five patients in the cluster who showed higher initial viral load. Whole genome sequencing revealed that all of the 5 isolates belong to the same clade, with only four nucleotide changes in two, while the remaining three showing identical viral genome.14

Figure 1. Transmission dynamics of patients at the superspreading event associated with COVID-19 in a hospital. The designated wards for isolation of COVID-19 cases were 9B, 13H and ICU. The cluster involved four hospital staff (patients 2–5), two families (patients 6 and 9) of the index case (patient 1), one accompanying person for an un-infected in-patient (patient 7), and one in-patient who stayed in the same ward (patient 8). Patients 2, 3, and 8 may acquire infection earlier than symptom onset of the index case. Patient 2 was a cleaner and performed cleansing work for the bed next to the bed of Patient 1 at the emergency room on February 14. Patient 3 was a nurse who cared patient 1 on February 16, and she also cared an un-infected in-patient (patient 7’s family) from February 21 to February 23. Patient 4 was a nurse who cared patient 1 on February 19. Patient 5 was a nurse practitioner who wore a surgical mask to swab patient 1 for a rapid influenza diagnostic test on February 24. She joined the team to care patient 1 for several days before the cluster. Patient 6 was patient 1’s daughter who accompanied patient 1 during her admission in the ward 5C. She was asymptomatic throughout the entire course. Patient 7 accompanied her un-infected husband during his admission to ward 5C for treatment before the cluster. Patient 9 was the index case’s son who stayed in the ward 5C for only one day on February 16. Patient 8 was admitted to the ward 5C from February 14 to February 20 for radiofrequency ablation of liver tumor. Patient 9 was tested negative twice before the end of quarantine on March 3. He developed cough on March 6, and a third testing was positive for SARS-CoV-2 on March 10. Except the asymptomatic patient 6, the serial intervals (in parentheses) of the infected were: patient 2 (0), patient 3 (–1), patient 4 (6), patient 5 (6), patient 7 (4), patient 8 (0), and patient 9 (16).
Discussion

SSEs are among the distinguishing features in disease transmission caused by human coronaviruses, which were readily described in SARS-CoV and MERS-CoV infections.\textsuperscript{6–9} Recent studies of transmission modeling also proved that SSE could increase the overall disease transmission heterogeneity of COVID-19.\textsuperscript{15,16} The drivers of SSEs vary, generally including pathogen, host, environmental, behavior, and response factors. Although several nosocomial clusters caused by SARS-CoV-2 have been reported in the pandemic, there is no comprehensive investigational report of an SSE yet.\textsuperscript{17–19} Herein we described an SSE associated with an index case, who was infected with SARS-CoV-2 and transmitted the virus before symptom onset in a large hospital. Surface samples taken in the room showed environmental contamination by the patient, suggesting probable fomite transmission, in addition to the transmission via respiratory droplets. Hospital response included screening for the hospital staff listed as close contacts, restriction of the number of visitors, reinforcement of adherence to infection control measures to all HCW, and environmental cleansing and disinfection. Early contact tracing and quarantine for the close contacts successfully limited the spread of SARS-CoV-2 in our hospital to one generation of transmission. In contrast, previous SSEs from

\begin{figure}
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\caption{Floor plan of the ward 5C, the locations of the patients 1, 7, and 8 during their stay in the ward, and results of environmental sampling in the event. Environmental sampling was performed at the room patient 1 stayed. Sites sampled were: 1) Sites next to the environment of patient 1: the table, the chair, the bed, the bedrails, wall, and floor; 2) Sites near other patients who stayed at the same room: the beds, the floor, and the lockers; and 3) Bathroom: the door handle, the sink, floor, and the toilet. The contaminated sites were the bed rails and mattresses of neighboring beds (one bed for another un-infected patient and another for the accompanying person) and the sink. The red diamonds indicate the contaminated sites, and the green diamonds the sites sampled with no contamination.}
\end{figure}
SARS-CoV or MERS-CoV usually involved multiple generations of spread. The secondary attack rate for HCW was 3.2%, which is significantly lower than that reported from a SARS SSE. The $R_t$ was less than 1, due to the advance deployment of control measures such as universal mask-wearing and reinforcement of hand hygiene before the event. The study highlights the importance of early detection, contact tracing and quarantine, and the timely implementation of infection control measures to confine an SSE in a hospital.

Although there is no consistent definition of SSE, reports suggested that most infected cases were transmitted by 10–20% primary cases in an outbreak associated with an SSE. Xu et al. has estimated that the threshold of observing SSEs is set as 3.78, meaning the occurrence of an SSE if 4 or more secondary cases were infected by one primary case. We presumed that the clustered cases were secondary to the index case and that transmission occurred within the ward. In this study, the investigation of the transmission chain was based on the timing of events, albeit it is possible that all transmissions within this SSE were neither nosocomial nor related to the putative index case.

The index case presented to the hospital with heart failure and later transmitted the virus to at least 3 persons before symptom start (patients 2, 3, 8 and possibly patient 9), which accounts for approximately half of the infected in the cluster. Silent spreading of SARS-CoV-2, or pre-symptomatic transmission, has been reported during the pandemic in February 2020. As the estimated serial interval of COVID-19 is shorter or close to its median incubation period, a significant proportion of secondary transmission may occur prior to disease onset. This phenomenon could be due to the high level of virus shedding in the upper respiratory tract during the pre-symptomatic period of the patients with COVID-19. Likewise, a contact tracing study by Taiwan CDC found that the transmissibility of SARS-CoV-2 was high before and immediately after symptom onset. Consequently, symptom-driven surveillance alone would miss asymptomatic cases and was not sufficient to control the spreading of COVID-19 in healthcare settings. The containment of the spreading of SARS-CoV-2 in the hospital heavily relied on rapid identification of the SSE and response, based on our understanding on the transmission dynamics associated with the virus.

COVID-19 can cause cardiac complications, including myocardial injury, heart failure, and arrhythmia. In particular, patients with heart failure are at increased risk for severe disease caused by SARS-CoV-2. The respiratory symptoms could become more severe when patients had chronic cardiovascular diseases, which might be associated with an increased level of angiotensin-converting enzyme 2 expression. The index patient of our cluster had coronary artery disease and myocardial infarction 1 year before admission, which may make the patient more vulnerable to myocardial injury and cytokine storm of COVID-19. In accordance with our observation, a high prevalence of cardiovascular disease associated with COVID-19 was reported; up to 22% of critically ill patients experienced myocardial injury from COVID-19. Patients with concomitant chronic cardiovascular disease and COVID-19 usually showed a worse in-hospital outcome. Respiratory symptoms of COVID-19 could be confused with symptoms attributed to heart failure, which might lead to more droplets, thereby causing a superspreading event. Our study suggests that particular attention should be paid to patients with cardiovascular disease during the pandemic of COVID-19.

We noticed that the index case was asked to wear surgical mask after admission according to our policy but frequently took it off because of respiratory distress caused by heart failure. In Asian countries, facemask wearing is a common practice among people who get sick and visit the hospital. Taiwan CDC has enforced compulsory facemask policies for the people taking public transit or visiting the hospital since COVID-19 pandemic occurred. Although there is no evidence to support that wearing a facemask could reduce the risk of transmission of COVID-19, facemasks are commonly used as part of droplet precautions when caring for patients with respiratory symptoms. It was confirmed that facemask wearing can reduce the virions of seasonal human coronavirus in aerosols, with a trend toward reduced detection of the virus in respiratory droplets. Therefore, use of facemask may reduce the viral shedding and prevent transmission of COVID-19 by the infected people, whether they are symptomatic or not. As SARS-CoV-2 can be transmitted asymptomatically or pre-symptomatically, hospital transmission can be reduced if all patients, visitors, and HCW wear facemasks in the hospital during the pandemic.

Environmental contamination by droplets or fomite was confirmed in the room where the patient has stayed. Nursing cares, with or without AGP, carried opportunities for droplet transmission or fomite transmission by close contact. Although patient 5 (a nurse practitioner) has cared patient 1 for only a short period of time, she might be infected through droplets or aerosol emission generated by the swabbing procedure for RIDT on February 24. Furthermore, two other nurses (patients 3 and 4) have cared the patient for only one shift. It remains intriguing that other nurses in the ward 5C, who were on regular shifts caring the patient for days, were not infected. Moreover, we did not identify direct exposure between the index case and patients 7 and 8. Based on the available information and evidence, we concluded that patients 7 and 8 were infected by fomite transmission. Since SARS-CoV-2 remains infectious in aerosols for hours and on surfaces for days, our findings indicate that pre-symptomatic transmission of SARS-CoV-2 through fomite or aerosols is of concern in crowded hospital settings.

Our study has some limitation. Responding to the outbreak, environmental cleansing was performed immediately after the identification of the index case such that public areas in the ward 5C were not sampled. However, the sampling of the surfaces in the public areas including family lounge, nurse’s station, and staff office, was negative for the virus after cleaning. The viral source of the index case was not identified. We acknowledged that delayed recognition of the index case is one reason for a super-spreading event to occur. The incubation period of COVID is known to be two to 14 days, though symptoms typically appear within five days after exposure. In the investigation, the index case revealed significant fever and respiratory symptoms 9 days after admission. COVID
infection was confirmed early when full-blown covid symptoms appeared. Therefore, prevention of transmission relies on quickly recognizing and identifying the infected cases and associated SSEs in the hospital settings. Although the environmental survey was limited to the room in which the index case stayed, our results support that fomite transmission and asymptomatic transmission are both important modes of transmission for the SSE in our hospital.

Conclusions

This is a detailed report and analysis of an SSE of COVID-19 in a hospital setting. This hospital cluster was characterized by non-specific symptoms and heart failure of the index patient, pre-symptomatic transmission, mild symptoms in the infected healthcare workers, evidence of environmental contamination, and timely response of the hospital to this outbreak. Rapid response and advance deployment of multi-level protection did mitigate the COVID-19 outbreak to one generation of transmission, significantly reducing its impact on the healthcare system. The study showed that the SSE is the combined result of multiple contributing factors including host factors, transmissibility of the virus, environment, and multiple modes of transmission. The study advanced our understanding on the superspreading event of SARS-CoV-2 and the way to stop its spread in the healthcare setting. Early recognition of the index case and prompt multidisciplinary interventions are key to mitigating COVID-19 transmission and preventing an SSE to occur.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board (202000853BO), Chang Gung Memorial Hospital.

Declaration of competing interest

The authors declare no conflicts of interest.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.07.006.