Journal of the Formosan Medical Association 121 (2022) 81—88

Available online at www.sciencedirect.com

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journal homepage: www.jfma-online.com

Original Article

The occurrence of and risk factors for developing acute critical illness during quarantine as a response to the COVID-19 pandemic

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Received 13 August 2020; received in revised form 16 November 2020; accepted 13 January 2021

KEYWORDS
Quarantine ward;
COVID-19;
Duration of quarantine (DOQ);
Acute critical illness;
Bedridden status

Background/Purpose: Early detection and timely quarantine measures are necessary to control disease spread and prevent nosocomial outbreaks of Coronavirus disease 2019 (COVID-19). In this study, we aimed to investigate the impact of a quarantine strategy on patient safety and quality of care.
Methods: This retrospective cohort study enrolled patients admitted to the quarantine ward in a tertiary hospital in southern Taiwan. The incidence and causes of acute critical illness, including clinical deterioration and unexpected complications during the quarantine period, were reviewed. Further investigation was performed to identify risk factors for acute critical illness during quarantine.
Results: Of 320 patients admitted to the quarantine ward, more than two-thirds were elderly, and 37.8% were bedridden. During the quarantine period, 68 (21.2%) developed acute critical illness, which more commonly occurred among patients older than 80 years and with a bedridden status, nasogastric tube feeding, or dyspnea symptoms. Bedridden status was an independent predictor of acute critical illness. Through optimization of sampling for COVID-19 and laboratory schedules, both the duration of quarantine and the proportion of acute critical illness among bedridden patients during quarantine exhibited a decreasing trend. There was no COVID-19 nosocomial transmission during the study period.
Conclusion: The quarantine ward is a key measure to prevent nosocomial transmission of COVID-19 but may carry a potential negative impact on patient care and safety. For patients with multiple comorbidities and a bedridden status, healthcare workers should remain alert to rapid deterioration and unexpected adverse events during quarantine.

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https://doi.org/10.1016/j.jfma.2021.01.013

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing global pandemic.[1,2] In response to the pandemic, the Central Epidemic Command Center (CECC) in Taiwan and the Taiwan Centers for Disease Control (TCDC) have taken steps to prevent the spread of COVID-19 in the country and have established guidelines for large-scale public gatherings,[3] clinical management,[4] and infection prevention. The stringency of border quarantine measures was enhanced, including 14-day home quarantine for any arrivals regardless of symptoms.[5] To minimize the risk of any community or hospital outbreak, the CECC has enhanced the community surveillance system since mid-February; patients with unresolved pneumonia or without specific microbiological evidence were recommended to quarantine for COVID-19 surveillance even without history of travel, occupation, cluster, or contact (TOCC).[6] Accordingly, these patients should be isolated in a single-patient room, with droplet and contact precautions. To protect both patients and healthcare workers (HCWs), various policies and measures of infection control have been developed. The respiratory surveillance ward system in Singapore has been proven to stop the spread of COVID-19 in the hospital and has demonstrated the benefits of isolation.[7] However, single-room isolation may hinder patient visibility[8] and may impede timely recognition of clinical deterioration. In addition, preparing personal protective equipment (PPE) may delay immediate response to unexpected events. We share the experience in our quarantine ward and assess the implications for patient safety under the strategy of COVID-19 surveillance.

Material and methods

Study design and setting

Based on recommendations by the CECC,[9] the strategy of managing a quarantine ward was implemented at National Cheng Kung University Hospital (NCKUH), a tertiary medical center in southern Taiwan. Patients with radiographic evidence of suspicious pulmonary infiltrates and symptoms of fever, dyspnea, or cough were admitted to the quarantine ward. If presenting with critical illness when arriving at the emergency room, patients would be transferred to the intensive care unit. The quarantine process is illustrated in Fig. 1. The quarantine ward, which began to operate on March 9, 2020, was composed of 10 single rooms with personal bathrooms inside. The patients were managed by pulmonologists or infectious disease specialists and were cared for with appropriate personal protective equipment (PPE). If necessary, hemodialysis therapy was performed within the quarantine ward. Respiratory specimens (namely, sputum samples or nasopharyngeal swabs) were collected for SARS-CoV-2 RNA detection using real-time reverse-transcription polymerase chain reaction (RT-PCR) for the E/RdRp1/RdRp2/N genes.[10] Multiplex PCR for rapid screening of other common respiratory pathogens (including adenovirus, human rhinovirus/enterovirus, influenza virus A, influenza virus B, influenza virus A/H1, influenza virus A/H1 **(novel)** 2009, influenza virus A/H3, respiratory syncytial virus, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 4, human metapneumovirus, coronavirus 229E, coronavirus HKU1, coronavirus OC43, coronavirus NL63, *Chlamydia pneumoniae*, *Bordetella pertussis*, *Bordetella parapertussis*, *Mycoplasma pneumoniae*) was also performed for most patients admitted to the quarantine ward (Biofire Filmarray RP panel, bioMérieux SA, France).[11]

Patient isolation was discontinued if results for the detection of SARS-CoV-2 RNA from at least two consecutive respiratory specimens collected ≥12 h apart (total of two negative specimens) were negative or if there was one negative result of SARS-CoV-2 RNA plus evidence of an alternative etiology (such as positive blood culture results, *Mycoplasma* IgM positivity, or other pathogens detected by multiplex PCR) at the same time that matched the patient's condition. Eventually, these patients were discharged or transferred to other ordinary wards for further inpatient care.

Participants

All patients who were admitted to the quarantine ward from March to May 2020 were eligible for inclusion. The study was approved by the NCKUH Institutional Review Board (B-BR-109-032).

Data collection

The electronic medical records and laboratory data for all the patients were thoroughly reviewed. Their clinical information was recorded in a standardized data collection form, including age, sex, site of care before admission, date of admission, initial clinical manifestations (such as fever, cough, or dyspnea), underlying disease (such as congestive heart failure, diabetes mellitus, structural lung disease, end-stage renal disease, solid-organ or hematologic malignancies), records of unstable conditions, and duration of quarantine (DOQ). Acute critical illness was defined as a rapid change in a patient's condition or an adverse event that occurred in the quarantine period and led to severe respiratory, cardiovascular or neurological derangement, combined with abnormal laboratory or physiological parameters. Examples of acute critical illness in our study included respiratory failure (with a PaO_2/FiO_2

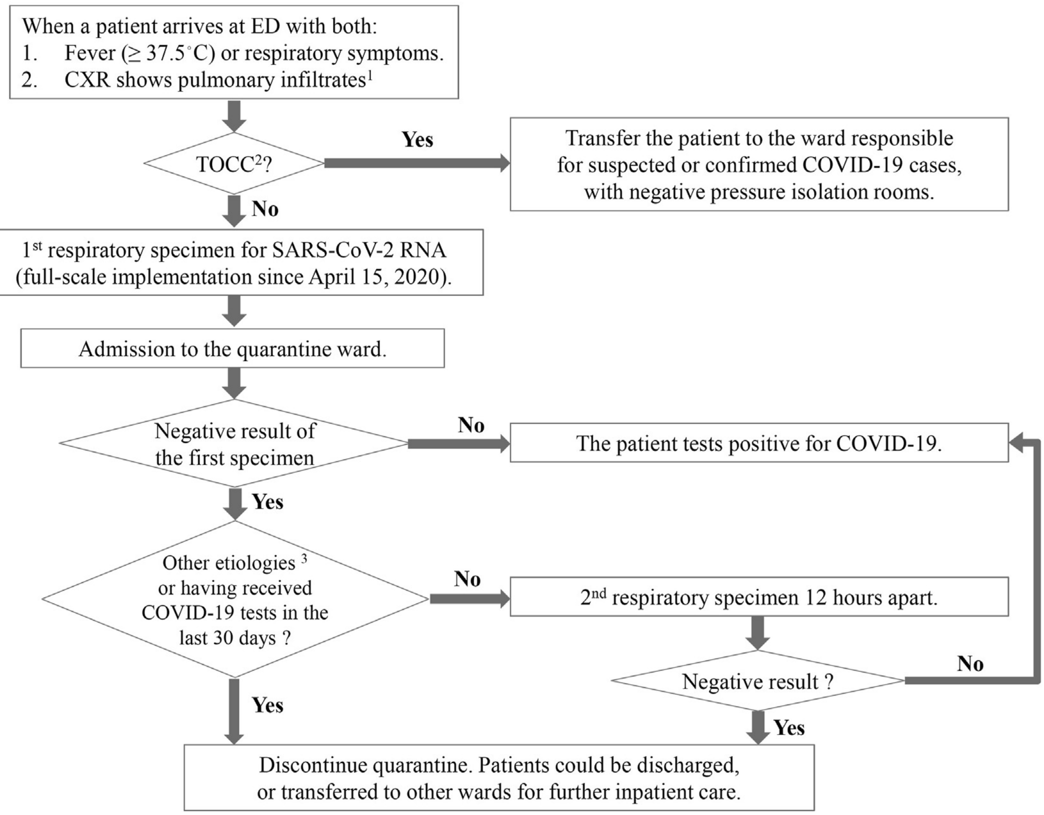


Figure 1 The algorithm for the management of quarantined patients at National Cheng Kung University Hospital. Footnotes: 1. Rapid interpretation of chest X-ray (CXR) by a radiologist, pulmonologist, or infectious disease specialist. 2. TOCC: recent history of traveling abroad or any record of occupation, cluster, or contact that may be associated with suspected or confirmed COVID-19 cases. 3. Other etiologies, such as bacteremia, urinary tract infection, or any pathogen other than SARS-CoV-2, that can explain the fever or respiratory symptoms of quarantined patients.

ratio $<$ 200), shock (systolic blood pressure $<$90 mmHg or mean arterial pressure $<$65 mmHg), uncontrolled hepatic encephalopathy, untreated acute myeloid leukemia, gastrointestinal bleeding, acute myocardial infarction, and cardiac arrest. We also determined the "reporting time", which reflects how long it takes to discontinue quarantine. The reporting time started upon the patient's arrival at the emergency department and ended when there were two negative results for SARS-CoV-2 RNA detection $\geq$12 h apart or there was one negative SARS-CoV-2 RNA result plus a positive result for other pathogens detected at the same time.

Measures and statistical analysis

Baseline demographic and clinical characteristics between patients with and without acute critical illness were analyzed using the Mann—Whitney U test for continuous nonparametric variables and the chi-square test for categorical variables. The association between candidate predictors and the risk of developing acute critical illness during quarantine was examined with the use of univariate and multivariable logistic regression and Cox proportional hazard regression (after ascertaining no violation of the assumption of proportional hazard by the Shoenfeld test). The median and mean "reporting time" and DOQ of all quarantined patients were also evaluated. A *p* value of less than 0.05 was considered to indicate statistical significance. Moreover, to determine the potential influence of a hypothetically unidentified confounder on the multivariable logistic regression models, sensitivity analysis was carried out using the R packages "survival" and "obsSens". Except for the sensitivity analysis, which was conducted using R (Version 3.6.1), all statistical analyses were performed using the statistical software IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., USA). Graphs were plotted using MedCal (Version 16.8.4, MedCal Software, Belgium) and GraphPad Prism (Version 8.0.0, GraphPad Software, Inc., USA).

Results

During the study period, 320 patients were admitted to the quarantine ward for surveillance of COVID-19. The clinical characteristics of these 320 quarantined patients are shown in Table 1. The median DOQ and the "reporting time" of all these patients were 23.99 (interquartile range, 20.52—27.79) hours and 27.90 (23.61—35.99) hours, respectively. Acute critical illness developed in 68 patients (21.3%) during the period of quarantine, including 38 (14.1%) with respiratory failure (with a PaO_2/FiO_2 ratio $<$ 200), 12 (3.8%) with shock, and 7 (2.2%) with

Table 1 Baseline characteristics and quarantine-related parameters and events among 320 patients admitted to the quarantine ward, as grouped into patients with and without acute critical illness during the quarantine.[a]

	In-quarantine acute critical illness (n = 68)	Without acute critical illness (n = 252)	*P* value
Age, years	82.5 (69.4–88.8)	71.7 (57.3–81.8)	<0.001
Age < 18	0 (0)	8 (3.2)	
18 ≤ age < 65	9 (13.2)	82 (32.5)	
65 ≤ age < 80	21 (30.9)	83 (32.9)	
Age ≥ 80	38 (55.9)	79 (31.3)	
Male sex	51 (75)	163 (64.7)	0.109
Physical status upon admission			
Nursing home resident	13 (19.1)	36 (14.3)	0.326
Bedridden status	42 (61.8)	79 (31.3)	<0.001
Long-term nasogastric tube feeding	27 (39.7)	57 (22.6)	0.004
Presence of pressure sores	48 (70.6)	119 (47.2)	0.001
Initial clinical manifestations			
Fever	57 (83.8)	205 (81.3)	0.638
Dyspnea	50 (73.5)	110 (43.7)	<0.001
Vomiting	4 (5.9)	19 (7.5)	0.639
Cough	34 (50)	148 (58.7)	0.197
Comorbidity			
Congestive heart failure	11 (16.2)	42 (16.7)	0.923
Recurrent pneumonia	21 (30.9)	52 (20.6)	0.074
Chronic obstructive pulmonary disease	5 (7.4)	19 (7.5)	0.959
Bronchial asthma	0 (0)	7 (2.8)	0.165
Bronchiectasis	2 (2.9)	11 (4.4)	0.598
Previous pulmonary tuberculosis	4 (5.9)	5 (2.0)	0.084
Diabetes mellitus	25 (36.8)	85 (33.7)	0.640
Chronic kidney disease	22 (32.3)	73 (29.0)	0.588
Long-term dialysis therapy	7 (10.2)	21 (8.3)	0.612
Previous cerebrovascular accident	16 (23.5)	60 (23.8)	0.962
Solid organ malignancy	25 (36.8)	71 (28.2)	0.170
Lung metastasis	4 (5.9)	23 (9.1)	0.393
Hematologic malignancies	2 (2.9)	4 (1.6)	0.465
Laboratory results			
White blood cell count, median, 10^9/L	10.4 (8.07–14.38)	10.2 (7.15–13.08)	0.294
Neutrophil-lymphocyte ratio	10.17 (5.18–21.29)	6.83 (4.17–12.98)	0.026
C-reactive protein, mg/L	95.9 (63.6–182.2) (n = 21)	43.1 (12.25–96.3) (n = 77)	0.002
Procalcitonin, ng/mL	1.32 (0.37–18.11) (n = 11)	0.27 (0.13–1.14) (n = 30)	0.064
Duration of quarantine (DOQ), hours			
March 9–April 14, 2020	25.04 (21.73–29.14)	25.13 (22.28–29.19)	0.650
April 15–May 10, 2020	21.24 (15.97–24.86)	21.92 (19.52–25.95)	0.257
Reporting time, hours			
March 9–April 14, 2020	29.35 (25.61–38.27)	29.17 (24.39–41.21)	0.831
April 15–May 10, 2020	28.28 (21.24–35.65)	24.82 (20.65–28.56)	0.145
Cause of in-quarantine acute critical illness			
Respiratory failure	38	–	
Shock	12	–	
Respiratory failure and shock	7		
Acute myeloid leukemia with altered mental status	3	–	
Hepatic encephalopathy	1	–	
Gastrointestinal bleeding	1		
Acute heart failure	1	–	
ST-elevation myocardial infarction	2	–	
Pulmonary embolism	1	–	
Sudden death	2	–	

[a] Data are expressed as the case number (%). Categorical data are presented as counts and percentages and continuous variables as the means (±standard deviation) or median (interquartile range) if non-normally distributed.

combined respiratory failure and shock. Other etiologies of acute critical illness are summarized in Table 1, including acute myeloid leukemia with altered mental status, hepatic encephalopathy, massive gastrointestinal bleeding, acute heart failure, pulmonary embolism, and ST-elevation myocardial infarction requiring emergent coronary intervention. Of note, cardiac arrest occurred in two patients (0.6%). In total, five patients (1.6%) needed to be transferred to the intensive care unit during their quarantine period. Two hundred and twenty-one (69.1%) of the quarantine patients were 65 years old or older. Notably, 117 (36.6%) patients were aged 80 years or above. One hundred and twenty-one patients (37.8%) were bedridden and needed intensive nursing care. Compared with those without acute critical illness, patients with acute critical illness had a higher neutrophil-lymphocyte ratio ($P = 0.026$) and higher serum levels of C-reactive protein ($P = 0.002$) and procalcitonin ($P = 0.064$; Table 1).

Etiologies other than COVID-19 that could explain fever or respiratory symptoms in the 320 patients in the quarantine ward are provided in Table 2. Of 287 patients for whom multiplex PCR for respiratory pathogens was carried out, rapid identification of alternative pathogens was reported for 19 (6.6%), which helped shorten the quarantine period of these patients. Four patients were newly diagnosed with acute myeloid leukemia (AML) based on peripheral blood smear and were admitted to the quarantine ward because of persistent fever, respiratory symptoms, and unspecified pulmonary infiltrates on their chest radiographs. One of them died due to intracerebral hemorrhage, a complication of untreated AML, on the fifth day of hospitalization. The rates of old age, bedridden status, presence of pressure sores, and nasogastric tube feeding were significantly higher among cases that progressed to acute critical illness than those without acute critical illness; dyspnea as the initial presentation was also more common among patients with acute critical illness (Table 1). Although age, bedridden status, long-term nasogastric feeding, and the presence of pressure sores were associated with a significantly increased risk of acute critical illness in univariate logistic regression analysis, only bedridden status remained a significant predictor in multivariable analysis, with the odds ratio 2.29 (95% confidence interval, 1.14 to 4.60; $P = 0.02$; Fig. 2A). When taken the effect of quarantine time into consideration, univariate and multivariable Cox proportional hazard regression analysis yielded concordant and supportive results, such that patients with bedridden status exhibited a significantly increased risk of developing acute critical illness (adjusted hazard ratio 2.05; 95% confidence interval, 1.13 to 3.72, $P = 0.018$; Fig. 2B), and therefore a significantly reduction in the probability of event-free survival (Fig. 3). Sensitivity analysis was also performed to evaluate the potential effect of a potentially unmeasured confounder; the results also supported bedridden status as a predictor of in-quarantine acute critical illness, as illustrated in the Supplementary Fig. 1. Moreover, shortening the length of quarantine might have reduced the risk of acute critical illness among bedridden patients. Following the adjustments in the timing of the first nasopharyngeal sampling for the COVID-19 testing and the optimization of the RT-PCR laboratory schedule, which became effective on April 15, the median DOQ since decreased by a median of 3.2 h compared with that before April 15 ($P < 0.001$, Fig. 4). Concurrently, the proportion of acute critical illness among bedridden patients in quarantine after April 15 also exhibited a decreasing trend compared with that before April 15 (28.9% vs 38.2%, $P = 0.301$).

Most of the patients (317 of 320 patients, 99.1%) were in desperate need of further inpatient care after their quarantine was discontinued. However, none of the 320 patients tested positive for SARS-CoV-2 RNA within 30 days of follow-up since being admitted for quarantine.

Table 2 Etiologies other than COVID-19 that could explain fever or respiratory symptoms in 320 patients in the quarantine ward.[a]

Urinary tract infection	20 (6.3)
Bacteremia	19 (5.9)
Infective endocarditis	1 (0.3)
Septic arthritis	1 (0.3)
Cellulitis	2 (0.6)
Shigellosis	1 (0.3)
Mumps	1 (0.3)
Positive results of multiplex PCR[b]	19 (6.6)
Other respiratory pathogens	(n = 287)
Mycobacterium tuberculosis	1 (0.3)
Mycobacterium kansasii	1 (0.3)
Mycobacterium avium complex	2 (0.6)
Aspergillus[c]	3 (0.9)
Pneumocystis jirovecii[d]	1 (0.3)
Mycoplasma pneumoniae[e]	7 (2.2)
Noninfectious etiologies	
Acute pulmonary edema	15 (4.7)
Acute myeloid leukemia	4 (1.2)
Acute myocardial infarction	2 (0.6)
Acute stroke	1 (0.3)

[a] Data are expressed as the case number (%).
[b] PCR, polymerase chain reaction.
[c] Diagnosed by suspicious pulmonary infiltrates and galactomannan antigen testing of bronchoalveolar lavage.
[d] Diagnosed by suspicious pulmonary infiltrates and PCR of sputum or bronchoalveolar lavage for *Pneumocystis jirovecii*.
[e] Diagnosed by suspicious pulmonary infiltrates and by either serum *Mycoplasma* IgM or *Mycoplasma pneumoniae* positivity using the Filmarray respiratory panel.

Discussion

To the best of our knowledge, this is the first report to evaluate the quality of patient care using a quarantine strategy among patients in isolation for COVID-19 during the global outbreak. Our study shows that patients who developed COVID-19-unrelated acute critical illness during quarantine were more likely than those without acute critical illness to have an older age, a bedridden status, and a nasogastric tube feeding. Baseline bedridden status, in particular, stands out as a predictor for the risk of in-quarantine acute critical illness. In general, clinical assessment, interventions and escalation of care should be unanimous for all patients irrespective of isolation status.

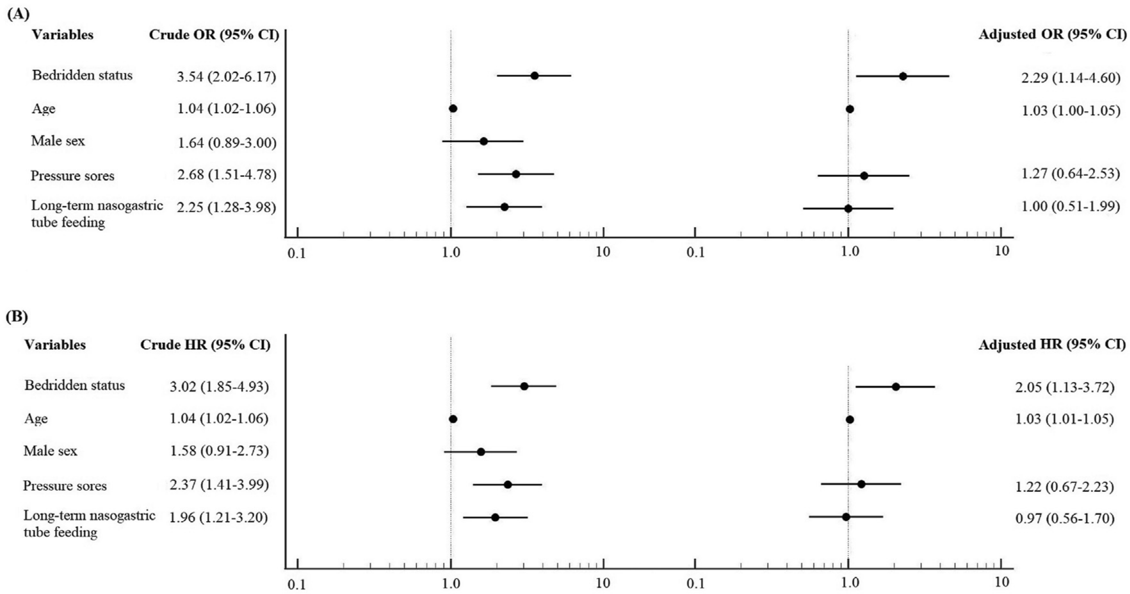


Figure 2 The Forest plots displaying the results of logistic regression (A) and Cox proportional hazard regression (B) analyses on candidate risk factors for acute critical illness during quarantine period. Footnotes: *OR, odds ration. HR, hazard ratio. CI, confidence interval.

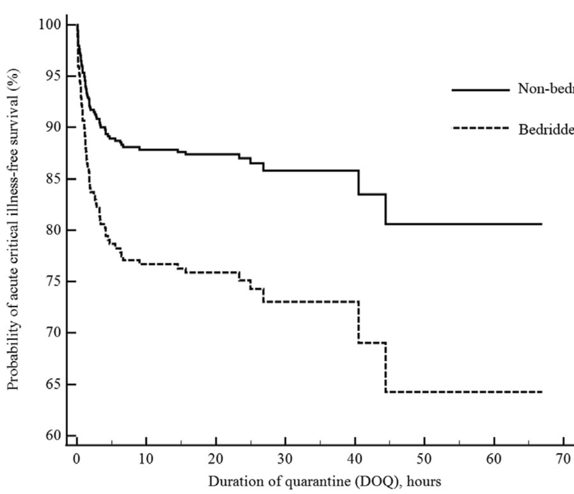
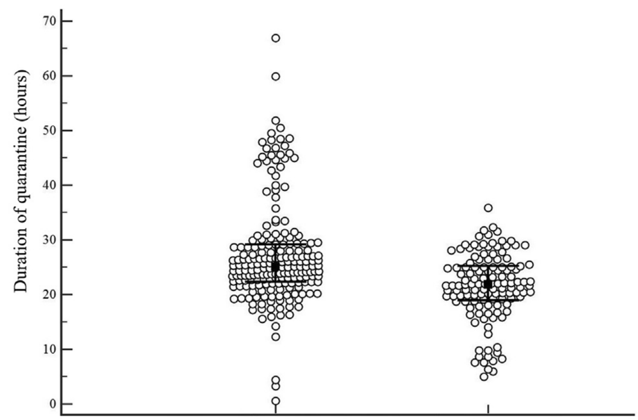


Figure 3 Multivariate Cox-proportional hazards model of acute critical illness-free survival in bedridden *versus* non-bedridden patient groups during the quarantine period.



The admission day	Before April 15 n = 198	After April 15 n = 122	*p* value
Duration of quarantine in hours (median, IQR)	25.1 (22.2–29.2)	21.9 (19.0–25.3)	<0.001
The rate of acute critical illness among bedridden patients	38.2%	28.9%	0.301

Figure 4 Comparison of the duration of quarantine (DOQ)* of 329 admissions to the quarantine ward before and after April 15, 2020. Footnotes: *DOQ is presented as the median (interquartile range). Statistics were performed with the Mann–Whitney U test for continuous nonparametric variables and with the chi-square test for categorical variables. A two-tailed *P* value of less than 0.05 was statistically significant.

Although there is no evidence to date suggesting that patients in isolation are more likely to develop clinical deterioration or unexpected adverse events,[8] it is still an essential responsibility of HCWs to recognize early and respond promptly to the first sign of clinical deterioration, even when confronted with all the precautions and inconveniences relating to quarantine,[12] particularly for at-risk patients, as implicated by the findings of our present study.

Recent studies have reported several COVID-19 outbreaks in hospitals or long-term care facilities (LTCFs) associated with unfavorable outcomes.[13–15] To prevent outbreaks in hospitals and in community settings, the quarantine policy was advised to enhance community surveillance of COVID-19. Delgado et al. found that the presence of respiratory tract infections is a predictor of unplanned ICU admission, and pre-existing comorbidities and age were also pertinent factors.[16] In our cohort, most patients had airway symptoms associated with radiologic evidence of pulmonary infiltrates and were elderly (the median age was 74.15 years), and the existing comorbidities of these patients increased the challenge to avoid adverse events in progression, such as in-hospital patient falls or sudden death.

It is also difficult to prevent the spread of a dangerous and highly contagious infection while minimizing compromise of patient safety and the quality of general care.[17] The PPE for suspected COVID-19 cases is more complicated than that for simple contact isolation and is associated with higher monetary costs; moreover, physicians and nurses must spend a considerable amount of time wearing and removing PPE.[18] The literature has shown that isolated patients are less likely to be examined by physicians.[19,20] Overall, access to quarantined patients is more difficult and may result in delay of emergent interventions (e.g., cardiopulmonary resuscitation or intubation) and discourage frequent care (e.g., changing position and chest physiotherapies for bedridden patients). In our study, advanced age, nasogastric tube feeding, pressure sores, and symptom of dyspnea were well-established predictors of poor prognosis for patients with pneumonia. Because bedridden patients are physically dependent and are unable to perform self-care, the rate of bedridden status among critically ill patients will undoubtedly be higher than among those not in a critical condition. Patients with these poor prognostic factors are at an enhanced risk of rapid deterioration. In our cohort, more than one-third of the patients were aged 80 years and older. Prior research has demonstrated that excessive containment may result in adverse psychological stress, such as depression, delirium, and anxiety, among isolated, elderly patients.[19,21,22] In addition, patients and their family members may hesitate to seek medical aid because of the threat of quarantine.[23]

The diagnosis of COVID-19 was based on PCR testing for SARS-CoV-2, which may be dependent on the quality and type of respiratory tract sample. Considering that quarantine may impair adequate monitoring and timely management of these patients, it is therefore important and beneficial to shorten the duration of quarantine whenever appropriate. The interval of two consecutive SARS-CoV-2 RNA detections in our cohort was at least 12 h apart. Thus, the mean reporting time was 1.26 days, and the mean DOQ was 1.04 days, both of which were much shorter than the times reported by the respiratory surveillance ward in Singapore (1.89 days),[7] without missing a diagnosis of COVID-19. However, there is no strong evidence showing that shortening the period between two respiratory specimens will decrease the sensitivity of COVID-19 testing.

There are some limitations of this study. This study was performed in a tertiary medical center; therefore, selection bias was inevitable. Moreover, this was a retrospective investigation, and it was not possible to include a parallel control group (consisting of patients with similar presentation but without quarantine) for comparison, as this would be a major violation of the policy of TCDC to contain the pandemic. The ultimate goal of this study was not to find predictors of unexpected adverse events but to disclose the potentially deleterious impact of quarantine on elderly and bedridden patients as well as the importance of maintaining a balance between patient safety and infection control in response to the COVID-19 global pandemic.

In conclusion, with a relatively low prevalence of COVID-19 in the community in Taiwan, we established a quarantine ward for surveillance and took measures to exclude COVID-19 while keeping the DOQ and the reporting time as short as possible. When confronted with patients with multiple comorbidities, particularly those with bedridden status, HCWs should be aware of critical or unexpected events during quarantine.

Financial support

This study was supported by National Cheng Kung University Hospital, Tainan, Taiwan, under grant NCKUH-11002055.

Transparency declarations

None to declare.

Author contributions

CS Tsai, NY Lee, and WC Ko conceived of the study. CS Tsai, TH Huang, PL Su, CZ Chen, and CW Chen provided the data collection. NY Lee, TH Huang, PL Su, and CS Tsai analyzed the data. NY Lee and CS Tsai prepared the manuscript. All authors reviewed and edited the manuscript.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2021.01.013.

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