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Adverse Events During Early Mobility Therapy are not Associated with Poor Prognosis in Patients with COVID-19-Related Acute Respiratory Failure

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Title page

Title:

Adverse Events During Early Mobility Therapy are not Associated with Poor Prognosis in Patients with COVID-19-Related Acute Respiratory Failure

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Authors' contributions
Nobuaki Hamazaki: study concept and design, data acquisition and analysis, and drafting of the article. Tomotaka Koike: study concept and data analysis. Hidenori Kariya: data acquisition and interpretation. Shuken Kobayashi: data acquisition and interpretation. Kazumasa Miida: data acquisition. Michinari Fukuda: article drafting and study supervision. All authors: critical revision, preparation, and final approval of manuscripts; all agree to be accountable for all aspects of the work, ensuring its integrity and accuracy.

This study was performed in an intensive care unit of Kitasato University Hospital, Japan.

The results presented in this study have not been previously presented.

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Introduction

The coronavirus disease 2019 (COVID-19) often causes hypoxemic respiratory failure and acute respiratory distress syndrome[1]. As severe respiratory failure subsequently causes physical impairment, including intensive care unit (ICU)-acquired weakness[2], early mobility therapy (EMT) is believed to improve the clinical outcomes[3]. On the other hand, severe hypoxemia and respiratory distress, which are hallmarks of the acute phase of COVID-19[4], may cause difficulties and barriers in implementing early rehabilitation. However, despite the several recommendations for EMT management and strategy procedures for COVID-19-related acute respiratory failure (C-ARF)[5,6], studies on the effectiveness and safety of EMT in ICUs are rare in these patients. In this report, we aimed to evaluate the incidence of adverse events during EMT in ICU as well as the correlation of EMT with the prognosis of patients with C-ARF.

Methods

This single-center prospective study enrolled consecutive patients who were admitted in the ICU of Kitasato University Hospital for C-ARF treatment from October 1, 2020, to September 30, 2021. Patient characteristics, including biomarkers and severity scores, were collected on patient admission, while information regarding respiratory therapy and rehabilitation sessions was obtained during intensive care and clinical course. This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Kitasato University (KMEO B20-360). Since all outcome measures are collected as a part of routine care, we obtained oral informed consent from all participants or their substitutes and made the information on the research public by opt-out[7].

The patients were assessed by an ICU team consisting of medical doctors, nurses, and physiotherapists within 24 h after being admitted to the ICU to determine whether rehabilitation could be initiated. EMT, particularly out-of-bed mobilization, was carried out based on specific medical recommendations[5,6]. EMT protocol consisted of monitoring of clinical conditions, evaluation of muscle strength by the Medical Research Council (MRC) scale, and prevention of disability by active limb exercises and out of bed exercise[6]. The level of out of bed exercise was assessed with the ICU mobility scale (ICU-MS) and determined based on the patient MRC scale[8]. Each EMT session was implemented by ICU nurses

and one of four physiotherapists who have specialized knowledge about intensive care. During all EMT sessions, the following adverse events stated in the global consensus were recorded: worsening dyspnea, respiratory rate > 30 beats/min, percutaneous oxygen saturation (SpO_2) < 93% on oxygen therapy, requirement of a fraction of inspired oxygen (F_IO_2) > 50% or positive end-expiratory pressure > 10 cmH_2O, respiratory distress, arterial hypertension or hypotension, bradycardia or tachycardia, intercurrent arrhythmia, or shock[6].

The endpoints of the study were the seven-category ordinal scale one month after the ICU admission and the in-hospital all-cause death. The seven-category ordinal scale consisted of the following categories: 1, not hospitalized and with resumption of normal activities; 2, not hospitalized but was unable to resume normal activities; 3, hospitalized but did not require supplemental oxygen; 4, hospitalized and required supplemental oxygen; 5, hospitalized and required nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6, hospitalized and required ECMO, invasive mechanical ventilation, or both; and 7, death[9]. The time period for in-hospital death was calculated as the number of days from the ICU admission to the date of death.

Statistical analysis

The clinical characteristics of patients who had adverse events during EMT, patients without adverse events, and patients who did not receive EMT were compared using Mann-Whitney's *U*-test for continuous variables and Chi-square or Fisher's exact test for categorical variables, as appropriate. The correlation of EMT implementation and adverse events with the endpoints was also assessed using Jonckheere-Terpstra test and multiple regression analysis for the seven-category ordinal scale and Kaplan-Meier survival curve with log-rank test and multivariate Cox proportional hazard model for in-hospital death. Based on the sample size of endpoints in the analyses, age, gender, body mass index (BMI), history of diabetes, episode of sepsis, and use of mechanical ventilation in the ICU, C-reactive protein, lactate dehydrogenase, ferritin, and Acute Physiology and Chronic Health Assessment II (APACHE II) scores were used as covariates for multiple regression analysis, while APACHE II score was used as a covariate for the Cox hazard model.

Results

Among the 782 hospitalized patients with COVID-19, 105 patients with C-ARF were admitted to the ICU. Rehabilitation was initiated for all patients in the ICU, and 90 patients (85.7%) underwent EMT. In a total of 315 EMT sessions, adverse events during mobilization were documented in 142 sessions (451 times/1000 sessions) of 53 patients (58.9%). The following events were more frequently noted: 98 sessions with $SpO_2 < 93\%$, 73 with worsening dyspnea, 56 with respiratory rate > 30 beats/min, and 25 with hypotension, while no serious events were documented. Two or more types of adverse events simultaneously occurred in 86 EMT sessions. No significant differences in clinical features were observed between with or without adverse events during EMT (Table 1). Conversely, patients without EMT had significantly older age, lower BMI, higher prevalence of sepsis in the ICU, higher use of noradrenaline agent and mechanical ventilation, and higher APACHE II and SOFA scores as compared to patients who underwent EMT with adverse events during mobilization (Table 1). Based on the mobility levels of 90 patients with EMT upon discharge from the ICU, 24 patients could sit on chairs, 30 could stand or march, and 36 could walk, without statistical differences in the ICU-MS between with or without adverse events ($P = 0.829$).

The presence of adverse events during mobilization was not associated with poor clinical outcomes in the seven-category ordinal scale, while patients who could not perform EMT had poor outcomes (Figure 1-a). The adjusted coefficients for the seven-category ordinal scale against EMT with adverse events were −0.29 (95% confidence interval [CI][3,6], −1.1 to 0.52; $P = 0.479$) for EMT without adverse events and 1.32 (95% CI, 0.25–2.37; $P = 0.016$) for non-EMT. During the median follow-up period of 18 days, 19 in-hospital deaths (18.3%) occurred. Figure 1-b shows the association between EMT implementation with or without adverse events and in-hospital mortality. No association between adverse events during mobilization and in-hospital death was consistently observed (log-rank: $P = 0.239$); however, non-EMT was associated with lower survival rates as compared with EMT with adverse events (log-rank: $P < 0.001$). Based on the presence of adverse events during EMT, the adjusted hazard ratios were 0.30 (95% CI, 0.04–2.41; $P = 0.259$) for EMT without adverse events and 5.34 (95% CI, 2.08–13.66; $P < 0.001$) for non-EMT.

Discussion

To our knowledge, this study is the first to reveal that patients with C-ARF during EMT in an ICU present a relatively high rate of non-serious adverse events despite the delayed initiation of mobilization in accordance to a recent study[10]. Nevertheless, in these patients, adverse events during EMT were not associated with poor clinical outcomes and higher in-hospital deaths. Therefore, the implementation of EMT may be a beneficial treatment for patients with C-ARF by controlling the risk of adverse events during mobilization.

The rate of adverse events during EMT in an ICU was reported to be lower than 10% in critical ill patients with acute respiratory failure[11]. The results confirmed that patients with C-ARF would likely present oxygen desaturation and tachypnea during EMT, although the exercise-induced oxygen desaturation was documented in survivors of COVID-19 after recovery from pneumonia[12]. A recent study, implementing a similar EMT procedure to our study, reported that deterioration during mobility therapy was associated with an increased length of hospital stay in patients with community-acquired pneumonia[13]. However, this association was not observed in our results with COVID-19 patients. The delayed initiation of EMT due to the instable conditions of patients with or without adverse events may be a cause of the differences in findings between the studies.

Several statements support the effectiveness of EMT for patients with COVID-19 to prevent physical dysfunction[3,6]. On the other hand, since the general conditions are unstable due to severe oxygenation disorders and "inflammatory storm" in the acute phase of C-ARF, a review mentions the doubts about the suitability of EMT[14]. In this study, we confirmed that although minor events during EMT were observed in high rates of participants, there were no serious complications. However, the patients who were not able to engage EMT had severer clinical conditions. A recent study reported the safety and usefulness of neuromuscular electrical stimulation in patients with severe COVID-19 who had difficulty with EMT due to unstable clinical conditions and ICU-acquired weakness[15]. Thus, it is considered to need the trial on optimal rehabilitation intervention for the patients with severe A-CRF who have unstable breathing during EMT.

Limitation

As this is an observational study, it is unclear whether EMT itself improved the patient outcomes. The

worse clinical condition of patients with non-EMT should also be considered in the interpretation of the results. The small sample size of the included patients should also be acknowledged as a limitation. Therefore, further interventional evaluation using additional samples to assess the effects of EMT on the clinical outcomes of patients with C-ARF is required.

Conclusions

Adverse events during the EMT are frequently observed without no-serious events in patients with C-ARF. Nevertheless, the adverse events during EMT implementation are not associated with poor outcomes in patients with C-ARF. These findings may be valuable in understanding and validating the EMT for patients with C-ARF to increase its risk management level and effectiveness.

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Figure Legend

Figure 1. Correlations between the implementation of early mobility therapy during mobilization with or without adverse events and the clinical outcomes

(a) Seven-category ordinal scale one month after ICU admission.

(b) Kaplan-Meier survival curves of the three groups based on the implementation of EMT with or without adverse events for in-hospital mortality. EMT with adverse events (green line) was not associated with higher in-hospital mortality compared to EMT without adverse events (red line).

EMT, early mobility therapy; ICU, intensive care unit.

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Table 1 Characteristics of patients who underwent EMT with and without adverse events and non-EMT patients

	Overall	Implementation of EMT n = 90		Non-EMT
	n = 105	Adverse events (+) n = 67	Adverse events (-) n = 23	n = 15
Age, y.o.	58 [48–73]	54 [47–70]	59 [50–70]	77 [63–81]**
Sex, n (%)				
Female	29 (27.6)	17 (25.4)	7 (30.4)	5 (33.3)
Male	76 (72.4)	50 (74.6)	16 (69.6)	10 (66.7)
BMI on admission (kg/m^2)	25.6 [23.6–29.8]	26.0 [23.8–29.9]	25.9 [24.0–32.8]	24.2 [22.6–26.1]*
Past history, n (%)				
Hypertension	46 (43.8)	27 (40.3)	11 (47.8)	8 (53.3)
Diabetes mellitus	44 (41.9)	27 (40.3)	7 (30.4)	10 (66.7)
Cardiovascular disease	14 (13.3)	9 (13.4)	2 (8.7)	3 (20.0)
Chronic kidney disease	5 (4.8)	3 (4.5)	1 (4.3)	1 (6.7)
COPD	5 (4.8)	4 (6.0)	1 (4.3)	0 (0.0)
Obesity	39 (37.1)	24 (35.8)	12 (52.2)	3 (20.0)
Current smoker, n (%)	11 (11.1)	8 (12.5)	1 (4.3)	2 (16.7)
Complications, n (%)				
Sepsis	26 (24.8)	14 (20.9)	3 (13.0)	9 (60.0)**
Viral pneumonia	31 (29.5)	19 (28.4)	4 (17.4)	8 (53.3)
Acute kidney injury	20 (19.0)	12 (17.9)	2 (8.7)	6 (40.0)
Pneumothorax	8 (7.6)	4 (6.0)	2 (8.7)	2 (13.3)
Delirium	16 (15.2)	9 (13.4)	5 (21.7)	2 (13.3)
ICU-AW	34 (32.4)	20 (29.9)	7 (30.4)	7 (46.7)
Medications, n (%)				
Dexamethasone	100 (95.2)	64 (95.5)	22 (95.7)	14 (93.3)
Remdesivir	82 (78.1)	52 (77.6)	20 (87.0)	10 (66.7)
Fentanyl	53 (50.5)	30 (44.8)	12 (52.2)	4 (26.7)
Midazolam	33 (31.4)	16 (23.9)	10 (43.5)	7 (46.7)
Propofol	42 (40.0)	23 (34.3)	11 (47.8)	8 (53.3)
Dexmedetomidine	84 (80.0)	52 (77.6)	20 (87.0)	12 (80.0)
Noradrenaline	34 (32.4)	18 (26.9)	7 (30.4)	9 (60.0)*
Respiratory management, n (%)				
Mechanical ventilation	49 (46.7)	26 (38.8)	12 (52.2)	11 (73.3)*
HFNC	83 (79.0)	58 (86.6)	20 (87.0)	5 (33.3)**
ECMO	12 (11.4)	6 (9.0)	3 (13.0)	3 (20.0)
CHDF	12 (11.4)	5 (7.5)	3 (13.0)	4 (26.7)
Prone positioning	54 (51.9)	39 (59.1)	9 (39.1)	6 (40.0)
Blood examination on admission				
Hemoglobin, g/dL	14.2 [12.8–15.3]	14.3 [12.9–15.5]	14.0 [13.3–14.8]	13.7 [12.4–15.6]
CRP, mg/dL	10.0 [6.8–14.9]	10.2 [7.2–14.8]	9.9 [5.9–16.5]	8.5 [7.0–11.2]
LDH, U/L	514 [418–674]	514 [414–670]	537 [429–656]	490 [431–664]
Ferritin, ng/mL	936 [494–1470]	970 [532–1485]	874 [511–1254]	479 [376–1358]
Creatinine, mg/dL	0.88 [0.74–1.24]	0.85 [0.71–1.18]	0.91 [0.76–1.14]	1.12 [0.82–1.77]
FDP, μg/mL	5.6 [4.4–8.2]	5.5 [4.4–8.4]	5.3 [4.2–6.8]	6.8 [5.2–9.3]
D-dimer, μg/mL	1.8 [1.4–2.8]	1.6 [1.4–2.9]	1.7 [1.3–2.3]	2.2 [1.8–3.8]
PaO_2, mm Hg	72.6 [59.4–89.1]	72.6 [63.0–85.8]	73.7 [59.1–95.2]	69.5 [47.6–80.6]
$PaCO_2$, mm Hg	34.1 [30.9–38.8]	34.2 [31.8–37.8]	32.7 [30.2–39.5]	34.3 [30.1–40.3]
APACHE II on admission	15 [12–24]	14 [12–20]	15 [9–24]	27 [20–31]**
SOFA score on admission	4 [3–7]	4 [3–5]	4 [3–8]	7 [6–8]**
PaO_2/F_IO_2 ratio on admission	174 [118–238]	158 [119–223]	181 [121–274]	223 [170–308]
Length of ICU stay, days	8 [4–15]	7 [5–14]	7 [2–13]	14 [10–23]**
Length of hospital stay, days	18 [12–26]	17 [13–25]	20 [12–29]	22 [16–26]

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Days from ICU admission to first mobilization, days	4 [2–10]	3 [2–8]	4 [1–11]	N.A.
Days from onset to first mobilization, days	13 [11–19]	12 [11–18]	13 [11–20]	N.A.
Mobilization during mechanical ventilation, n (%)	18 (35.3)	15 (53.6)	3 (25.0)	N.A.
Number of sessions of ICU rehabilitation	4 [2–8]	5 [3–8]	4 [2–10]	3 [1–6]*
Number of sessions of ICU mobility therapy	2 [1–4]	3 [2–5]	2 [2–3]	N.A.
Number of adverse events during ICU mobilization	1 [0–2]	2 [1–3]	N.A.	N.A.
MRC score at the first assessment	55 [39–58]	56 [42–60]	55 [41–60]	32 [24–41]**
Mobility scale during ICU	5 [1–8]	6 [3–8]	6 [4–8]	N.A.

Data, median [interquartile range].
*P <0.05; **P <0.01 versus EMT with adverse events.
APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CHDF, continuous hemodiafiltration; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; EMT, early mobility therapy; FDP, fibrin/fibrinogen degradation products; F_IO_2, fraction of inspired oxygen; HFNC, high flow nasal canula; ICU, intensive care unit; ICU-AW, ICU-acquired weakness; LDH, lactate dehydrogenase; MRC, Medical Research Council; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SOFA, sequential organ failure assessment.

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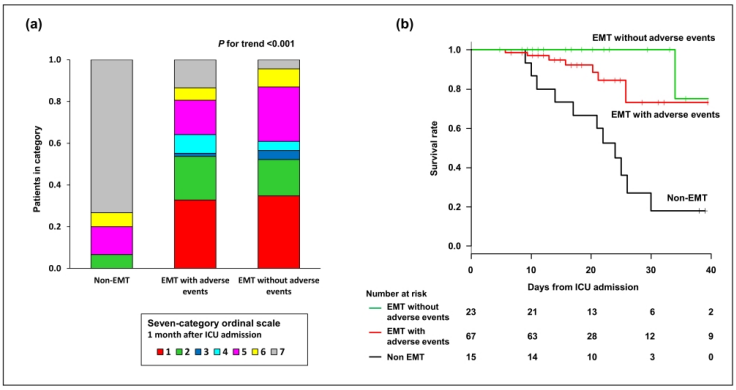

Figure 1

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