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ORIGINAL ARTICLE

Long-term Health-related Quality of Life and Physical Function of COVID-19 Survivors with ICU-acquired Weakness

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Objectives: This study examined the long-term health-related quality of life (HRQOL) and physical function of coronavirus 2019 (COVID-19) survivors diagnosed with intensive care unit-acquired weakness (ICU-AW). The correlation between muscle weakness at ICU discharge and HRQOL was assessed. **Methods:** A retrospective study was conducted on COVID-19 patients admitted to the ICU at Hyogo Medical University Hospital between January 2021 and November 2021. The HRQOL was evaluated using the SF-36 questionnaire, and physical function, including muscle strength assessed by the Medical Research Council Sum Score (MRC-SS), grip strength, and the 6-min walk distance (6MWD), were assessed 18 months after the onset. ICU-AW was diagnosed in patients with an MRC-SS of less than 48 at ICU discharge. We investigated the correlations between the MRC-SS at ICU discharge and the long-term clinical outcomes. **Results:** We included 26 patients, with 13 having ICU-AW. In the long-term follow-up, the ICU-AW group had significantly lower scores than the no ICU-AW group in the SF-36 subscales such as Physical Functioning (PF), Role Limitation-Physical (RP), Bodily Pain (BP), Vitality (VT), Social Functioning (SF), and Role Limitation-Emotional (RE), as well as in the Physical Component Summary Score (PCS). The muscle strength was also decreased in the ICU-AW group. The MRC-SS at ICU discharge was positively correlated with PF, RP, BP, SF, RE, and PCS in SF-36 at the 18-month follow-up. **Conclusions:** COVID-19 survivors with ICU-AW experienced a long-term decline in HRQOL, and muscle weakness at ICU discharge was correlated with the long-term HRQOL.

Key Words: coronavirus disease 2019; HRQOL; MRC-SS; muscle weakness

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been a major concern in clinical medicine since November 2019. In Japan, the total number of deaths caused by this pandemic through to February 2023 exceeds 70,000.[1] Besides its mortality, the sequelae of this disease affecting physical and mental health have been widely reported.[2,3] Especially in severe cases treated in the intensive care unit (ICU), various sequelae may persist 6 months after onset.[4] Among these, muscle weakness has been particularly common in critical cases.[4] The causes of muscle weakness associated with COVID-19 include direct invasion of the virus into muscles, muscle atrophy as a result of inactivity and malnutrition, and the degeneration of muscles or nerve axons caused by inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha.[5] Furthermore, critical COVID-19 patients are at high risk of ICU-acquired weakness (ICU-AW) because of factors that include prolonged ventilator management, deep sedation, steroid use, and an increased susceptibility to diabetes mellitus.[6]

Previous studies have consistently demonstrated that non-

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COVID-19 ICU survivors, especially those with ICU-AW, exhibit persistent clinical manifestations and reduced physical function, imposing a considerable burden on their long-term well-being.[7–9] However, there is a paucity of available reports on the long-term outcomes of COVID-19 patients with ICU-AW.

In this study, we assessed the long-term health-related quality of life (HRQOL) and physical function of COVID-19 survivors complicated with ICU-AW. Furthermore, we investigated the relationships between muscle weakness in the ICU and long-term outcomes for the HRQOL and physical function.

MATERIALS AND METHODS

Patients

In this study, we retrospectively collected data from patients who were admitted to our ICU in Hyogo Medical University Hospital and stayed for more than 48 h between January 2021 and November 2021. Depending on the patient's respiratory condition, respiratory management was performed using either high-flow nasal cannula oxygen therapy or mechanical ventilation (MV). Patients who required prolonged MV (typically 2 weeks) underwent tracheostomy. The decision to initiate extracorporeal membrane oxygenation (ECMO) was made by the intensivists in cases where adequate management with appropriate MV did not control the progression of hypoxemia (e.g., FiO_2 >0.9, PaO_2/FiO_2 <150 mmHg, Murray score: 2–3).[10,11] In this study, to clarify the impact of COVID-19, we limited our study sample to patients who were younger than 75 years old, were independent in activities of daily living (ADL) before their hospitalization, and had a Charlson Comorbidity Index (CCI) of less than 3. We also excluded patients who were unable to participate because of psychiatric or cognitive disorders (e.g., dementia). Patients who were discharged to nursing homes were also excluded. The study protocol was approved by the Hyogo Medical University Ethics Committee (No. 4431) and informed consent was obtained via the opt-out method.

During the ICU stay, rehabilitation management and treatment were typically conducted as follows: physical therapy was initiated within 24 h after ICU admission and started with passive mobilization and positioning, including prone positioning. Pharmacological therapy for COVID-19 (e.g., dexamethasone) was administered, and neuromuscular blocking agents were used to aid MV. Active mobilization and active muscle strengthening was then started when the patient could follow verbal commands. Sitting over the edge of the bed was initiated when the patient's hemodynamic condition became stable. Upright training and walking exercises were initiated after the patient's respiratory status improved. In addition, occupational therapy for the upper limbs and ADL training and speech–language therapy for voice and swallowing training were initiated after isolation concluded. Prior to home discharge, therapists provided guidance to patients regarding home exercise. Patients requiring further functional improvement for discharge were transferred to local convalescent rehabilitation hospitals.

Outcome Measurements

Muscle Strength Assessment

Data were retrieved from medical records, including demographic characteristics (age, sex, and smoking status) and clinical characteristics (comorbidities, treatments, length of ICU stay, and length of hospital stay). Patients underwent the Medical Research Council score (MRC; null to full, 0–5) assessment[12] and grip strength testing for clinical assessment of muscle strength at ICU discharge and at hospital discharge. The MRC score assessments were conducted for shoulder abduction, forearm flexion, wrist flexion, hip flexion, knee extension, and ankle dorsiflexion for the right and left sides. The total summations of the obtained MRC scores (MRC-SS; ranging from 0 to 60) were then calculated. Handgrip strength assessments were performed with the patient seated holding the dynamometer (TKK 5101; Takei, Tokyo, Japan) with the elbow at 90° flexion. Two 5-s maximal trials were performed on each side and the higher values were recorded. The ratio of the actual measured grip strength relative to the normative value for age and sex was calculated based on data reported by the Ministry of Health, Labor and Welfare[13] to give the normalized grip strength.

Diagnosis of ICU-AW

Patients with an MRC-SS of less than 48 at ICU discharge and had no other neuromuscular disorders were diagnosed with ICU-AW.[12] Based on this cut-off, subjects were classified into the ICU-AW group and the no ICU-AW group.

Long-term Follow-up and the SF-36 Questionnaire

After hospitalization, an appointment was arranged for each patient to attend our outpatient clinic 18 months after the onset. During this visit, MRC-SS, grip strength, and 6-min walk distance (6MWD) were recorded. The measurement methods for MRC-SS and grip strength were the same as those used during hospitalization. The 6-min walk test was performed without the use of oxygen therapy as per the recommended guidelines.[14] Similar to the grip strength data, the raw data for 6MWD were divided by the predicted values derived from the study of Troosters et al.[15] to give normalized 6MWD values.

Besides these physical function assessments, we also obtained HRQOL scores through use of the SF-36 questionnaire.[16,17] The SF-36 comprises eight multi-item scales: Physical Functioning (PF), Role Limitation-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Limitation-Emotional (RE), and Mental Health (MH). Using these subscale scores, compartment summary scores were calculated to provide global measures of the physical component summary (PCS) and mental component summary (MCS). The details of the constituent elements of subscales for both PCS and MCS were described in a previous study.[18] Both subscales and summary scores range from 0 to 100, with higher scores indicating a better health status. The scores were transformed to a normalized score using 50 as the population mean and 10 as one standard deviation.[18]

Statistics

First, the demographic distributions were assessed for data collected 18 months after the onset: MRC-SS, grip strength (normalized values), and 6MWD (normalized values). Second, the distribution of the subscales and summary scores of SF-36 at 18 months of follow-up were assessed in reference to the Japanese national norms.[18] Thereafter, we compared patients' characteristics and outcomes at the 18-month follow-up appointment between the ICU-AW and no ICU-AW groups. The Mann–Whitney U test was employed for between-group comparisons. Categorical variables were compared using the chi-square test. Third, the relationships between MRC-SS at ICU discharge and the long-term outcomes were assessed using Spearman's rank correlation. The long-term outcomes for the analyses were the eight subscales (PF, RP, BP, GH, VT, SF, RE, MH) and summary scores (PCS, MCS) of SF-36, MRC-SS, grip strength (normalized values), and 6MWD (normalized values). All variables were presented as the median and interquartile range. All statistical analyses were performed using the JMP software package (SAS Institute, Cary, NC, USA). P values of less than 0.05 were considered statistically significant.

RESULTS

During the study period, 55 patients suffering from COVID-19 were admitted to the ICU of our university hospital. Of these, 13 patients were either unable to be contacted or declined to participate, 7 patients developed other illnesses after discharge, 6 patients were aged at least 75 years, 1 patient had a CCI score of 3, and 2 patients were discharged to a nursing home. Consequently, 26 patients were entered into our final analytical database. Thirteen of these patients were diagnosed with ICU-AW, and the remaining 13 patients were assigned to the no ICU-AW group. **Table 1** shows the baseline characteristics of the study participants. The patients in the ICU-AW group had a higher median age (66 years) than those in the no ICU-AW group (57 years). The between-group differences in body mass index and comorbidities (diabetes, hypertension, kidney disease) were not significant. Prone positioning was significantly more implemented in the ICU-AW group than in the no ICU-AW group (92.3% vs. 53.9%, P=0.027). Furthermore, the ICU-AW group had significantly longer hospital and ICU stay durations (P<0.001 for both). MV and tracheostomy were significantly more commonly used in the ICU-AW group (P<0.001). The duration of MV was also significantly longer in the ICU-AW group (P<0.001). Functional outcomes, as measured by MRC-SS and grip strength (normalized values) at ICU and hospital discharge, were lower in the ICU-AW group than in the no ICU-AW group (P<0.001 for both).

Table 2 shows the long-term outcome data for the ICU-AW group and the no ICU-AW group. The ICU-AW group had significantly lower scores than the no ICU-AW group in PF, RP, BP, VT, SF, RE, and PCS in SF-36 (P=0.003 for PF; P<0.001 for RP, BP, SF, PCS; P=0.018 for VT; P=0.026 for RE). In comparison with the Japanese national normative data, the ICU-AW group had smaller median scores for PF, RP, BP, SF, and PCS; the VT median value was slightly below the national norm. Contrarily, in the no ICU-AW group, all subscale scores of the SF-36 surpassed the Japanese national norms. As for physical function measures, the ICU-AW group showed significantly lower scores for MRC-SS (P=0.007) and normalized grip strength (P<0.001). **Figure 1** illustrates the box plots of data obtained for the SF-36 summary score. In the ICU-AW group, a significant decrease in PCS was observed; however, no significant difference in MCS was observed between the two groups. It is noteworthy that, as a group, the scores for PCS were lower than the Japanese national norm, whereas those for MCS exceeded the norm.

Table 3 shows the results of the correlation analysis. MRC-

Table 1. Baseline characteristics of study participants

Characteristic	All patients (n = 26)	ICU-AW (n = 13)	No ICU-AW (n = 13)	P value
Age, years	58 (54–67)	66 (53–71)	57 (54–60)	0.116
Male sex	22 (84.6)	10 (76.9)	12 (92.3)	0.267
BMI, kg/m^2	26.5 (22.5–34.1)	24.9 (21.6–34.8)	26.7 (24.7–29.4)	0.878
Comorbidities				
T2DM	9 (38.5)	7 (53.9)	3 (23.1)	0.226
Hypertension	14 (57.7)	7 (53.9)	8 (61.5)	0.691
CKD	2 (7.7)	1 (7.7)	1 (7.7)	0.999
APACHEII score at admission	19 (17–20)	20 (18–21)	18 (15–19)	0.062
Use of dexamethasone	26 (100)	13 (100)	13 (100)	0.999
Use of NMBA	6 (23.1)	5 (38.5)	1 (7.7)	0.160
Prone positioning	19 (73.1)	12 (92.3)	7 (53.9)	0.027
ICU LOS, days	18 (10–26)	24 (19–50)	10 (8–16)	<0.001
Hospital LOS, days	42 (20–75)	71 (47–131)	19 (13–31)	<0.001
Respiratory management				
MV	17 (65.4)	13 (100)	4 (30.8)	<0.001
ECMO	14 (19.2)	4 (30.8)	1 (7.7)	0.322
Tracheostomy	8 (30.8)	8 (61.5)	0 (0)	<0.001
Duration of MV, days	10 (1–22)	22 (13–57)	2 (1–8)	<0.001
MRC-SS at ICU discharge	46 (32–60)	32 (26–41)	60 (56–60)	<0.001
MRC-SS at hospital discharge	59 (46–60)	46 (34–52)	60 (59–60)	<0.001
GS (nv) at ICU discharge, %	61.1 (24.2–72.1)	25.1 (0–36.0)	71.6 (63.7–81.4)	<0.001
GS (nv) at hospital discharge, %	64.3 (42.8–80.9)	42.9 (31.8–49.3)	77.4 (71.1–102.5)	<0.001

Data are presented as median (interquartile range) or number (percentage).

APACHEII, Acute Physiologic Assessment and Chronic Health Evaluation II; BMI, body mass index; CKD, chronic kidney disease; GS, grip strength; nv, normalized value; LOS, length of stay; MRC-SS, Medical Research Council Sum Score; NMBA, neuromuscular blocking agents; T2DM, type 2 diabetes mellitus.

Table 2. Clinical outcomes at 18-month follow-up

Variable	ICU-AW (n = 13)	No ICU-AW (n = 13)	P value
SF-36			
PF	43.5 (34.0–50.3)	57.1 (51.7–57.1)	0.003
RP	42.3 (32.2–46.7)	56.7 (55.3–56.7)	<0.001
BP	43.8 (39.3–51.6)	61.1 (61.1–61.1)	<0.001
GH	50.8 (42.9–59.1)	57.0 (53.2–62.2)	0.076
VT	49.8 (48.3–59.0)	59.0 (57.5–62.0)	0.018
SF	46.4 (38.0–52.1)	57.7 (57.7–57.7)	<0.001
RE	56.8 (43.8–56.8)	56.8 (56.8–56.8)	0.026
MH	54.5 (47.0–60.9)	59.6 (52.0–65.9)	0.093
PCS	43.0 (29.6–48.3)	54.6 (52.3–59.1)	<0.001
MCS	57.3 (48.4–62.1)	60.9 (53.8–65.2)	0.065
Physical function			
MRC-SS	60 (56–60)	60 (60–60)	0.007
GS (nv), %	77.2 (58.9–85.1)	107.5 (91.1–113.0)	<0.001
6MWD (nv), %	61.1 (54.3–76.7)	73.7 (68.9–86.1)	0.054

Data are presented as median (interquartile range).

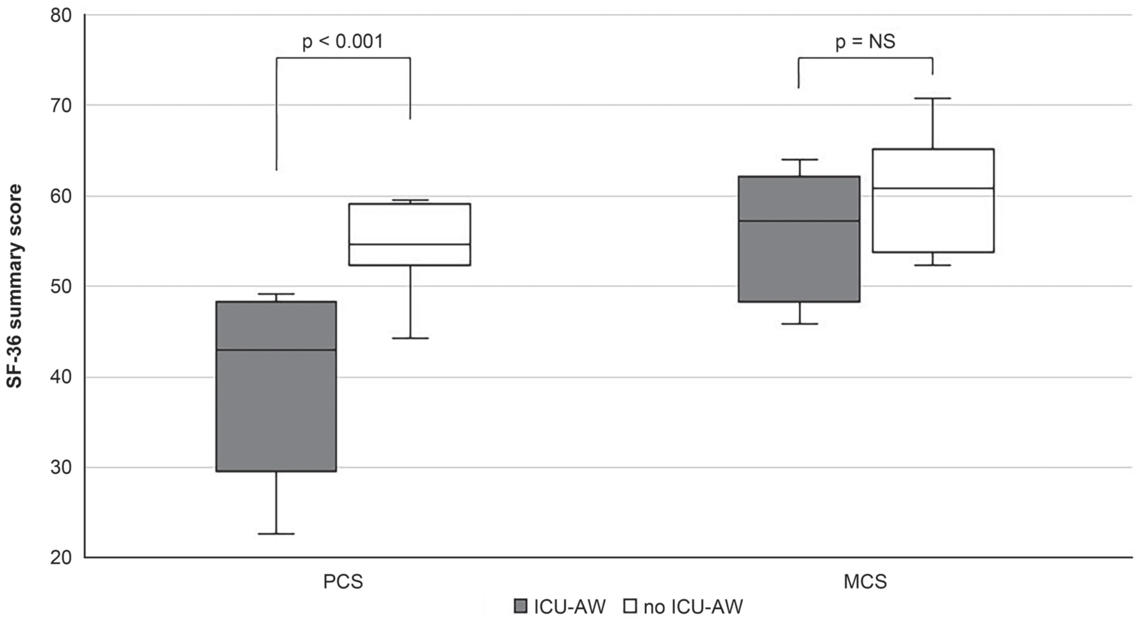

Fig. 1. Comparison of SF-36 summary scores at the 18-month follow-up appointment for the ICU-AW and no ICU-AW groups. Norm-based scoring was used, ensuring that the scores were recalculated to align with the national standard for the general population in Japan (2017 data). The national standard average score was set at 50, with a standard deviation of 10. For PCS, the ICU-AW group scored below the Japanese national norm (median 43.0) and significantly below the no ICU-AW group (P<0.001). For MCS, both groups scored above the national norm, and the scores of the two groups were not significantly different. NS, not significant.

Table 3. Correlation between MRC-SS at ICU discharge and clinical outcomes at 18-month follow-up

Measurement	Variable	r	P value
SF-36			
	PF	0.47	0.015
	RP	0.56	0.003
	BP	0.65	<0.001
	GH	0.33	0.103
	VT	0.36	0.073
	SF	0.67	<0.001
	RE	0.40	0.044
	MH	0.33	0.105
	PCS	0.61	<0.001
	MCS	0.32	0.108
Physical function			
	MRC-SS	0.57	0.003
	GS (nv)	0.66	<0.001
	6MWD (nv)	0.41	0.043

SS at ICU discharge showed a positive correlation with the following subscales of SF-36 at 18 months after the onset: PF (r=0.47), RP (r=0.56), BP (r=0.65), SF (r=0.67), RE (r=0.40), and PCS (r=0.61). Furthermore, MRC-SS at ICU discharge showed positive correlations with MRC-SS, normalized values of grip strength, and 6MWD assessed at the 18-month follow-up appointment.

DISCUSSION

In this study, we observed that COVID-19 patients who experienced ICU-AW exhibited significant declines in HRQOL 18 months after the onset of the condition. Notably, these patients showed marked reductions in the physical aspects of HRQOL, whereas their mental well-being was relatively preserved. This result highlights the enduring impact of ICU-AW on long-term outcomes, emphasizing the importance of targeted interventions to address the physical sequelae and enhance overall well-being in this subgroup of patients with severe COVID-19.

To our knowledge, this is the first study to comprehensively investigate the relationship between ICU-AW and the long-term HRQOL and physical function beyond a year after onset in COVID-19 survivors. The strength of our study lies in its inclusion of a well-defined ICU-AW group and its comparison with a no ICU-AW group, as well as the utilization of the Japanese national norm as a reference.[18] In addition, the study cohort was well controlled in terms of initially having no severe underlying comorbidities, being independent in ADL, and ensuring a stable prognosis upon acute phase recovery. Furthermore, the long-term effects of ICU-AW were evaluated, not only from a physical perspective but also from the social and psychological aspects of HRQOL, allowing for a more comprehensive investigation.

In this study, the ICU-AW group exhibited a significant decline in PCS scores in the SF-36 at 18 months, accompanied by mild residual muscle weakness. Although there are limited studies reporting health outcomes beyond 1 year for severe COVID-19 survivors, previous research has generally produced results similar to those observed in this study.[19,20] In a large-scale cohort study conducted in China, the health status of COVID-19 survivors showed a trend of improvement over the 2-year period following onset. However, the group that received advanced respiratory support still experienced persistent fatigue or muscle weakness and impaired lung function. The improvement in health status, including HRQOL, did not reach the level observed in the general population.[20] COVID-19 survivors who required ICU management exhibited a prolonged recovery period for improvement toward their pre-onset health status.

In our study, positive correlations were observed between muscle weakness at ICU discharge and the long-term HRQOL and physical function at 18 months after onset. Another finding of interest in our study was that in the no ICU-AW group, long-term HRQOL and muscle strength were preserved. These results indicated that muscle strength in the ICU could serve as a valuable prognostic indicator for the long-term HRQOL and physical function of COVID-19 survivors. These findings are consistent with the results of previous studies conducted in non-COVID-19 settings.[21,22] Van Aerde et al.[22] reported that muscle strength at ICU discharge, which is measured using the MRC-SS, is a predictor of grip strength, 6MWD, and PCS for SF-36 at 5 years of follow-up. The association between early stage muscle strength and long-term health outcomes in COVID-19 survivors has not been elucidated in previous studies. Further investigations are needed to validate rehabilitation strategies aimed at preventing muscle weakness during ICU treatment.

Our study also revealed that ICU-AW in COVID-19 survivors not only affects the long-term physical aspects of HRQOL but also impacts the role/social functioning represented by SF-36 subscales such as RP, SF, and RE. Previous research focusing on non-COVID-19 ICU survivors had shown that ICU-AW had a long-term impact on the physical aspects of HRQOL.[8,9,22,23] Meanwhile, the results regarding HRQOL in terms of role/social functioning were diverse.[8,24] In a study involving COVID-19 patients in Japan, Ando et al.[25] reported an association between a history of intubation and extensive COVID-19 pneumonia with decreased HRQOL in social activities up to 6 months after the onset. However, a cohort study following Spanish patients who suffered from COVID-19 pneumonia found marked declines in RP, SF, and RE at the 3-month follow-up, but these were improved after 12 months of follow-up.[26] Our study suggests a decline in HRQOL concerning long-term social activities in ICU-AW patients, and in evaluations conducted within a shorter timeframe, such as within 1 year post-onset, there is a possibility that further deterioration may have been observed. The COVID-19 pandemic itself has had significant social and economic impacts, and understanding the enduring social consequences faced by COVID-19 survivors with ICU-AW is important. To facilitate the reintegration of these patients into society and maintain their social interactions, there is a need for a comprehensive and multi-faceted approach that goes beyond physical function recovery as the sole focus.

Contrarily, in the patient cohort analyzed in this study, no significant decline was observed in the mental aspect of HRQOL. In a large-scale study by Deana et al.[27] involving COVID-19 with acute respiratory distress, similar to our study, a decrease in PCS scores was observed 1 year after ICU discharge, whereas MCS scores were maintained. However, some previous reports have highlighted the prevalence of psychological symptoms following COVID-19, especially among severe cases.[28,29] In a study of COVID-19 patients with sequelae lasting more than 4 weeks after onset, Poudel et al.[30] reported that being female was a significant determinant associated with an MCS score below 50 on the SF-36. In addition, Combret et al.[31] reported that frailty at admission is associated with low MCS scores 1 year after hospitalization for COVID-19. The inclusion of patients limited to those under the age of 75 years who were independent in ADL before admission, along with the lower proportion of females, may have influenced the results in this study. Furthermore, our study has conducted evaluations solely at a single time point after the onset of COVID-19. Therefore, it is imperative to conduct further follow-up assessments to examine the longitudinal progression, especially concerning the mental aspects of HRQOL.

This study has several limitations. First, it is a singlecenter study with a limited sample size, which may limit the generalizability of its findings. Second, because of the unpredictable nature of ICU admission, pre-admission assessments of HRQOL and physical function were not performed, thereby making it difficult to establish a baseline for comparison. However, the patients were relatively young, were independent in ADL, and presented few comorbidities at baseline; therefore, it is reasonable to assume that these patients would not have low SF-36 scores or poor physical function at baseline. Third, although all patients were provided with instructions upon discharge for self-training at home, the continuity of these exercises and subsequent exercise habits were left to the patients themselves. Frequent outpatient rehabilitation visits were not possible because of the impact of the pandemic. Fourth, some patients who experienced symptom recovery and had no significant impairment in daily life failed to attend follow-up visits. This could restrict the extrapolation of this study's findings to a broader population. Despite these limitations, our study reveals the enduring impact of ICU-AW on the HRQOL of COVID-19 survivors.

CONCLUSION

The results of this study provide valuable insights into the complex challenges faced by COVID-19 survivors with ICU-AW and underscore the importance of a comprehensive approach to their care. Although the global public health emergency related to COVID-19 has subsided, continued follow-up and support are needed for COVID-19 survivors with ICU-AW. Furthermore, there is a need to investigate rehabilitation strategies to prevent the development of muscle weakness following ICU admission.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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