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Evaluating early mobilisation in critically ill COVID-19 patients: secondary analysis from the ESICM UNITE-COVID-II multicentre observational study

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Running Title: Early Mobilisation in Critically Ill COVID-19 Patients

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Abstract

Background

Early mobilisation (EM) within the first 72 hours of ICU admission is essential for preventing ICU-acquired weakness; however, mobilisation rates remained low among mechanically ventilated (MV) COVID-19 patients during the pandemic waves. This study aimed to characterise the association between EM and 60-day outcomes.

Methods

A multicentre observational study conducted by the European Society of Intensive Care Medicine (ESICM) examined mobilisation strategies during the second COVID-19 wave (UNITE-

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COVIDed2021). All patients with confirmed SARS-CoV-2 infection who were in the ICU on the peak day between 1 January and 1 June 2021 were included. The analysis expanded on the UNITE-COVIDed2020 study, comparing the first and second COVID-19 waves using a combined dataset.

Results

Data from 2,053 patients during the second wave across 103 ICUs in 35 countries were analysed and compared with 4,190 patients from the first wave. EM was achieved in 801 (39%) *vs.* 1114 (27%), $p<0.001$, respectively. In the combined cohort, MV on admission significantly reduced the likelihood of EM (OR 0.29, 95% CI: 0.25–0.33, $p=0.001$). While EM did not improve ICU or hospital length of stay, it was associated with reduced 60-day mortality (OR 0.74, 95% CI: 0.64–0.86, $p=0.001$) and transfer rates to other care facilities (OR 0.74, 95% CI: 0.59–0.94, $p=0.001$).

Conclusion

EM is feasible and beneficial for critically ill COVID-19 patients. It was associated with reduced mortality and lower transfer rates to other care facilities, which underscores the critical role of EM in enhancing patient recovery during a pandemic.

Trial Registration

ClinicalTrials.gov, registration number NCT04836065

Keywords:

Early Mobilisation, COVID-19 patients, multicentre study, ICUAW, ESICM, UNITE-COVID

Highlights

- Early mobilisation (EM) increased during 2nd pandemic wave significantly.
- Mechanical ventilation is the main barrier for EM in a peak pandemic situation.
- EM associated with lower mortality and discharge to facility in COVID-19 patients.

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Introduction

The coronavirus pandemic has placed significant strain on healthcare systems worldwide. The number of patients requiring intensive care has increased rapidly, exceeding the capacity of existing intensive care units (ICUs) [1]. To maintain optimal patient care, hospitals implemented redistribution strategies, temporarily increasing the number of ICU beds, also known as surge capacity beds. Capacities were increased by 33-55% [1, 2]. Staffing levels were increased, and non-ICU nurses were reallocated to ICUs in 85% of cases and doctors from other departments in 58%, resulting in an increased workload and a worse nurse-to-patient ratio [2].

In 2017, a study by Jolley *et al.* found that ICU staffing played a key role in patient mobilisation. The presence of trained physiotherapists significantly improved mobilisation rates in mechanically ventilated patients [3].

Intensive care unit-acquired weakness (ICUAW) is common in COVID-19 patients and was reported in up to 72% at ICU awakening and in 52% at ICU discharge [4]. To counteract ICUAW, mobilisation plays a crucial role in preventing disease advancement [5]. However, overall mobilisation rates are low for COVID-19 patients and particularly for patients receiving mechanical ventilation (MV). A global study across 135 ICUs found that only 7% of COVID-19 patients on MV were mobilised, despite mobilisation being recommended to prevent ICUAW [6]. EM, defined as mobilisation within the first 72 hours of ICU admission [7], improves functional recovery further compared to standard mobilisation and was provided to 27% of COVID patients who were included in the UNITE-COVID I study. Factors with lower odds of initiating EM were MV at admission, age, asthma and pre-existing kidney disease [8].

During the first COVID-19 wave, healthcare systems responded by establishing measures to manage the crisis. By the second wave, efforts focused on better coordination, such as collaborative structures between hospitals and governments. In Germany, central COVID-19 coordination centres helped to prevent healthcare system overload [9]. Telemedicine was rapidly implemented, improving knowledge sharing and collaboration between hospitals [10, 11]. Drug and vaccine development became a priority to control the spread of the virus [12]. Despite these advances, the second wave exposed significant challenges for frontline staff, especially in Italy, where emotional exhaustion and depersonalisation increased, adversely affecting patient care [13]. The primary aim of this study was to report on the provision of EM during the peak of the second pandemic wave. Secondary aims included analysing its effects on ICU and hospital length of stay (LOS) and 60-day outcomes, comparing these findings to those observed during the first COVID-19 wave.

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Methods

In 2020, the European Society of Intensive Care Medicine (ESICM) led the UNITE-COVID study to evaluate the global impact of COVID-19 in ICUs. Following a multicentre observational study during the first COVID-19 wave [2, 14], this article presents findings from a second data inquiry conducted between 1 January 2021 and 1 June 2021, focusing on the day with the highest number of ICU admissions in the relevant ICUs. The study, approved by Ghent University Hospital's Ethics Committee (BC07826) and registered on ClinicalTrials.gov (NCT04836065), expanded the original UNITE-COVID study. Patient data covering ICU stays of up to 60 days were extracted from medical records, collated at each centre, and securely uploaded to Clinfile in Vélizy-Villacoublay, France.

Inclusion/Exclusion

Patients included in the data collection met the following criteria: 1) aged 18 years or older; 2) admitted to an ICU or another area of the hospital under the care of the intensive care team on the day when the ICU recorded the highest number of COVID-19 patients, between 1 January 2021 and 1 June 2021; and 3) confirmed SARS-CoV-2 infection, as determined by polymerase chain reaction testing or a similar method. Patients who tested positive for SARS-CoV-2 without a COVID-19 diagnosis were excluded from the dataset. Our sub-analysis focused on patients with EM and excluded those lacking EM data, as well as patients who had prior ICU stays during the same hospitalisation, to avert bias concerning the initiation time of mobilisation.

Mobilisation

EM was defined as passive mobilisation, assisted-active mobilisation, and active mobilisation initiated within 72 hours of ICU admission. The minimal criteria for passive mobilisation included passive movement of all extremities in all physiological directions, passive cycling, passive vertical mobilisation, or passive rehabilitation in a chair. Positioning the patient did not constitute a form of EM. The primary outcome was the initiation of EM (yes or no) and the factors influencing this. The secondary outcomes were (1) patient status 60 days after ICU admission (*i.e.*, death at any time point, discharged alive, still hospitalised, palliative discharge, transfer to another care facility), (2) ICU, and (3) hospital LOS.

Statistical analysis:

In the descriptive presentation, categorical variables were reported as frequencies in absolute numbers and percentages, while continuous variables were described using either the median and interquartile range or the mean and standard deviation. Group differences were tested using Chi-square tests for categorical data, the Mann-Whitney U test for continuous data, or the t-test for normally distributed continuous data. Group differences in the distribution of the ICU Mobility Scale were tested using the Wilcoxon rank test. We combined both datasets from wave 1 (2020) and wave 2 (2021) for the analysis

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of the endpoints EM, LOS, and 60-day outcomes. To analyse the factors influencing EM, a multivariable mixed logistic model with a random effect for the country was employed, using EM as the outcome parameter. Odds ratios were calculated to determine the association between case characteristics and EM. To evaluate the impact of EM on ICU and hospital LOS, we applied multivariable mixed linear models, again with a random effect for the country. In the model adjustment process, the variables selected in 2020 were utilised. Subsequently, the variables exhibiting a significant association with EM in the multivariate regression were chosen. Finally, the outcome models were adjusted for the following factors: the wave of the pandemic, history of cardiac disease, age, and MV at admission. A negative binomial regression was employed to calculate the incidence rate ratio (IRR) and assess the relative impact of EM on hospital and ICU length of stay (LOS). For the 60-day outcomes data, separate multivariable mixed logistic models were used for each endpoint, adjusting for the covariates significantly associated with EM.

As a sensitivity analysis, all analyses were repeated on a matched subset of the data, which included only centres participating in both wave 1 and wave 2 (see supplement). Additionally, propensity score matching was applied using logistic regression to balance key covariates (wave, age, cardiac disease, and mechanical ventilation), ensuring comparability between mobilised and non-mobilised patients.

The analysis was conducted using the statistical software R (version 4.3.2 released 31.10.2023). Packages used for the analysis were “tidyverse, ggplot2, lme4, tableone, car” [15-18]. The confidence interval (CI) was within 95%, and the significance level was set at $p<0.05$.

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Results

Baseline Characteristics

From the original dataset, patients without data on mobilisation and those who had previously been admitted to ICU were excluded, leading to a total of 2,053 patients diagnosed with COVID-19 across 103 ICUs in 35 countries in 2021 (see Figure 1). They were compared to 4,190 patients from the 2020 dataset.

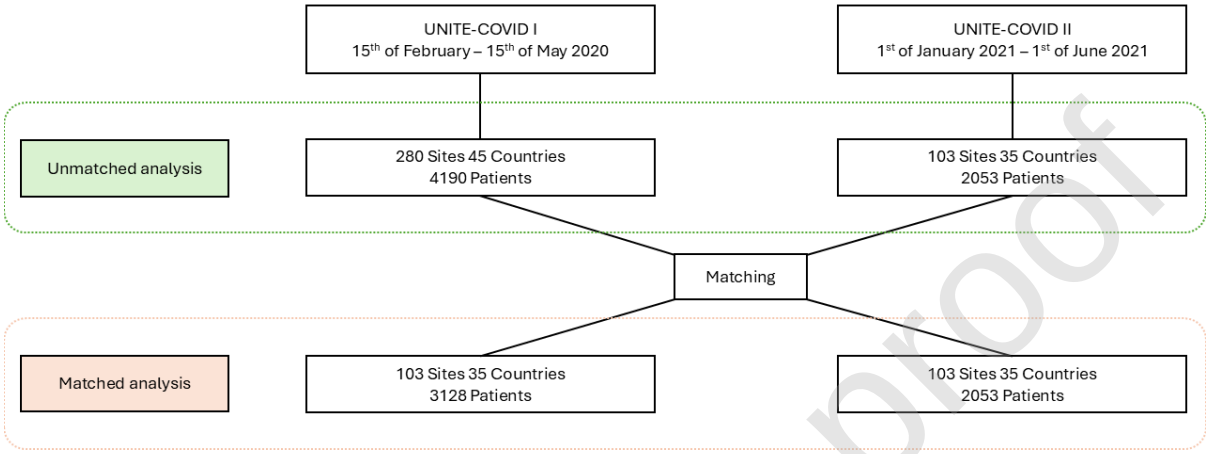

Figure 1 Strobe Diagram of UNITE COVID I and UNITE COVID II before and after matching the ICU Sites

Respiratory failure was the primary reason for ICU admission among 1,933 patients (2021), similar to the 2020 dataset. In 2020, 71% of participants were male, slightly decreasing to 67% in 2021. Arterial hypertension remained the most prevalent comorbidity, exceeding 50%, followed by diabetes and chronic pulmonary diseases, the latter showing an increase in 2021 but not after matching. Thromboembolic events were initially more common in 2021 but displayed no significant difference post-matching. Upon admission, 48.5% of patients admitted in 2020 required mechanical ventilation (MV), compared to 33.6% in 2021. However, a greater number of patients transitioned to MV during their ICU stay in 2021 (44.6% *vs.* 36.8%), and a higher proportion entirely avoided it (21.7% *vs.* 14.8%), even in matched comparisons (see Table 1 for unmatched data; see Suppl. Table 1 for matched data; see Suppl. Table 2 for baseline characteristics divided by EM).

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Table 1. Baseline characteristics of patients during COVID-19 wave 1 and COVID-19 wave 2

	Wave 1	Wave 2	*p*	SMD
Number of patients	4,190	2,053		
Sex (male) (%)	2974 (71.0)	1368 (66.8)	0.001	0.091
Age	62 [54, 70]	63 [54, 71]	0.176	0.02
BMI	28 [25, 32]	28 [25, 32]	0.709	0.02
Cardiac disease	643 (15.5)	331 (16.4)	0.374	0.024
Liver disease	106 (2.6)	68 (3.4)	0.088	0.047
Hypertension	2089 (50.3)	1080 (53.4)	0.024	0.062
Neurological disease	256 (6.2)	142 (7.0)	0.225	0.033
Pulmonary disease	375 (9.0)	241 (12.0)	<0.001	0.094
Diabetes	1314 (31.7)	632 (31.5)	0.877	0.005
Asthma	349 (8.4)	170 (8.4)	1.00	0.002
Malignant neoplasm	225 (5.5)	141 (7.0)	0.019	0.063
Kidney disease	298 (7.2)	176 (8.7)	0.038	0.056
Immunosuppression	205 (5.0)	133 (6.6)	0.011	0.068
Thromboembolic complication at admission	1041 (24.8)	305 (14.9)	<0.001	0.255
Co-infection	603 (14.4)	400 (19.5)	<0.001	0.137
Mechanical ventilation (%)			<0.001	0.327
• Intubation at admission	1997 (48.5)	675 (33.6)		
• Intubation during ICU stay	1516 (36.8)	895 (44.6)		
• No	608 (14.8)	436 (21.7)		

BMI=Body-Mass-Index, Data presented as mean (SD) or median [IQR], SMD=absolute standardized mean differences.

Initiation of EM

On the peak day of the 2020 wave, the rate of EM was 27% compared to 39% during the 2021 wave. The higher rate of mobilisation resulted in a similar score on the ICU Mobility Scale (in 2020: median 1 [0-4], in 2021: median 1 [1-5]), but with a higher interquartile range (see Table 2). For the results of the matched comparison see Suppl. Table 3.

Table 2. Initiation of Early Mobilisation within 72h and the score on the ICU Mobility Scale (IMS). Data presented as n (%) or median [IQR].

	Wave 1	Wave 2	*p*
Number of Patients	4,190	2,053	
Early Mobilisation (%)	1114 (27)	801 (39)	<0.001
ICU Mobility Scale	1.00 [0, 4.0]	1.0 [1.0, 5.0]	0.001

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Factors Influencing Initiation of EM

This study used logistic regressions to identify predictors of EM among COVID-19 patients during two pandemic waves: Wave 1 (2020) and Wave 2 (2021). The wave of hospitalisation was the strongest predictor, with higher odds of EM in Wave 2 compared to Wave 1 (OR = 1.32, 95% CI: 1.08–1.63, *p*=0.008). Additional significant factors that increased EM were a history of cardiac disease, older age, and MV (see Table 3).

Table 3. Factors associated with EM from the multivariate logistic regression model.

	Odds Ratio ± (95% CI)	*p*-value
Wave (2020 vs. 2021)	1.32 (1.08, 1.63)	**0.008**
History of Cardiac Disease	1.21 (1.00, 1.46)	**0.046**
Age decades	0.91 (0.86, 0.96)	**0.001**
Mechanical Ventilation at admission	0.29 (0.25, 0.33)	**0.001**
History of Liver Disease	0.85 (0.57, 1.27)	0.429
History of Diabetes	0.90 (0.78, 1.04)	0.155
History of Asthma	0.90 (0.71, 1.13)	0.35
History of Pulmonary Disease	1.07 (0.86, 1.33)	0.53
History of Neurological Disease	0.87 (0.66, 1.14)	0.314
History of Malignant Neoplasm	0.97 (0.73, 1.28)	0.813

Outcomes

The median ICU and hospital LOS) were shorter in Wave 2 compared to Wave 1. After adjusting for covariates, patients with EM experienced a 6% longer ICU stay (IRR 1.06 (1.01, 1.11), *p*=0.005) and a 5% longer hospital LOS (IRR 1.05 (1.01, 1.10), *p*=0.032) (see Table 4). Similar results are observed in the matched analysis, which includes only data from centres that participated in both waves, indicating that patients with EM had a 7% longer hospital LOS (IRR 1.07 (1.01, 1.13), *p*=0.024) and an 8% longer ICU LOS (IRR 1.08 (1.02, 1.13), *p*=0.001).

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Table 4. Length of stay in ICU and hospital of unmatched cohorts

	Wave 1	Wave 2	*p*-value
Number of patients	4,190	2,053	
Hospital LOS	29.0 [18.0, 45.0]	23.0 [13.0, 39.75]	0.001
• IRR for EM	1.05 (1.01, 1.1)		0.032
ICU LOS	17.0 [10.0, 28.0]	16.00 [9.0, 27.0]	0.001
• IRR for EM	1.06 (1.01, 1.11)		0.005

LOS=Length of stay, IRR=Incidence Rate Ratio, Hospital LOS and ICU LOS presented as median ± [IQR], IRR [95% CI]

At 60 days post-ICU admission, EM demonstrated significant benefits in patients included in the combined dataset (waves 1 and 2). After adjusting for covariates such as wave, history of cardiac disease, age, and MV on admission, patients receiving EM had a 26% lower risk of mortality (OR 0.74 (0.64, 0.86), *p*=0.001). They exhibited higher rates of discharge alive (OR 1.34 (1.17, 1.54), *p*=0.001) and lower rates of transfer to other care facilities (OR 0.74 (0.59, 0.94), *p*=0.017). At the same time, it was observed that more patients receiving EM remained hospitalised beyond 60 days (OR 1.33 (1.01, 1.74), *p*=0.019) (see Table 5). In the matched analysis, similar findings were observed (see Suppl. Table 4). As an additional sensitivity analysis, propensity score matching was applied to further reduce confounding, and similar trends in 60-day outcomes were observed (see Suppl. Table 5).

Table 5. 60-day outcomes of Wave 1 and Wave 2 combined unmatched

	Odds Ratio (95% CI)	*p*.adj
Deceased	0.74 (0.64, 0.86)	**0.001**
Discharged alive	1.34 (1.17, 1.54)	**0.001**
Hospitalized (not in ICU)	1.33 (1.01, 1.74)	**0.019**
Transferred to other care facilities	0.74 (0.59, 0.94)	**0.017**
Palliative	0.81 (0.25, 2.59)	0.721
Still in ICU	1.06 (0.74, 1.52)	0.693

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Discussion:

This study demonstrated that during the second COVID-19 wave, when the ICUs experienced their highest number of COVID-19 patients, that is, the period of maximum ICU burden, EM was achieved in 39% of patients, compared to 27% in the first wave. Although EM did not reduce LOS in the ICU or hospital, after adjusting for covariates, EM was associated with improved 60-day outcomes, such as mortality rates, transfers to other care facilities, and the likelihood of being discharged alive, in both the matched and unmatched cohorts.

A study by Liu *et al.* across 135 ICUs in 33 countries highlighted significant differences in mobilisation rates between COVID-19 and non-COVID-19 patients [6]. Among non-ventilated patients, 60% of COVID-19 patients were mobilised compared to 34% of non-COVID-19 patients. However, mobilisation rates for patients on MV were low in both groups, at 7% and 9%, respectively. This indicates that while non-ventilated COVID-19 patients were prioritised for mobilisation, overall rates remained suboptimal, particularly among critically ill, ventilated patients [6]. Other studies reinforce the variability in mobilisation practices. Uhlig *et al.* reported a median mobilisation initiation time of 6 days for ICU COVID-19 survivors, with ventilated patients starting later (8 days) than non-ventilated patients (2.5 days) [19]. Similarly, McWilliams *et al.* found that mobilisation among ICU COVID-19 patients occurred even later, with a mean initiation time of 14 ± 7 days due to the severity of illness [20].

International guidelines consistently advocate for EM to improve patient outcomes [7, 21, 22]. Evidence from studies, including the network meta-analysis by Ding et al., indicates that initiating mobilisation within 48 to 72 hours of MV reduces the incidence of ICUAW and shortens both the duration of ventilation and the length of ICU stay [23]. Daum *et al.* support these findings, demonstrating that EM decreases both ICU and hospital stays in non-COVID-19 patients [24]. However, literature on the timely initiation of mobilisation for COVID-19 patients remains limited. Recommendations from organisations such as the World Health Organization (WHO), the Turkish Society of Physical Medicine and Rehabilitation, and the Australian Physiotherapy Management guidelines emphasise the importance of EM for COVID-19 patients to prevent complications and reduce days on MV [25-27].

Our UNITE-COVID studies reflect evolving mobilisation practices during the pandemic. In 2020, EM rates were 27%, increasing to 39% in 2021, likely due to improved familiarity with COVID-19 treatment, better resource allocation, and refined protocols [8]. In comparison, high EM rates were reported in the SAMDS-ICU study, where 96.5% of survey respondents indicated EM practices, although patient-level implementation rates in clinical practice were unclear [28]. In a recent study, Lorenz *et al.* examined the effect of a cut-off value of 40 minutes for mobilisation on functional outcomes. Their findings suggest that the key determinant of functional outcome is not the duration of

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mobilisation but rather the level of mobilisation achieved [29]. The IMS in UNITE-COVID remained at a median of 1, indicating that most patients were mobilised to sitting or exercising in bed. Nevertheless, a shift towards higher IMS values within the confidence interval in 2021 compared to 2020 suggests gradual progress and may explain the improved 60-day outcomes one year later.

Despite the burden on our healthcare system during the COVID-19 pandemic, EM was performed in patients in the ICU. The results of initiating EM and the extent to which patients were mobilised are comparable to other mobilisation studies conducted in non-pandemic settings. These data illustrate the capabilities that can be achieved during a pandemic at a time of maximum capacity usage.

A systematic review encompassing 39 articles about EM in the ICU reported a reduction in LOS in both the ICU and the hospital [30]. Specifically, the review found a mean reduction in ICU LOS of 2.74 days (95% CI: -3.52, -1.97) and in hospital LOS of 3.71 days (95% CI: -5.70, -1.71). These results are confirmed by a recent systematic review and meta-analysis by Daum *et al.*, who reported a reduction in hospital LOS if EM is initiated according to current guideline recommendations [24, 31]. In contrast, our results indicate prolonged LOS in both the ICU and the hospital. Both systematic reviews included a broader range of critically ill patients, unlike our COVID-19-specific patient cohort, and reported more substantial and statistically significant reductions in ICU and hospital LOS [30, 32]. The unique challenges and severity associated with COVID-19, including the high incidence of ICUAW and the necessity for prolonged MV, potentially limited the effectiveness of EM. Additionally, our study's time frame coincided with the pandemic, which may have influenced outcomes due to variations in clinical practices and resource availability. The broader and statistically robust findings of the systematic review support the generalisability of EM benefits, while our study highlights its feasibility within the context of COVID-19.

The association between EM and mortality in COVID-19 patients in ICUs and hospitals remains unclear, as most available data focuses on non-COVID-19 patients. Systematic reviews, such as the one by Waldauf *et al.*, demonstrated reduced MV duration and ICU LOS but no impact on mortality [33]. Similarly, studies by Zhang *et al.* and Zang *et al.* linked EM to higher home discharge rates, reduced ICUAW, and shorter ICU/hospital stays, yet found no effect on mortality [5, 34]. Even when Wang *et al.* accounted for the dose of EM, no mortality benefits were observed [30]. Despite these findings, our analysis of combined data from COVID-19 waves 1 and 2 revealed that EM not only led to improved functional outcomes – such as fewer transfers to other care facilities and higher discharge-alive rates – but also showed a significant reduction in mortality.

In light of these findings, it is crucial to acknowledge the limitations and confounding factors that have influenced our analysis. The study was conducted during the second wave of the COVID-19 pandemic, a period characterised by the redistribution of resources and staff. Consequently, the findings may not be directly applicable to non-pandemic settings, where the prioritisation of mobilisation might vary.

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Additionally, key disease severity parameters routinely collected in non-pandemic conditions, such as the SOFA and APACHE scores, were unavailable, limiting our ability to differentiate between patient groups based on illness severity. Furthermore, it was not possible to collect in-depth data, such as the duration of early mobilisation, nor was it feasible to measure functional responses, like grip strength. These limitations restrict our capacity to evaluate the intensity and effectiveness of mobilisation interventions comprehensively. Moreover, our study did not include subgroup analyses to individualise mobilisation therapy. In contrast, a study by Fuest *et al.* employed artificial intelligence-based analysis to identify clusters within the ICU, uncovering four distinct subgroups [35]. This approach facilitated the tailoring of mobilisation strategies to specific patient groups, suggesting that personalised mobilisation regimes could yield better outcomes.

Despite these limitations, the findings underscore the significant benefits of mobilisation for COVID-19 patients. However, it is concerning that mobilisation rates remained low during the early phase of the pandemic. The experiences from the COVID-19 pandemic highlight crucial pathways for managing future pandemics. The international exchange of knowledge and global collaboration facilitated the rapid dissemination of research results, enabling countries to learn from one another and coordinate their responses more effectively. Research conducted between the first and second waves enhanced the understanding of the disease, allowing healthcare workers to apply lessons learned and refine patient care strategies. As staff developed greater expertise in managing the complexities of the disease, patient outcomes improved through reduced errors and a greater application of evidence-based medicine. Our study results underscore the critical importance of structured guidelines, experiential learning, and global collaboration in creating resilient healthcare systems for future pandemics.

Author contributions

All authors contributed to the study conception and design. MG, TC, JJW and MC maintained the data-sharing platform and were responsible for the data curation. MM, ML, AP, conducted the data analysis. The first draft of the manuscript was written by MM, AP, ND, SJS. All authors revised and approved on the final manuscript.

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Prior Publications:

We confirm that the content of the manuscript has not been published or submitted for publication elsewhere.

Data Statement

The datasets analysed during the current study are available from the corresponding author on reasonable request. The data curation pipeline and data quality assessment (version 3.1) are publicly available https://doi.org/10.5281/zenodo.6063905

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