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# Early mobilisation in critically ill COVID-19 patients: a subanalysis of the ESICM-initiated UNITE-COVID observational study

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## Abstract

**Background** Early mobilisation (EM) is an intervention that may improve the outcome of critically ill patients. There is limited data on EM in COVID-19 patients and its use during the first pandemic wave.

**Methods** This is a pre-planned subanalysis of the ESICM UNITE-COVID, an international multicenter observational study involving critically ill COVID-19 patients in the ICU between February 15th and May 15th, 2020. We analysed variables associated with the initiation of EM (within 72 h of ICU admission) and explored the impact of EM on mortality, ICU and hospital length of stay, as well as discharge location. Statistical analyses were done using (generalised) linear mixed-effect models and ANOVAs.

**Results** Mobilisation data from 4190 patients from 280 ICUs in 45 countries were analysed. 1114 (26.6%) of these patients received mobilisation within 72 h after ICU admission; 3076 (73.4%) did not. In our analysis of factors associated with EM, mechanical ventilation at admission (OR 0.29; 95% CI 0.25, 0.35;  $p=0.001$ ), higher age (OR 0.99; 95% CI 0.98, 1.00;  $p\leq 0.001$ ), pre-existing asthma (OR 0.84; 95% CI 0.73, 0.98;  $p=0.028$ ), and pre-existing kidney disease (OR 0.84; 95% CI 0.71, 0.99;  $p=0.036$ ) were negatively associated with the initiation of EM. EM was associated with a higher chance of being discharged home (OR 1.31; 95% CI 1.08, 1.58;  $p=0.007$ ) but was not associated with length of stay in ICU (adj. difference 0.91 days; 95% CI  $-0.47, 1.37$ ,  $p=0.34$ ) and hospital (adj. difference 1.4 days; 95% CI  $-0.62, 2.35$ ,  $p=0.24$ ) or mortality (OR 0.88; 95% CI 0.7, 1.09,  $p=0.24$ ) when adjusted for covariates.

**Conclusions** Our findings demonstrate that a quarter of COVID-19 patients received EM. There was no association found between EM in COVID-19 patients' ICU and hospital length of stay or mortality. However, EM in COVID-19 patients was associated with increased odds of being discharged home rather than to a care facility.

*Trial registration* ClinicalTrials.gov: NCT04836065 (retrospectively registered April 8th 2021).

**Keywords** COVID-19, SARS-CoV-2, Early ambulation, Critical care, Intensive care units, Physical therapy specialty, Bed rest, Mobilisation

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## Introduction

Infection with the SARS-CoV-2 virus can lead to respiratory failure, requiring respiratory support and admission to an intensive care unit (ICU) [1]. Due to impaired muscle activity during critical illness, loss of muscle mass, muscle weakness, and functional limitations have been described in critically ill patients [2, 3]. The adverse impact of this so-called intensive care unit-acquired weakness (ICUAW) on weaning from mechanical ventilation and ICU and hospital length of stay are well-known [4, 5]. A Belgian single-centre study reported an incidence of ICUAW in coronavirus disease 2019 (COVID-19) patients of 52% at ICU discharge and 27% at hospital discharge [6]. COVID-19 patients affected by ICUAW had a median of 11-day longer ICU stay and low levels of mobilisation at ICU discharge, defined as being unable to sit independently at the edge of the bed. These significant functional limitations align with findings of another single-centre study from the United States investigating the outcome of COVID-19 patients after mechanical ventilation, which showed that 22% of patients required assistance with walking upon hospital discharge [7]. This occurred even though 94% of patients were functionally independent before admission to the hospital. Functional impairments of ICUAW can persist for years after discharge from ICU, leading to reduced quality of life, increased health care costs, and prolonged inability to work [4, 8]. Early mobilisation (EM) is an intervention that counteracts the described impairments. EM has demonstrated beneficial effects on functional independence and mobility at ICU discharge, resulting in shorter ICU and hospital lengths of stay and reduced duration of mechanical ventilation. Patients who received EM had a lower incidence of delirium and a higher likelihood of being discharged home [9, 10]. EM also revealed an improvement in the long-term outcome. It was observed that mobilised patients had less ICUAW and fewer long-term impairments one year after hospital discharge [11]. Due to this evidence, several guidelines recommended EM for all critically ill patients, provided there are no specific contraindications [12–14]. It is recognised that there is also the risk of adverse events with very intensive and active forms of EM [15]. However, as far as available, prevalence data demonstrate implementation rates between 0 and 33% [16–23].

With the SARS-CoV-2 pandemic starting in 2019, the number of patients with critical COVID-19 and severe acute respiratory syndrome increased rapidly [24]. At the pandemic's beginning, a patient population at high risk of developing ICUAW encountered healthcare systems trying to cope with limited bed capacity and staff resources [25]. Whether the COVID-19 pandemic impacted the implementation of EM is unknown.

The present study aimed to determine the implementation of EM in critically ill COVID-19 patients during the first wave of the pandemic in ICUs worldwide. Second, the study explored the factors associated with the implementation of EM and the outcomes of critically ill COVID-19 patients who underwent mobilisation.

## Methods

An international steering committee was established in 2020 by the European Society of Intensive Care Medicine (ESICM) to determine the burden of the novel COVID-19 disease in ICUs worldwide. ICUs were invited to participate in an international, multicenter, observational study (ESICM UNITE-COVID study). The methodology and data collection have been extensively described by Greco et al. [25] in the first analysis and Conway Morris et al. [26]. The study was approved by the Ethics Committee of Ghent University Hospital (registration number BC07826) and received institutional approval at each participating site. The trial was registered at ClinicalTrials.gov (NCT04836065). The requirements for informed consent were compliant with local regulations. This study is a pre-planned subanalysis with a focus on EM. Data are available from 280 ICUs in 45 countries worldwide.

## Patients

Data were collected from patients who met all of the following inclusion criteria: (1) age 18 years or older; (2) admission to an ICU or another area in the hospital under the care of the intensive care team on the day of the ICU's highest number of COVID-19 patients between February 15th and May 15th 2020; and (3) confirmed SARS-CoV2 infection by polymerase chain reaction or equivalent. Patients with SARS-CoV-2 infection but without COVID-19 diagnosis were excluded. In keeping with the observational study design, no additional interventions or measurements were performed, and patient care was delivered to local standards.

## Data management and extraction

Patient data were extracted from medical records from the day of admission up to day 60 of the ICU stay. Patient data were collected in the individual centres and submitted to a secure data-sharing platform (Clinfile, Vélizy-Villacoublay, France). The data were then curated according to the DAQCOR checklist; details were published previously [25]. The curation pipeline and code are publicly available on GitHub [27]. For our subanalysis, we excluded patients with missing data on EM (yes/no) and patients transferred from another ICU to avoid bias regarding the actual initiation of mobilisation.

## Variables

A priori, we selected relevant variables and cofactors for the analysis. To avoid any bias, we did not perform an imputation of missing data. Therefore, we excluded variables with more than 100 missing values to sustain an adequate number of observations. Control variables were then divided into: (1) demographics/admission data: sex, age, secondary comorbidities at admission (yes/no for each variable): chronic cardiac disease, chronic liver disease, history of hypertension, chronic neurological disease, chronic pulmonary disease, diabetes, asthma, malignant neoplasm, chronic kidney disease, immunosuppression, thromboembolic complications at admission, infection at admission, and country; (2) medications and supportive care during ICU stay at any point (yes/no for each variable) including antivirals, corticosteroids, antimalarial drugs, sedation, renal replacement therapy (RRT), inotropes/vasopressors, and tracheostomy.

## Outcomes

The primary outcome was the implementation of EM (yes/no) and influencing factors. EM included passive mobilisation, assisted-active mobilisation, and active mobilisation performed within 72 h after admission to the ICU, regardless of the duration [12, 28]. Passive mobilisation entailed at least the passive motions of all extremities in all physiological directions, passive cycling (bed pedal exerciser), passive vertical mobilisation (tilting table, standing frame), or passive transfer to rehabilitation chair. Positioning was not considered as early mobilisation. The level of mobility was assessed using the ICU Mobility Scale (IMS), a graded scale designed to document the highest level of mobility achieved by adult patients in an ICU [29]. The secondary outcomes that might be influenced by EM were the patient's status 60 days after admission to the ICU (yes/no for each variable): death at any time point, discharged alive, still hospitalised, palliative discharge, transfer to another care facility and still in ICU. Furthermore, we looked at ICU and hospital length of stay (number of days). There are several clinical practice guidelines available for EM. We aimed to determine whether these guidelines impacted the implementation of EM. For each country, the percentage of patients receiving EM was determined and we explored if a national clinical practice guideline for EM was available.

## Statistical analysis

Statistical analyses were done in R [version R 4.1.1. (2021-08-10)]. Descriptive statistics: categorical variables are expressed as frequencies (percentages), and continuous variables are described with median and interquartile

ranges. Significance testing for group differences was done with Chi-square tests for categorical data and Wilcoxon signed-rank test for continuous data using the `tableone`-package [30] and base R. For the primary and secondary analyses, we used mixed-effect multivariate linear and logistic models in combination with type III Anova using the `car`-package [31] and `lme4`-package [32]. Country was added as a random effect in all mixed models. To analyse factors associated with the initiation of EM (primary analyses), we built one multivariate mixed logistic model with EM (yes/no) as an outcome. For the secondary outcomes ICU and hospital length of stay, we used multivariate linear mixed models. For the secondary outcomes after 60 days, we built multivariate logistic mixed models for each endpoint separately. As described above, demographics, comorbidities, admission data, and medication and supportive care were included as covariates in the analyses of the secondary outcomes.

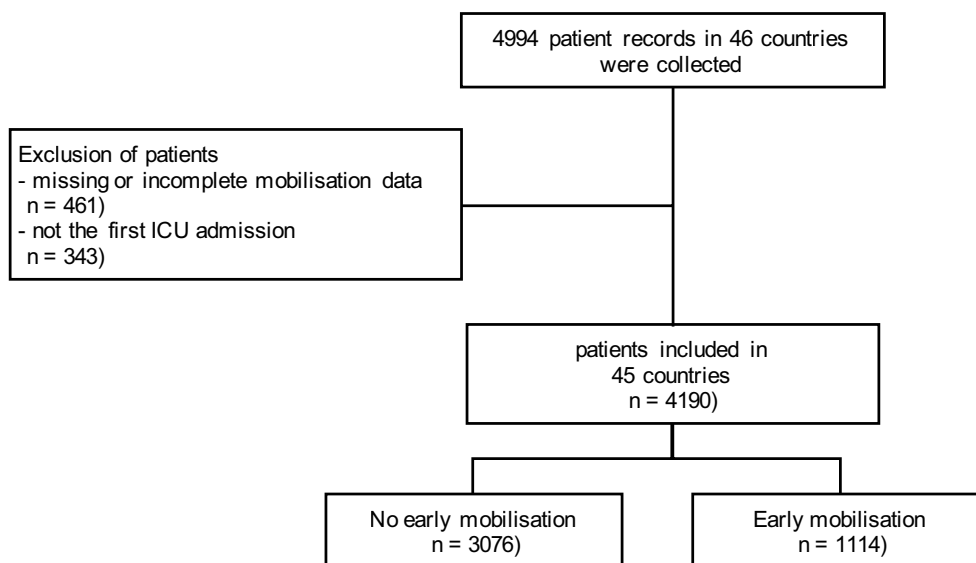
For primary analysis with EM as outcome, we only considered the effect of demographics, comorbidities and admission data; medication and supportive care received during the stay could have been received before or after the initiation of mobilisation since we did not record the exact dates and time of these interventions in our dataset. Therefore, we did not include them in the primary analysis. However, to present a comprehensive picture, we performed an association analysis comparing treatment differences and EM status.

The analysis considered guidelines identified through a systematic review by Lang et al. [33] and a literature search in PubMed using Medical Subject Headings (MeSH terms). Relevance was assessed based on title, abstract, and full text. Certain international mobilisation guidelines lacked specific country scopes, so country assignments were based on authors' affiliations. Guidelines with defined scopes also aligned with this assignment approach. We used a t-test to analyse the effect of existing guidelines on EM rates and calculated a permuted *p*-value to account for heterogeneity and differences in sample sizes between countries.

A nominal alpha level of 0.05 was considered statistically significant.

## Results

In total, data from 4190 critically ill patients with COVID-19 admitted to 280 ICUs in 45 countries were analysed after excluding patients with missing mobilisation data (EM yes/no) or with secondary ICU admission to capture EM accurately (see Fig. 1). A comparison between the included patients and those excluded due to missing EM data can be found in Additional file 1: Table S1. 1114 patients (26.6%) received EM, with a median ICU Mobility Scale (IMS) of 1 [0,



**Fig. 1** Flow diagram of available data, exclusion reasons, and missing data

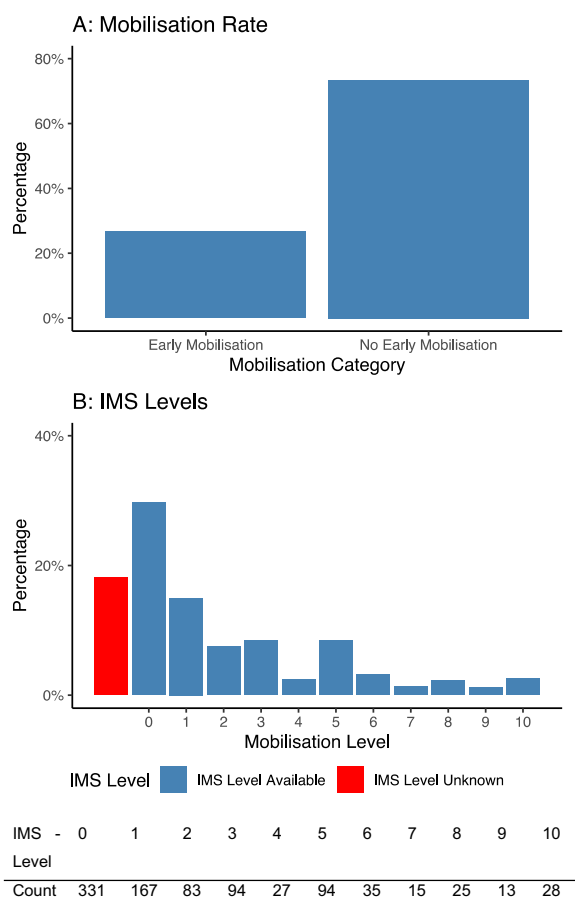
4] (Fig. 1). 70.8% of patients were male, and the median age was 62 [54, 70]. The most common reason for ICU admission was respiratory failure due to critical COVID-19 (95.8%), followed by other complications of COVID-19 (2.1%) or other diagnoses with coincident COVID-19 (2.0%). The most frequent comorbidity was arterial hypertension (50%). Baseline characteristics

are shown in Table 1, and an overview of the number of included observations and missingness for each variable is given in Additional file 1: Table S2. The illustration shows the percentage distribution of the two groups receiving EM and no EM, along with the frequency of achieved levels of mobilization(Fig. 2).

**Table 1** Patient demographics, admission data, and comorbidities at admission

	No EM = 3076	EM = 1114	p-value
Sex (male)	2176 (70.8)	798 (71.6)	0.61
Age	63 [54, 71]	60 [52, 69]	<0.001
Body mass index	27.9 [25.3; 32.2]	28.0 [24.9; 32.2]	0.44
Chronic cardiac disease	464 (15.3)	179 (16.2)	0.49
Chronic liver disease	83 (2.7)	23 (2.1)	0.27
History of hypertension	1529 (50.3)	560 (50.4)	0.98
Chronic neurological disease	198 (6.5)	58 (5.2)	0.14
Chronic pulmonary disease	281 (9.3)	94 (8.5)	0.47
Diabetes	955 (31.5)	359 (32.4)	0.62
Asthma	269 (8.8)	80 (7.2)	0.10
Malignancy	165 (5.5)	60 (5.4)	0.99
Chronic kidney disease	232 (7.6)	66 (5.9)	0.07
Immunosuppression	154 (5.1)	51 (4.6)	0.55
Thromboembolic complications at admission	106 (3, 4)	48 (4, 3)	0.22
Additional infection at admission	440 (14.3)	163 (14.6)	0.84
Mechanical ventilation			<0.001
Intubated at admission	1669 (54.9)	328 (30.3)	
Intubated during stay	1084 (35.7)	432 (39.9)	
Non-invasively ventilated during ICU stay	286 (9.4)	322 (29.8)	

Data are presented as n (%) or median [IQR]



**Fig. 2** ICU Mobility Scale (IMS)—level and count in the EM group. **A** Illustrates the percentage distribution of the two groups receiving EM and no EM. **B** Shows the frequency of mobilisation levels achieved within the first 72 h after admission to the intensive care unit according to the ICU Mobility Scale. The x-axis displays the ICU Mobility Scale as an ordinal scale, and the y-axis illustrates the percentage of observations. The exact values are presented in the table below. IMS-Level: 0—Nothing (lying in bed), 1—Sitting in bed, exercises in bed, 2—Passively moved to chair (no standing), 3—Sitting over edge of bed, 4—Standing, 5—Transferring bed to chair, 6—Marching on spot (at bedside), 7—Walking with assistance of 2 or more people, 8—Walking with assistance of 1 person, 9—Walking independently with a gait aid, 10—Walking independently without a gait aid

**Early mobilisation**

Variables present at admission that were associated with lower odds of initiating EM (see Additional file 1: Fig. S3) were mechanical ventilation at admission (OR 0.29; 95% CI 0.25, 0.35;  $p=0.001$ ), age (OR 0.99; 95% CI 0.98, 1.00;  $p= \leq 0.001$ ), pre-existing asthma (OR 0.84; 95% CI 0.73, 0.98;  $p=0.028$ ) and pre-existing kidney disease (OR 0.84; 95% CI 0.71, 0.99;  $p=0.036$ ). The variable positively associated with the initiation of EM was cardiac disease (OR 1.14, 95% CI 1.01, 1.29;  $p<0.030$ ). There were differences

in the type of supportive care and medications received during ICU admission when comparing patients receiving EM to those not receiving EM (Additional file 1: Table S3). The number of observations and missingness for each variable are provided in Additional file 1: Table S4. Countries with published mobilisation guidelines ( $n=16$ ) for critical care had significantly higher EM rates than countries without ( $n=29$ ; mean  $\pm$  SD EM rate:  $33 \pm 25\%$  vs  $17 \pm 16\%$ ,  $p=0.031$ , respectively). Countries’ EM rates are visualised in Additional file 1: Fig. S2, while details and guidelines are presented in Additional file 1: Table S5.

**Length of stay and 60-day outcomes**

Overall, there was no significant difference in length of stay in ICU (adj. difference 0.91 days; 95% CI 0.47, 1.37,  $p=0.34$ ) or hospital (adj. difference 1.4 days; 95% CI -0.62, 2.35,  $p=0.24$ ) when adjusted for covariates (Table 2).

There was no significant difference in mortality between patients receiving EM and those not receiving EM (OR 0.88; 95% CI 0.7, 1.09,  $p=0.24$ ) when adjusted for covariates. Patients who received EM were more likely to be discharged home than those not receiving EM (OR 1.31; 95% CI 1.08, 1.58,  $p=0.007$ ) and less likely to be discharged to another care facility (OR 0.69; 95% CI 0.48, 0.98,  $p=0.036$ ). In Fig. 3, the 60-day outcomes for the No EM and EM groups were visualised in a Sankey diagram.

**Discussion**

This analysis of a large international cohort of COVID-19 patients in the ICU provides a reasonable estimate of the implementation of EM during the 1<sup>st</sup> COVID-19 pandemic wave, with 27% of critically ill COVID-19 patients receiving mobilisation within the first 72 h of ICU admission. In addition, there were apparent differences in implementation; countries with published mobilisation guidelines for critical care had significantly higher EM rates. Initiation of EM was related to mechanical ventilation, age, and known comorbidities. Patients who received EM were more likely to be discharged home. Correspondingly, patients without EM were significantly more likely to be transferred to a care facility. However, we could not demonstrate a benefit of EM on length of stay or mortality.

Demographics and baseline comorbidities of our patient cohort were comparable to previous COVID-19 reports; the median age was 62 years, and male participants predominated. This is consistent with previous studies showing a higher risk of COVID-19 infection, more severe illness, and higher risk of ICU admission in men and older patients [34–36]. The most prevalent

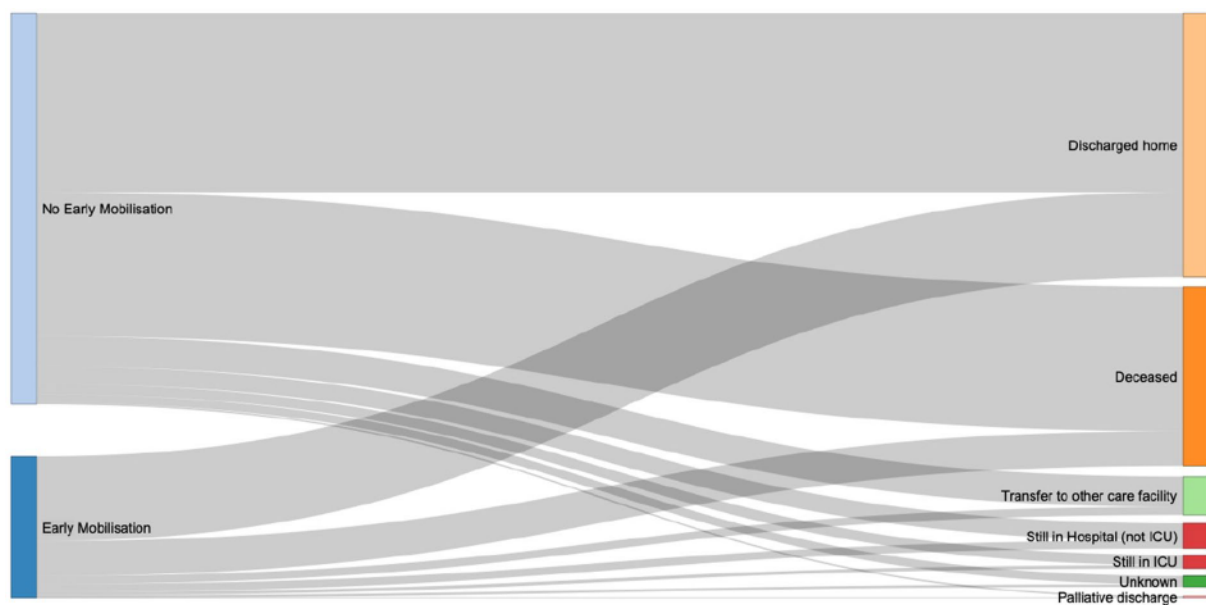
**Table 2** Outcomes

	No EM = 3076	EM = 1114	P (unadj.)	OR / adjusted <sup>a</sup> (95% CI)	P (adj.) <sup>a</sup>
ICU length of stay	18.00 [10.00, 28.00]	16.00 [8.00, 28.00]	0.001	0.91 (− 0.47, 1.37)	0.34
Hospital length of stay	30.00 [19.00, 45.00]	26.00 [16.00, 42.00]	< 0.001	1.4 (− 0.62, 2.35)	0.24
Outcome at 60 days					
Still in ICU	81 (2.6)	27 (2.4)	0.79	OR 0.76 (0.44, 1.32)	0.33
Still in hospital (not ICU)	137 (4.5)	62 (5.6)	0.16	OR 1.15 (0.79, 1.66)	0.47
Discharged home	1408 (45.8)	666 (59.8)	< 0.001	OR 1.31 (1.08, 1.58)	0.007
Transfer to other care facility <sup>b</sup>	239 (7.8)	63 (5.7)	0.023	OR 0.69 (0.48, 0.98)	0.036
Palliative discharge	13 (0.4)	2 (0.2)	0.38	OR 0.11 (0.01, 1.54)	0.10
Deceased	1132 (36.8)	274 (24.6)	< 0.001	OR 0.88 (0.7, 1.09)	0.24

Data are presented as n (%) or median [IQR]. OR odds ratio; CI confidence interval. Sixty-six patients in the No EM cohort and 20 in the EM cohort with unknown/undefined/other outcomes. An overview of the count of included observations and missingness for each variable is given in Additional file 1: Table S6

<sup>a</sup> The analysis was adjusted for the following variables: demographics/admission data: sex, age; secondary comorbidities at admission: chronic cardiac disease, chronic liver disease, history of hypertension, chronic neurological disease, chronic pulmonary disease, diabetes, asthma, malignant neoplasm, chronic kidney disease, immunosuppression, thromboembolic complications at admission, infection at admission, and country; medications and supportive care during ICU stay at any point: antivirals, corticosteroids, antimalarial drugs, sedation, renal replacement therapy (RRT), inotropes/vasopressors, and tracheostomy

<sup>b</sup> Other care facility refers to institutions where patients are transferred after hospital if they could not independently care for themselves at home due to their health condition. This may include rehabilitation facilities or residential care facilities



**Fig. 3** Sankey diagram. Sankey diagram representing the 60-day outcomes according to the No EM and EM group

comorbidities were arterial hypertension and diabetes mellitus, similar to other studies [23, 37]. Respiratory failure was the main reason for admission to ICU (96%), resulting in a high intubation rate of 48% at ICU admission, again consistent with previous studies [34].

Günster et al. [36] analysed more than 8679 COVID-19 patients and showed a 26.8% readmission rate for any cause within 180 days of discharge and an increase in all-cause in-hospital mortality from 25 to 30% after 6 months. Consequently, the long-term effects of

COVID-19 disease are serious. ICUAW was not recorded in these patients. Günster et al. showed that patients on mechanical ventilation, one of the main risk factors for ICUAW, had a higher readmission rate and worse outcomes. In the study by McWilliams et al. [23], all COVID-19 patients suffered from ICUAW at awakening. Frail patients had worse functional outcomes, which also influenced hospital discharge destination. The median time to first active mobilisation was 14±7 days, i.e. there was no implementation of EM [23]. Pun et al. also