Title	**Rehabilitation to enable recovery from COVID-19: a rapid systematic review**
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Competing Interests:

SL was on the Health Technology Assessment (HTA) Additional Capacity Funding Board, HTA End of Life Care and Add-on Studies Board, HTA Prioritisation Group Board and the HTA Trauma Board. The other authors declare no competing interests.

Contributor and guarantor information:

The following authors contributed to planning (VG, LA, AB, AC, JC, AD, JTC, SL) and conduct (VG, LA, AB, AC, JC, JD, MH, NM, JTC) of the study. All contributed to reporting.

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Structured Abstract

Objectives: To establish the evidence for rehabilitation interventions tested in populations of patients admitted to ICU and critical care with severe respiratory illness, and consider whether the evidence is generalizable to patients with COVID-19.

Methods: We undertook a rapid systematic review. Medline (via OvidSP), CINAHL Complete (via EBSCOhost), Cochrane Library, Cochrane Database of Systematic Reviews and CENTRAL (via Wiley), Epistemonikos (via Epistemonikos.org), PEDro (via pedro.org.au) and OTseeker (via otseeker.com searched to 7 May 2020. We included systematic reviews, RCTs and qualitative studies involving adults with respiratory illness requiring intensive care who received rehabilitation to enhance or restore resulting physical impairments or function. Data were extracted by one author and checked by a second. TIDier was used to guide intervention descriptions. Study quality was assessed using Critical Skills Appraisal Programme (CASP) tools.

Results: 6903 titles and abstracts were screened; 24 systematic reviews, 11 RCTs and 8 qualitative studies were included. Progressive exercise programmes, early mobilisation and multicomponent interventions delivered in ICU can improve functional independence. Nutritional supplementation in addition to rehabilitation in post-ICU hospital settings may improve performance of activities of daily living. The evidence for rehabilitation after discharge from hospital following an ICU admission is inconclusive. Those receiving rehabilitation valued it, engendering hope and confidence.

Conclusions: Exercise, early mobilisation and multicomponent programmes may improve recovery following ICU admission for severe respiratory illness that could be generalizable to those with COVID-19. Rehabilitation interventions can bring hope and confidence to individuals but there is a need for an individualised approach and the use of behaviour change strategies. Further research is needed in post-ICU settings and with those who have COVID-19.

Registration: Open Science Framework https://osf.io/prc2y

Contribution of the paper

- Due to the novel nature of COVID-19, there is currently no evidence specifically evaluating the benefits of rehabilitation for those in recovery.
- We found evidence that some rehabilitation programmes for adults requiring ICU for severe respiratory illness could be beneficial for people recovering from COVID-19
- There is limited evidence for programmes that could aid longer term recovery after discharge from hospital following severe respiratory illness that required an ICU admission

Key words: COVID-19; rehabilitation; systematic review

Background

On March 11th 2020 the World Health Organisation (WHO) classified COVID-19 as a pandemic. In December 2020 in the UK, there were over 1.75 million confirmed cases, with 62,033 deaths [1]. The main focus of all health services has been to maximise survival in those infected with a strong emphasis on sufficient critical care facilities and pharmacological treatments, along with the development of a vaccine. Observational studies describe acute shortness of breath, myalgia and fatigue as presenting symptoms [2], similar to other severe respiratory illnesses such as influenza [3]. However, it has also been recognised that ongoing symptoms may last several months after being infected including pain, fatigue, difficulty thinking, vertigo and insomnia [4]. Critical care can also result in muscle atrophy, weakness and functional impairment [5].   In addition, many who present with COVID-19 are older and some have pre-existing frailty, which is exacerbated during acute clinical care [6]. Some of these short and long terms symptoms may be responsive to rehabilitation to aid recovery, such as pain and fatigue which will impact on functional ability, participation and quality of life. However, the field of rehabilitation has been neglected [7] and experienced significant disruption during this pandemic [8].

Pragmatic recommendations were quickly developed including acute physiotherapy management of those with COVID-19 [9] focussing on respiratory care and COVID-19 specific precautions. However, when dealing with a new disease, we also need to utilise relevant and best available research from studies of similar, severe respiratory illnesses. Thus, we aimed to establish the evidence base for rehabilitation interventions tested in populations of patients admitted to an intensive care unit (ICU) and critical care with severe respiratory illness, and to consider whether this evidence is generalizable to patients with COVID-19. Our primary objective was:

• To establish whether rehabilitation interventions could improve functional ability and quality of life for adults recovering from severe COVID-19.

Secondary objectives were:

• To establish whether rehabilitation interventions could improve functional ability and quality of life in older people (aged 65+) and people with pre-existing conditions or frailty recovering from severe COVID-19?

• To explore the views and experiences of those undergoing such rehabilitation.

Methods

We undertook a systematic review of rehabilitation interventions for those with severe respiratory illness requiring intensive or critical care such as Severe Adult Respiratory Syndrome (SARS) where there are symptom parallels [3, 10]. We followed Cochrane rapid review methods guidance [11] and reported according to PRISMA guidelines [12]. The protocol was registered (https://osf.io/prc2y).

Data Sources and Search Strategy

Seven bibliographic databases (Medline (via OvidSP), CINAHL Complete, Cochrane Library, CDSR and CENTRAL, Epistemonikos, PEDro and OTseeker) were searched from inception to May 2020 using a search strategy (Supplementary Data).

Inclusion and Exclusion Criteria (Figure 1)

Study Selection and Data Extraction

We used a stepwise approach starting with systematic reviews. 25% of titles and abstracts were dual-screened with one reviewer screening remaining abstracts and a second screening all excluded abstracts. One reviewer screened all, and a second screened excluded full text papers. A third reviewer was involved where necessary. Any RCTs and primary qualitative studies included in the systematic reviews were listed to avoid inclusion in the subsequent study selection. The same screening process was then followed for RCTs and qualitative studies.

Data were extracted by one reviewer, checked by a second. Data included population, intervention, setting, outcomes, participants and results. Study quality was assessed using the relevant Critical Appraisal Skills (CASP) tools [13].

Analysis

In order to categorise interventions, we modified an existing intervention taxonomy [14] and added additional categories for mobility training, early mobilisation and neuromuscular electrical stimulation (NMES). *'Other'* was used where there was no description of an intervention other than, e.g. the term physical rehabilitation. We explored the impact of primary studies appearing in multiple included reviews. A narrative synthesis was undertaken, structured by intervention type and setting.

Results

Searches identified 6903 articles: twenty-four systematic reviews, with eleven RCTs and eight qualitative studies (that were not included in any of the reviews) were included (Figure 2).

Tables 1 and 2 summarise the included studies with intervention components reported as Supplementary Data. Figure 3 provides an overall summary of findings.

Study and Participant characteristics

Systematic reviews

Sixty-one unique RCTs and three unique qualitative studies were included in the 24 systematic reviews. Thirty studies were included in more than one review. Two different papers that were included reported the same Cochrane review [15, 16]. Where reported, the total sample sizes ranged from 136 to 2510 participants.

RCTs

Eleven additional RCTs that were not included in any of the reviews, were undertaken in ten countries with 993 participants. The majority reported a mean or median age between 60 and 69 years. The mean proportion of men was 52.6% (490/993). Where described, interventions tended to be delivered by physiotherapists. Outcomes varied between studies in term of follow up time points (longest was a year) and the measures used.

Qualitative studies

Of the eight qualitative studies not included in any of the reviews, four were undertaken in the UK. Sample sizes ranged from eight to 25 with three studies interviewing both patients and family. Studies included a broad range of ages up to 89 years, with men accounting for 45% to 80% of participants overall.

Quality of included studies

Methodological quality of the included studies is reported in Supplementary Files. The quality of the systematic reviews was generally good with all but one assessing the quality of the included studies. However, 8/24 (33%) were deemed to not have considered all important outcomes and only ten (24%) considered potential harms. The quality of RCTs and qualitative studies was more variable. Four of the eleven RCTs (36%) did not describe the method of randomisation, only six accounted for those recruited at follow-up and only three reported harms. As is common in trials of rehabilitation, it is not always possible to blind participants and those delivering the interventions to allocation, but assessors were blinded in eight RCTs (73%) although this was unclear in two RCTs. Most trials (8/11; 73%) did not clearly report adverse outcomes. For the qualitative studies, the recruitment strategy was not clear in half of the studies and the relationship between the researcher and participants was only considered in four of the eight studies. However, analysis appeared sufficiently rigorous in six of the studies.

Summary of Evidence by Intervention and Setting

Exercise

Four high quality RCTs and one qualitative study [17-21] involving 659 participants evaluated exercise interventions. Four included participants who were aged 65 and over [18-21]. No adverse events were recorded in two trials [18, 19] and one reported a tracheostomy issue.

ICU: One exercise programme (90 minutes, five days/week) was compared with usual care (30 minutes rehabilitation per day during ICU stay) [20]. No differences in any outcomes at any point during the six-month follow-up were found, with the exception of one secondary outcome measure. The Functional Independence Measure at three months showed an effect in favour of the exercise group (adjusted mean difference 9.7, 95% CI 0.9 to 18.5). Those undergoing a progressive exercise programme for 40 minutes daily, five days/week, compared with daily mobilisation, were more likely to be independent at discharge (Relative risk 0.07, 95% CI 0.02 to 0.23) .

Post-hospital discharge: Lau at al [17] and Battle et al [18] evaluated six-week outpatient exercise programmes. Lau reported improvements in the six-minute walk test (6MWT). However, this was not supported by Battle who found no differences in any outcome (including 6MWT) at discharge, six or twelve months. These inconclusive findings may be due to the high loss to follow-up (42%; 26/62) resulting in an underpowered study. In addition, Lau [17] included a younger population (in their 30s) with SARS whereas Battle [18] included an older sample (median 62 years; IQR 49 to 72) with medical/surgical conditions.

Ferguson and colleagues found that undertaking an exercise programme brought feelings of hope for both physical and mental health recovery [21]. However, lower levels of physical ability and mental health created barriers to engagement whereas individually tailored programmes provided confidence and motivation.

Exercise and Mobility Training

Four systematic reviews [15, 16, 22, 23] and two RCTs [24, 25] examined exercise plus mobility training. The mean age range was 60- 69 years. Few adverse events were reported.

ICU: Tipping et al [22] evaluated exercise and mobility programmes in a high quality systematic review and found a reduction in muscle weakness using the Medical Research Council Sum Score (pooled mean difference 8.62, 95% CI 1.39 to 15.86) and increased probability of walking independently at hospital discharge (Odds ratio 2.13, 95% CI 1.19 to

3.83) in favour of the intervention. There was no difference in mortality at six months (risk difference 0.01, 95% CI -0.06 to 0.08).

Post-ICU: Connolly et al [15, 16] included six RCTs in a Cochrane review examining interventions delivered post-ICU. Narrative analysis concluded that inconsistent findings, issues with methodological rigour and heterogeneity prevented conclusions being reached. One low quality trial [25] conducted a carer delivered, home-based rehabilitation programme with cardiorespiratory/neurological participants recovering following acute respiratory failure. Benefits were reported for cardiorespiratory participants in some respiratory function measures in the intervention group, but there was no of benefit in ADL, muscle strength or quality of life. No serious adverse events were reported although there were more deaths in the control group (6/24) compared with the rehabilitation group (2/24).

In a mixed-methods systematic review of barriers and facilitators to physical activity and mobilisation in ICU and post-ICU settings [23] there were only three included qualitative studies relating to patient experiences (out of 89 included studies). Physical and psychological factors, and, motivations and beliefs about physical activity were key considerations when promoting recovery following critical illness.

Early mobilisation

Nine systematic reviews [26-34] and three qualitative studies of mixed quality focussed on early mobilisation in ICU. Sixteen trials were reported in more than one review. One review [28] included 23 RCTs and over 2300 participants and found a reduced incidence of ICU–Acquired weakness (ICU-AW) (relative risk 0.6; 95% confidence intervals 0.4, 0.9) following early mobilisation programmes comprising flexibility, strength and mobility training. However, no benefit was identified in muscle strength at ICU discharge (Weighted Mean

Difference WMD 0.95 [95% CI -1.72, 3.61]). The network meta-analysis undertaken by Ding and colleagues found that optimum time to commence early mobilisation to reduce ICU-AW was during the first 72 to 96 hours of mechanical ventilation (Mean 0.11, 95% CI 0.02 to 0.58) [27].

Functional ability, in particular walking, was consistently found to improve following early mobilisation [26, 28-30, 34]. One study of 7 RCTs and 774 participants [29] reported improved walking independently (RR 1.42, 95% CI 1.17 to 1.72). Two systematic reviews [28, 33] found no difference in ICU length of stay or HRQoL. Reporting adverse events was not consistent across studies but, where reported, there were few [28, 30, 31, 34]. No detrimental effect on mortality due to early mobilisation was found in two studies [28, 33].

One qualitative study highlighted conflicting feelings of participants regarding fear and safety concerns versus moving around [35]. Laerkner and colleagues' ethnographic study explored nurse-patient interactions of mobilisation on intensive care [36] and demonstrated different perspectives of nurses and patients where patients found the idea of mobilisation engendered feelings of fear and harm whereas nurses viewed this positively. In contrast, participants using in-bed cycling in ICU described positive feelings of recovery, control and normalisation [37].

Neuromuscular electrical stimulation

Five studies, comprising two low quality RCTs [38, 39] and three mixed quality systematic reviews [40-42] evaluated NMES.

ICU: Although early systematic reviews [41, 42] suggested possible benefits from NMES in reducing muscle weakness, a meta-analysis [40], which included six RCTs with 718 participants, was inconclusive for impairment, service or adverse event outcomes. The most recent RCT finding also supports this [39].

Post-ICU: A small RCT [38] in a sub-acute hospital setting with older participants (mean age [SD] 75.8 [16] years) reported an improvement in muscle strength in favour of the intervention.

Multicomponent interventions

Eight studies, including six systematic reviews of generally good quality [43-48], and two RCTs [49, 50] evaluated interventions that comprised multiple components including exercise, mobilisation or NMES. The studies varied in their combined components (Supplementary Data).

ICU: Anekwe et al [43] evaluated early mobilisation and/or NMES in nine RCTs involving 841 participants. They reported a reduced likelihood of developing ICU-AW (Odds Ratio 0.71; 95% CI 0.53 to 0.95) in favour of the intervention group. One small, low quality RCT [49], with 30 participants evaluating NMES vs NMES plus strength training vs strength training alone, found no differences in muscle strength between the different arms.

ICU and post-ICU: An overview of reviews examining multicomponent rehabilitation programmes across the care continuum concluded that exercise and mobilisation programmes based in ICU may improve muscle strength and are safe but interventions targeting those discharged from ICU are inconclusive [47].

Post ICU: One high quality RCT [50] involving patients on a general hospital ward after transfer from ICU found no difference in outcomes although reported overall hospital costs were lower for those who received the intervention. Taito and colleagues [45] found no difference in the SF-36 physical and mental components scales, respectively (SMD 0.06, 95% CI -0.12 to 0.24; -0.04, -0.20 to 0.11).

Other interventions

Two systematic reviews and one RCT evaluated the effectiveness of other interventions. Four qualitative studies explored experiences of those undergoing rehabilitation.

ICU: Suwardianto and colleagues [51] reported improvements in bed transfers and cognition following a physical and cognitive rehabilitation programme compared with no rehabilitation, however both the intervention content and study details were poorly described.

Qualitative studies illustrate how setting rehabilitation goals, early in ICU, may not be a priority for patients or families who could only focus on survival. They described initially needing a paternalistic approach to goal setting [52, 53]. Critical care survivors described a lost sense of self which rehabilitation began to rebuild: therapy staff were perceived as trusted advocates who could provide motivation and person-centred approaches to help reconstruct a new future [53].

Post-ICU: One well conducted systematic review evaluating nutritional interventions in addition to rehabilitation in hospital suggested short-term benefits on the Barthel Index (SMD 0.30, 95% CI 0.02 to 0.58) in favour of the intervention group but no effect on quality of life [54]. A mixed quality narrative systematic review of post-ICU rehabilitation both in hospital and after discharge included a broad range of rehabilitation interventions and models of care, such as follow-up programmes. This concluded that post-traumatic stress disorder may be reduced but found no effect on other outcomes [55].

In a mixed-methods process evaluation examining the effectiveness of hospital-based multidisciplinary rehabilitation following ICU discharge, the importance of individualised rehabilitation was raised by participants. They described physiotherapy and nutritional care as particularly important in recovery [56].

Discussion

This systematic review aimed to synthesise current evidence for physical rehabilitation interventions performed in adults who were admitted to ICU or critical care that may be generalizable to adults with or recovering from severe COVID-19. We found evidence in those with severe respiratory illness and in mixed respiratory and surgical populations that interventions could improve muscle strength, walking and functional ability. These findings in relation to the 6MWT and Barthel index suggest effect sizes were both statistically and clinically significant [57, 58]. However findings regarding quality of life were inconclusive. The quality of included studies varied. No studies were identified for those with COVID-19. Almost all studies included some older people who are often excluded from research studies [59]. It has been recommended that during the current pandemic, if capacity becomes limited, then critical care should be prioritised for those most likely to survive, which would likely exclude those living with pre-existing frailty [60]. As none of the included studies reported exclusion criteria related to frailty and none reported pre-admission frailty status, we cannot be sure our findings apply to this population, although the overarching rehabilitation principles are unlikely to be very different. Most interventions were delivered in intensive care with a paucity of research conducted after hospital discharge. Outcomes reported were varied and often short term. Where reported, adverse events were few in number while there is good evidence that individually tailored exercise programmes can reduce the deleterious effects of inactivity without harm in ICU and acute settings [61].

Qualitative research showed that rehabilitation can bring hope and build confidence on the recovery journey, however an individualised approach is needed. These are key issues for those surviving COVID-19 [62]. Behaviour change strategies, such as goal setting, were perceived to be key components of motivation and recovery in the qualitative literature but these were not component parts of the interventions evaluated in our review. When developing and delivering rehabilitation programmes to support recovery from COVID-19 the inclusion of behaviour change should be integral and must be explicit and well described to facilitate implementation in healthcare settings [63].

The strength of this systematic review is the comprehensive search developed by a multidisciplinary team and adherence to best practice methodological guidance [11]. Where necessary, we prioritised findings from the most recent and highest quality systematic reviews to minimise the impact on our findings from individual primary studies that were cited in multiple reviews. This approach also reduced the contribution to our findings from earlier reviews that were generally narrative syntheses and included observational studies as well as RCTs. Nonetheless, there are some limitations. Firstly, by the rapid nature of this review, we could have omitted relevant studies by not e.g. undertaking forwards/backwards citation chasing. However, the broad range of databases searched would minimise missing key published studies [11]. In addition, our screening process identified eleven potentially relevant papers that were not available in English as full-text, which is a limitation. Secondly, by limiting inclusion criteria to those with severe respiratory illness requiring intensive care, these findings may not address the emerging rehabilitation needs of all those recovering from

COVID-19, such as those who required hospital care but were not deemed critical or those who were not admitted to hospital. The inclusion of studies with mixed respiratory and surgical populations could be seen as non-generalizable to a COVID-19 population. However, in these studies, all included participants with severe respiratory illness and rehabilitation interventions predominantly focussed on the cardiorespiratory and musculoskeletal impairments experienced by both these groups of patients, which have also been observed in those with COVID-19, such as muscle weakness. The mechanistic reasoning underpinning how the interventions may work [64], e.g. strength training to improve neuromuscular function could apply to those from both COVID-19 and non-COVID-19 medical and surgical populations requiring critical care, and to those who may have less severe symptoms. The participants in our review tended to be slightly younger than those admitted to hospital with COVID-19 in the UK [2]. Since we conducted our review, there have been increasing reports of additional wide ranging manifestations of COVID-19, such as delirium, peripheral neuropathy, dizziness and mood disorders. In the absence of COVID-19 specific evidence for managing these symptoms, NICE recommend individually tailored self-management, multidisciplinary rehabilitation and social care interventions [4]. Finally, our use of the CASP tools to assess study quality was for pragmatic reasons as it enabled multiple study designs to be assessed within the same framework.

A number of other reports are emerging providing recommendations for the rehabilitation of those recovering from COVID-19. Some suggest broad approaches in relation to service delivery rather than recommendations for specific interventions [65-67]. Others have combined a literature review with consensus statements [68, 69]. Our review now provides a rigorous evidence base to support the consensus statements, that had been developed using less robust methods, regarding the benefits of mobilisation and exercise in the acute setting

[9], goal setting and individualised rehabilitation [66]. Uniquely, our review also included programmes targeting post-hospital rehabilitation which is important not just for those who are discharged from hospital, but also to those with COVID-19 not admitted to hospital. This said, there was a paucity of evidence in this setting with limited benefit of interventions, and no studies based in residential/nursing care homes. There is also a lack of consensus on which outcome measures should be used but these should reflect what is important to those affected by COVID-19 [70].

Where reported, interventions were delivered mainly by physiotherapists. There were no studies reporting programmes delivered by a multidisciplinary team. This may be as a result of our search strategy as we excluded cognitive rehabilitation, which is more likely to be delivered by occupational therapists or psychologists. However, it is equally plausible that no research has been published including these professionals. This also limits application of existing evidence as these professionals are clearly supporting the rehabilitation of patients with COVID-19.

There remain unanswered questions about recovery and rehabilitation from COVID-19. We do not yet fully understand the short and long term rehabilitation needs of survivors, and importantly but this is starting to change through recent research funding. The PHOSP-COVID study is investigating the longer term recovery from COVID-19 following hospital admission (https://www.leicesterbrc.nihr.ac.uk/themes/respiratory/research/phosp-covid/). The Research and Innovation for Post-COVID-19 Rehabilitation Unit (RICOVR) has also been established to understand what interventions may work to aid physical, psychological, social and economic recovery (https://www.shu.ac.uk/research/specialisms/advanced-wellbeing-research-centre/ricovr). Commonly cited issues for survivors of COVID-19 include frailty, sarcopenia and fatigue, all of which may be amenable to rehabilitation interventions - but there are currently no RCTs underway to establish the effectiveness of programmes. Such trials should include outcomes that are important to those with the disease and consider cost-effectiveness as well as clinical effectiveness. Moving forwards, clinicians and academics need to agree on core outcomes for documenting recovery from COVID-19 to examine progress accurately. Any future rehabilitation research also needs to take into account practical considerations, such as personal protective equipment, as well as considering the use of technology to deliver and monitor programmes and the location of care.

Conclusion

Based on the best available evidence, our rapid systematic review found that those with severe respiratory illness and mixed respiratory and surgical populations admitted for critical care may benefit from progressive exercise, early mobilisation and multicomponent programmes to improve functional independence and walking. Qualitative evidence from those participating in these rehabilitation programmes valued an individualised approach and the bringing of hope and confidence to their recovery. This evidence could be generalised to those with, or recovering from, COVID-19. This said, there is room for improvement in the quality of research in this field and there is a paucity of evidence for effective interventions after discharge from ICU. There is a lack of evidence specifically relating to older people and those with frailty and a lack of consensus regarding outcome measures. Future research needs to better understand the trajectory and rehabilitation needs of those with COVID-19 across the care continuum in order to develop and evaluate relevant interventions.

Declarations

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Table 1 Description of study characteristics and findings by Intervention type

Source	Study design	Setting	Participants	Outcome domains	Primary Outcome Measure (Time point)	Intervention details	Study characteristics	Key Findings
EXERCISE ONLY								
Battle et al 2019 (UK)[18]	RCT	Outpatient	Adults, who had been patients on ICU	Impairment	6MWT (7 weeks, 6 months, 12 months)	Six- week, twice weekly individualised exercise programme including cardiopulmonary, balance and strengthening exercises. Control – usual care	62 mixed medical/surgical patients; Median age (IQR) 62 (49-72) years; 31/60 (52%) male	Mean difference in 6MWT at 7 weeks was -70.5 (95% CI -179.1 to 38.0). No difference in any outcome at any time point
Ferguson et al 2019 (UK)[21]	Qualitative using semi-structured interviews	Outpatient/home	ICU survivors taking part in an RCT	Perceptions	Perceptions of exercise programme	ICU survivors taking part in RCT of a six-week programme including aerobic and strength exercises	21 mixed medical patients; Mean age (SD) 53 (13) years; 10/21 (48%) male	Benefit of exercise more likely if pre-existing and new issues optimally managed.

								Personalisation of programme is a key facilitator
Schujmann et al 2019 (Brazil)[19]	RCT	ICU	Adults on ICU with 100 points on Barthel Index 2 weeks prior to admission	Impairment; Activity limitation	Barthel Index (Discharge from ICU)	Individualized progressive programme of strength and aerobic exercises and gait training during ICU stay. Control - usual care.	135 mixed medical/surgical patients; Mean (SD) age controls 55 (12) and intervention 48 (15); 85/135 (63%) male	Differences in Barthel (76 +/- 20 vs 97 +/- 5; 95% CI -26.3 to -14.5). Improvements in functional independence, mobility and light/moderate physical activity; inconsistent findings in muscle and respiratory function
Wright et al 2018 (UK)[20]	RCT	ICU	Adults requiring MV	Impairment; Activity limitation;	Physical Component Summary (PCS) of	Individualised and progressive strength	308 mixed medical/surgical patients; Mean (SD) age controls 64 (16) and	Mean difference in PCS at 6 months was -1.1

				HRQoL; Service outcomes	the SF-36 (6 months)	training 90 minutes a day, 5 days a week whilst on ICU. Control - usual care	intervention 60 (16) years; 180/308 male (58%)	(95% CI -7.1 to 5.0). No difference in outcomes at any time point except in Functional Independence Measure at 3 months.
Lau et al 2005 (China)[17]	RCT	Outpatient	People referred for physiotherapy from the SARS review clinic	Impairment; HRQoL	6MWT (6 weeks)	Six-week group aerobic and strength training programme (4-5 sessions per week). Control – usual care	133 patients with SARS; Mean age (SD) intervention 35.9 (9.3) and controls 38.3 (11.2) years; 45/133 male (34%)	6MWT -56.7 (95% CI -86.7 to -26.8). Inconsistent findings in muscle strength; no difference in SF36 domains
EXERCISE AND MOBILITY TRAINING								
Amundadottir et al 2019 (Iceland)[24]	RCT	ICU	Adults requiring MV for >48hours	Impairment; Activity limitation; HRQoL; Service	Duration of mechanical	Twice daily, progressive strength, balance and mobility training	50 mixed medical/surgical patients; Median (IQR) age intervention participants =	Median difference in ventilation

				outcomes; Adverse events	ventilation, ICU and hospital LoS	Control – Daily passive and active exercises and transfers	62 (50-70) and controls = 64 (58-74) years; 33/50 (66%) male	duration -0.8 days (95% CI -4.3 to 3.0). No difference in any outcome at any time point
Parry et al 2017[23]	Mixed methods SR	ICU and post-ICU	Adults admitted to ICU	Perceptions	Barriers and enablers to physical activity	Any physical activity	89 studies of mixed medical/surgical patients (4 RCTs; 4 qualitative studies of patient experiences. No summary data regarding participants	Barriers and enablers are multidimensional and include: Physical and psychological capacity; safety; culture and team; motivation and beliefs; environment

Tipping et al 2017[22]	Meta-analysis	ICU	Adults admitted to ICU > 24 hours	Impairment; Activity limitation; Adverse events	Mortality (hospital discharge)	Active mobilisation and rehabilitation	14 RCTs/CCTs; 1753 mixed medical/surgical patients. No summary data regarding participants.	Risk difference in mortality 0.02 (95% CI -0.01 to 0.05). Improved muscle weakness, activity limitation and participation.
Vitacca et al 2016 (Italy)[25]	RCT	Patients' home	Adults discharged from rehabilitation unit following critical care	Impairment; Activity limitation; HRQoL; Service outcomes;	Maximum Inspiratory Pressure (6 months)	6-month, daily home based programme supervised by carer including flexibility, mobility training, strengthening and aerobic exercises. Control – usual care	48 mixed medical/surgical patients; Mean age (range) controls 63 (43-81) and intervention 68.3 (49-83) years; 22/48 (46%) male	Effect sizes not reported. Inconsistent findings in respiratory outcomes; no difference in strength, quality of life or survival. No adverse events

Connolly et al 2015 & 2016[15, 16]	Narrative SR	Post ICU (hospital and community)	Adults admitted to ICU > 24 hours	Impairment; Activity limitation; HRQoL; Adverse events	Not specified	Exercise interventions	6 RCTs; 483 mixed medical/surgical patients. No summary data regarding participants.	No difference in outcomes
EARLY MOBILISATION								
Ding et al 2019[27]	Network meta-analysis	ICU	Adults undergoing MV	Impairments; Service outcomes	ICU-AW (not specified)	Early mobilization versus usual nursing care	15 RCTs; 1726 mixed medical/surgical patients. No summary data regarding participants.	Improved ICU-AW when started within 72-96 hours of MV compared with 24-48 hours (Mean difference 0.11, 95% CI 0.02 to 0.58); no difference in LoS
Okada et al 2019[33]	Meta-analysis	ICU	Adults admitted to ICU	HRQoL; Service outcomes; Adverse events	In hospital mortality, length of ITY/hospital stay and SF-36 (not specified)	Early mobilisation started within 1 week of ICU admission	12 RCTs; 1322 mixed medical/surgical patients. No summary data regarding participants.	Difference in mortality 1.12 (95% CI 0.80 to 1.58). No

								difference in outcomes
Zhang et al 2019[28]	Meta-analysis	ICU	Adults admitted to ICU	Impairment; Activity limitation; Service outcomes; Adverse events	Muscle strength, ICU-AW, functional mobility, duration of MV, ventilator free days, mortality rates, adverse events (not specified)	Early mobilisation versus routine care	23 RCTs; 2308 mixed medical/surgical patients. Mean ages ranged from 44.9 to 65.5 years. 1352/2308 (59%) male	Improved mobility, incidence of ICU-AW (relative risk 0.60, 95% CI 0.40 to 0.90) and discharge home rate. Reduced duration of MV. No different in mortality or adverse events
Laerkner et al 2019 (Denmark)[36]	Qualitative (Ethnography) with semi-structured interviews	ICU	Adult undergoing MV	Interactions	Nurse-patient interactions in relation to mobilisation	Mobilisation	13 interviews with mixed medical/surgical patients; age range 30-86 years; 8/13 (62%) male	Mobilisation is more than physical activity and involves negotiation and

	and observation						N=25 observations; age range 37-80 years; 17/25 (68%) male	behaviour change techniques
Doiron et al 2018[30]	Narrative SR	ICU	Adults admitted to ICU	Impairment; Activity limitation; Service outcomes; Adverse events	ADLs	Early mobilisation or active exercise of criticality ill participants either during or after MV	4 RCTs and quasi-RCTs; 690 mixed medical/surgical patients. Mean/median age range from 56 to 62 years. No summary data on sex.	No difference in outcomes
Fuke et al 2018[32]	Meta-analysis	ICU	Adults admitted to ICU	Impairments; HRQoL	ICU-AW, delirium free days, HADS (during hospitalisation)	Early rehabilitation	6 RCTs; 709 mixed medical/surgical patients. No summary data on participants.	Difference in incidence of ICU-AW (Odds ratio 0.42 (95% CI 0.22 to 0.82); no difference in other outcomes
Ringdal et al 2018 (Sweden)[37]	Qualitative involving semi-structured interviews	ICU	Adults in ICU	Experiences	Experiences of early mobilisation and in bed cycling	In bed cycling, 20 minutes a day for 5 consecutive days	11 mixed medical/surgical patients; age range 31-77 years; 5 (45%) male	Activity enables feelings of engagement, control and normalisation

Doroy 2016 (USA)[35]	Qualitative (Phenomenology) using semi-structured interviews	ICU	Adults on ICU employing a care bundle including early mobilisation	Experiences	Experiences of receiving care using an early mobility care bundle	Care bundle included pain management, breathing/awakening trials, sedation choice, delirium monitoring , early mobility/exercise and family involvement	12 ICU patients; age range 25-65 Years; 6 (50%) male	The care bundle not sufficient to improve patient experience of ICU. The role of follow up care needs to be considered
Da Silva Azevedo et al 2015 [26]	Narrative SR	ICU	Adults admitted to ICU	Activity limitation	Not specified	Early mobilisation	4 RCTs and 2 cohort studies; 806 mixed medical/surgical patients. No summary data on participants	Improved function
Castro- Avila et al 2015[29]	Meta-analysis	ICU	Adults admitted to ICU > 48 hours	Functional status; Walking ability; muscle strength; HRQoL; Duration of MV, LoS; Time in rehab	Functional status (not specified)	Early rehabilitation	7 RCTs/CCTs; 774 mixed medical/surgical patients. 481/774 (62%) were male.	Walking without assistance improved (Risk ratio 1.42; 95% CI 1.17 to 1.72); no difference in other outcomes

Laurent et al 2015[31]	Narrative SR	ICU	Adults admitted to ICU under MV	Adverse events	Unclear	Early exercise	22 studies (19 RCTs; 2 case series; 1 retrospective study); 2,307 mixed medical/surgical patients. No summary data on participants	Safe and feasible.
Silva et al 2014[34]	Narrative SR	ICU	Adults admitted to ICU	Impairment; Activity limitation; HRQoL; Service outcomes; Adverse events	Function; duration of MV and ICU (not specified)	Early mobilisation	8 RCTs; 731 mixed medical/surgical patients. No summary data on participants	Improvement across all outcomes
NMES								
Zayed et al 2020[40]	Meta-analysis	ICU	Adults admitted to ICU	Impairment; Service outcomes; Adverse events	Muscle strength (not specified)	NMES applied to different muscle groups	6 RCTs; 718 mixed medical/surgical patients. Mean age (SD) 60 +/- 15.3 years; 435.718 (60.6%) male	Mean difference in muscle strength 0.45 (95% CI -2.89 to 3.80). No difference any outcomes

Chen et al 2019 (Taiwan)[38]	RCT	Sub-acute care	Adults requiring MV > 21 days	Impairment; Activity limitation; Service outcomes	Pulmonary function, muscle function and physical function (10 days)	Daily electrical stimulation for two 30 minute sessions per day 5 days a week for 2 weeks on vastus lateralis and rectus femoris bilaterally. Control group had similar electrode placement but stimulator power was turned off	33 mixed medical/surgical patients; Mean (SD) age controls 73.8(17.8) and intervention 77.7 (14.3) years; 17/33 (52%) male	Inconsistent findings in muscle function. No difference in other outcomes
Koutsioumpa et al 2018 (Greece)[39]	RCT	ICU	Adults requiring >96 hours MV	Impairment; Service outcomes	Histologically diagnosed myopathy on 14th day of ICU admission	Transcutaneous electrical neuromuscular stimulation on bilateral quadriceps for 60 minutes for 10 days Control - usual care	80 mixed medical/surgical patients; Mean (SD) age controls 66 (13.1) and intervention 64 (12.4) years; 60/80 (75%) male	Effect sizes not reported. No difference in any outcomes
Maffiuletti et al 2013[41]	Narrative SR	ICU	Adults with critical illness	Impairment	Muscle strength and mass (not specified)	NMES using a defined protocol	8 RCTs; 172 mixed medical/surgical patients. 126/172 (73%) were male. No summary data on age of participants.	Improved muscle weakness; No difference in muscle mass

Parry et al 2013[42]	Narrative SR	ICU	Adults admitted to ICU	Impairment	Not specified	Electrical muscle stimulation applied to peripheral muscles	9 RCTs/CCTs; 136 mixed medical/surgical patients. No summary data on participants.	Improvements in strength for those with long-term admissions
MIXED INTERVENTIONS (combination of exercise/mobility training/early mobilisation/NMES								
Anekewe et al 2020[43]	Meta-analysis	ICU	Adults with critical illness	Impairment; Service outcomes	ICU-AW	Early mobilisation and/or NMES compared to usual care.	9 RCTs; 841 mixed medical/surgical patients. No summary data on participants.	Improved ICU-AW with early rehabilitation (Odds ratio 0.71, 95% CI 0.53 to 0.95); more likely to return home
Taito et al 2019[45]	Meta-analysis	Post ICU (hospital and community)	Adults discharged from ICU	Activity limitation; HRQoL; Adverse events	SF36 physical and mental component scores, ADL function and mortality (1 month and 6 months)	Protocolised rehabilitation following ICU discharge earlier than/more intensive than usual care	10 RCTs; 1,110 mixed medical/surgical patients. Mean/median age raged from 40.5 to 68.5 years. No summary data on sex	SMD for PCS 0.06 (-0.12 to 0.24). No difference in other outcomes

Akar et al 2017 (Turkey)[49]	RCT	ICU	Adults with COPD requiring MV for >24hours	Impairments; Activity limitation;	Muscle strength; mobility (not specified)	Group 1 – Active extremity exercise training plus NMES bilaterally on deltoid, quadriceps 5 days per week for 20 sessions; Group 2 – NMES only. Group 3 – active extremity training only	30 people with COPD; Mean (SD) age Group 1 70 (12.3), Group 2 62.3 (6.8), Group 3 68 (17.8) years; 15/30 (50%) male	No effect sizes presented. No difference in any outcome
Gruther et al 2017 (Austria)[50]	RCT	General hospital ward	Aged >16 with > 5 days ICU stay	Impairments; Service outcomes; Adverse events	Number of days from discharge to general ward until hospital discharge	Early rehabilitation (aerobic and resistance exercises programme and NMES) 2 hours a day, 5 days a week versus usual care	50 mixed medical/surgical patients; Median (IQR) age controls 59 (48-70) and intervention 64 (46-70) years; 14/50 (28%) male	No effect sizes presented. No difference in outcomes. Hospital costs were lower in the intervention group. No adverse events
Connolly et al 2016[47]	Narrative SR of reviews	ICU; post ICU	Adults with critical illness	Impairments; HRQoL; Service	Not specified	Physical rehabilitation that addressed exercise and/or	5 systematic reviews; 2479 mixed medical/surgical	Improvements (short-term) in strength, LoS and

				outcomes; Adverse events		mobility programme, use of cycle ergometry or NMES	patients. No summary data on participants.	duration of MV; Inconclusive outcomes post discharge; few adverse events reported
Kayambu et al 2013[44]	Meta-analysis	ICU	Adults with critical illness	Impairments; Activity limitation; HRQoL; Service outcomes; Adverse events	Mortality, length of hospital and ICU stay, physical function, quality of life, muscle strength, ventilator free days (not specified)	EMS, exercise, mobility training	10 RCTs; 790 mixed medical/surgical patients. Mean age was 59.3 years (control) and 63.6 (intervention). Amongst controls 69% were male and 73% of intervention participants.	Improvements across a range of outcomes including physical function (pooled effect size 0.46, 95% CI 0.13 to 0.78); no difference in mortality
Stiller 2013[46]	Narrative SR	ICU	Adults admitted to ICU	Impairments; Activity limitation; Service outcomes; Adverse events	Not specified	Any physiotherapy interventions	85 studies of mixed medical/surgical patients (12 systematic reviews; 20 RCTs; 8 CCTs; 22	Improvement in function and LoS; Inconsistent

							observational studies; 15 surveys; 3 opinion papers). No summary data on participants	evidence for NMES
Pinheiro et al 2012[48]	Narrative SR	ICU	Adults admitted to ICU	Impairments; Activity limitation; Service outcomes; Adverse events	Not specified	Physiotherapy, mobility and mobilisation in the ICU. Included electrostimulation, cycle ergometry and kinesiotherapy	8 studies (7 RCTs); 332 mixed medical/surgical patients. Unclear data on participant characteristics	Improvements in strength and function

Table 2 Description of study characteristics and findings for other interventions

Source	Study design	Setting	Participants	Outcome domains	Primary Outcome Measure (Time point)	Intervention details	Study characteristics	Key Findings
OTHER INTERVENTIONS								
Van Willigen et al 2020 (UK)[52]	Qualitative using semi-structured interviews	ICU	ICU survivors	Perspectives	Patient and family perspectives on physical rehabilitation	Physical rehabilitation	N=5; age range 23-68 years; 4 (80%) male N=5 family members	Rehab should focus on building relationships and good communication, be consistent and start as soon as possible.
Kou et al 2019[54]	Meta-analysis	Hospital	Adults with an acute and critical illness	Impairments; Activity limitation; HRQoL; Adverse events	ADLs (not specified)	Nutritional interventions (lectures, counselling, fortified	2 RCTs; 293 mixed medical patients. No summary data on paticipants	Improvements in muscle mass; Short term improvements

			undergoing rehabilitation			foods, oral nutritional supplements or parenteral/enteral nutrition) plus rehabilitation (defined as comprehensive or individualised expert programme)		in Barthel Index at 6 months (SMD 0.30, 95% CI 0.02 to 0.58). No effect on HRQoL. Adverse events not reported
Corner et al 2018 (UK)[53]	Qualitative (Grounded theory) using semi-structured interviews	ICU and post discharge	ICU survivors and family members	Experiences	Experience of rehabilitation and recovery	Physical rehabilitation	N=15 mixed medical/surgical patients; age range 30-89 years; 11/15 (73%) male 4 family members (dyads)	Need to recalibrate past, present and future self and differences between expectation and reality; recovering autonomy

								needs motivation and support
Suwardianto et al 2018 (Indonesia)[51]	RCT	ICU	Adults admitted to ICU > 24 hours	Impairments; Activity limitation. MMSE, PFIT	Not specified	Physical and cognitive therapy. Control no intervention	N=64 mixed medical patients; mean (SD) age controls 48 (11.4) and intervention 59.9 (11) years; 35/64 (55%) male	Effect sizes not clearly reported. Improved bed transfers and cognitive function
Felten-Barentz et al 2018 (Netherlands)[71]	Qualitative (Phenomenology) using semi-structured interviews	ICU and post discharge	Ventilated adults receiving hydrotherapy	Experiences	Meaning and experience of hydrotherapy	Hydrotherapy	N=8 mixed medical/surgical patients; age range 33-73 years; 4/8 (50%) male	Feelings of safety and ability to move that can involve families. A turning point in the recovery journey

Ramsay et al 2016 (UK)[56]	Mixed methods process evaluation using a questionnaire and focus groups	Hospital (post-ICU)	Participants from an RCT (intervention and control) RECOVER trial	Experiences	Experiences of rehabilitation and quality of care	Physical (MDT) rehabilitation (enhanced physiotherapy, nutritional care and information provision, case management. Usual care comparator	N=14 focus group participants (+8 family members) 182 experience questionnaires. Median age (IQR for intervention participants 55 years (36, 69) and controls 70 years (63, 78). 50% of intervention participants were male and 66% controls	Individualised care and information highly valued. Enabled greater access to physiotherapy and nutritional care
Mehlhorn et al 2014[55]	Narrative SR	Post ICU (hospital and community)	Adults post ICU admission	Impairments; Activity limitations; HRQoL; Service outcomes; Adverse events	Not specified	Rehabilitation	19 studies (9 RCTs); 2,510 mixed medical/surgical patients. No summary data of participants	PTSD may be reduced; no effect on other outcomes

Figure 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adults with respiratory illness that required intensive or critical care. This could be part of a mixed medical or surgical population • Received rehabilitation to enhance or restore physical impairment or disability • Measured impairments, functional ability, participation, quality of life or patient experience of rehabilitation	• Adults receiving palliative care • Focus was cognitive rehabilitation or respiratory physiotherapy • Intervention was delivered in a hospice • Staff experiences • Conference abstracts, opinion papers, non-systematic reviews, and non-randomised trials. • Non-English language

Figure 2 PRISMA flow diagram

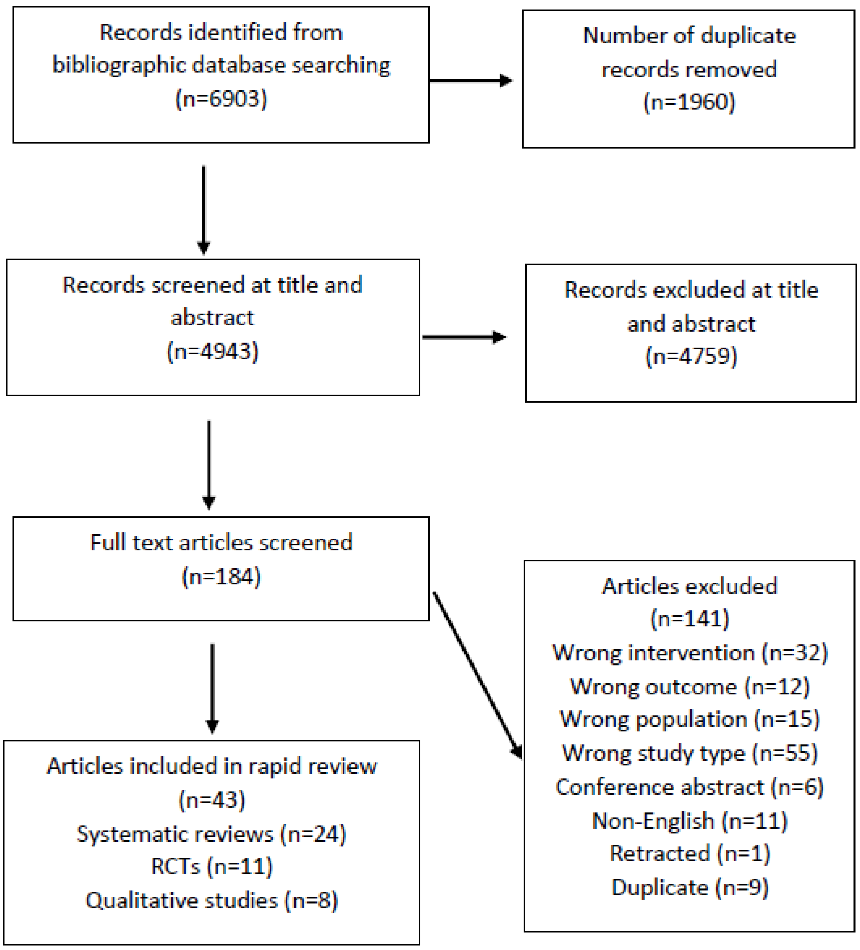

Figure 3 Summary of findings

- Progressive exercise programmes delivered in ICU can improve functional independence
- Exercise may increase aerobic capacity in younger patients following hospital discharge but for those middle and older age the findings are inconclusive.
- There is inconclusive evidence for NMES in ICU. For older patients in a sub-acute hospital setting, muscle strength may improve with NMES.
- Exercise and mobility training or early mobilisation +/- NMES in ICU can improve muscle strength and independent walking.
- Exercise and mobility training supervised by carers in the home may improve respiratory function.
- Early mobilisation in ICU may reduce ICU-AW and improve functional ability and walking. The optimal time to commence early mobilisation is between 72 and 96 hours of starting mechanical ventilation.
- Nutritional supplementation combined with rehabilitation may improve performance in activities in daily living in post-ICU hospital settings
- This evidence could be generalizable to those with, or recovering from, COVID-19 who required critical care.