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A systematic review and meta-analysis of the effects of early mobilization therapy in patients after cardiac surgery

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Abstract

Background: Prolonged hospitalization and immobility of critical care patients elevate the risk of long-term physical and cognitive impairments. However, the therapeutic effects of early mobilization have been difficult to interpret due to variations in study populations, interventions, and outcome measures. We conducted a meta-analysis to assess the effects of early mobilization therapy on cardiac surgery patients in the intensive care unit (ICU).

Methods: PubMed, Excerpta Medica database (EMBASE), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro), and the Cochrane Library were comprehensively searched from their inception to September 2018. Randomized controlled trials were included if patients were adults (≥18 years) admitted to any ICU for cardiac surgery due to cardiovascular disease and who were treated with experimental physiotherapy initiated in the ICU (pre, post, or perioperative). Data were extracted by 2 reviewers independently using a pre-constructed data extraction form. Length of ICU and hospital stay was evaluated as the primary outcomes. Physical function and adverse events were assessed as the secondary outcomes. Review Manager 5.3 (RevMan 5.3) was used for statistical analysis. For all dichotomous variables, relative risks or odds ratios with 95% confidence intervals (CI) were presented. For all continuous variables, mean differences (MDs) or standard MDs with 95% CIs were calculated.

Results: The 5 studies with a total of 652 patients were included in the data synthesis final meta-analysis. While a slight favorable effect was detected in 3 out of the 5 studies, the overall effects were not significant, even after adjusting for heterogeneity.

Conclusions: This population-specific evaluation of the efficacy of early mobilization to reduce hospitalization duration suggests that intervention may not universally justify the labor barriers and resource costs in patients undergoing non-emergency cardiac surgery.

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Abbreviations: CI = confidence interval, CINAHL = Cumulative Index of Nursing and Allied Health Literature, EMBASE = Excerpta Medica database, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, ICU = intensive care unit, ICU-AW = intensive care unit-acquired weakness, PRISMA-P = Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols, PEDro = Physiotherapy Evidence Database, RCTs = randomized controlled trials, RR = relative risk, SMD = standardized mean difference, WMD = weighted mean difference.

Keywords: cardiac surgery, intensive care unit (ICU), meta-analysis, mobilization

1. Introduction

Prolonged intensive care hospitalization has been linked to increased morbidity and long-term mortality after hospital discharge.[1] It has been estimated that up to 46% of intensive care unit (ICU) patients acquire intensive care unit-acquired weakness (ICU-AW) during their stay.[2] ICU-AW includes polyneuropathy, myopathy, and/or muscular atrophy which can prolong immobilization and inhibit long-term physical and cognitive function.[3] Early physical rehabilitation has been associated with improved physical function and is recommended for ICU patients by the European Society of Intensive Care Medicine.[1] While independent studies have reported a variety of benefits of early mobilization therapy, including reduced mechanical ventilation days, reduced hospital length of stay, and functional outcomes,[4] various reviews have confirmed only the short-term benefits of early mobilization intervention, calling into question whether the high resource and labor costs offset these short-term benefits.[5]

Other reviews of early mobilization therapy in critically ill patients have yielded conflicting findings, with either no or inconsistent effects on functional recovery, quality of life, length of ICU or total hospitalization stay, and long or short-term mortality.[6,7] Conflicting findings may be due to several factors including intervention differences, variations in reporting, quality of available resources, etc. Moreover, it should be noted that some systematic reviews have entirely deemed the current body of literature suboptimal for comparison due to lack of consistency or reliability in the delivered intervention.[8] For example, Reid et al[8] report that out of 117 studies evaluated, none reported the same intervention in exactly the same way. Thirty-seven percent did not report intervention start time and 26% did not report overall intervention duration, limiting understanding and generalizability of the interventions. Another potentially confounding factor is the variety of patient populations (and acuities) evaluated across studies of ICU early mobilization, which often include patients admitted for cardiac disease, respiratory illness, and acquired brain injury, among other critical illnesses. Toward the aim of improving homogeneity of patient populations, an increasing number of targeted studies are being undertaken.

It has been reported that 58% of cardiac surgery patients are vulnerable to post-operative complications and subsequent delays in hospital discharge and functional recovery. While currently, early mobilization and prophylactic respiratory physiotherapy are post-operatively prescribed for cardiac surgery patients, no consensus exists regarding optimal mobility protocols nor how these interventions impact hospitalization duration, post-operative complications, or functional recovery of cardiac surgery patients specifically.

To address the lack of conclusive evidence of the effect of early mobilization on cardiac surgery patients in critical care settings, this systematic review and meta-analysis aimed to evaluate randomized controlled trials exclusively evaluated in cardiac surgery patients treated experimentally with early mobilization.

2. Methods

2.1. Study design

This systematic review of randomized controlled trials (RCTs) was performed to evaluate the effects of early mobilization therapy on cardiac surgery patients in the ICU. We followed the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplementary Checklist).

2.2. Search strategy

The following databases were used to search for relevant keywords: PubMed, Excerpta Medica database (EMBASE), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro), and the Cochrane Library from inception to September 20, 2018 (Table 1). Two independent investigators (XY and DD) screened titles, keywords, and abstracts for relevant indicators and abbreviated adherence to inclusion/exclusion criteria. If a publication cited other relevant titles not already identified by the initial search strategy, effort was made to track down and screen those titles. A second, full-text screening of all qualifying entries was subsequently performed according the criteria listed below. Effort was taken during screening to identify and mitigate potential sources of publication bias such as the independent assessment of a randomized controlled trial based on methodology rather than claim or title and the inclusion of qualifying cardiac populations included in larger intensive care unit studies, where the cardiac population could be extracted from the data set. However, factors inherent to randomized trials such as the bias of publication of positive findings as well as our exclusion of studies published in non-English languages should be considered.

2.3. Methodological quality assessment

A methodological quality assessment of studies was performed by 2 investigators (XZ and DL) independently using the PEDro scale.[9] The PEDro scale has demonstrated acceptable validity and reliability among physiotherapy trials[10] and was selected due to its high interrater reliability and strong convergence with the Cochrane Back and Neck (CBN) risk of bias tool.[11,12] The scale evaluates 11 items including: *inclusion criteria and source, random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, completeness of follow up, intention-to-treat analysis, between-group statistical comparisons, and point measures and variability.* Each item is rated as either a "yes" or "no" and the total PEDro score is tallied by the total number of "yes" items (excluding the inclusion criteria and source item). In a few instances, discrepancies regarding study qualification or methodological quality scores were resolved between investigators by discussion after scores/lists had been generated independently. In these cases the authors worked together to come to an agreement on inclusion/exclusion or quality score.

2.4. Participants

The authors included studies of adult patients (≥18 years) admitted to any ICU for cardiac surgery due to cardiovascular disease and who were treated with experimental physiotherapy initiated in the ICU (pre, post, or peri-operative).

2.5. Interventions and comparators

Interventions could include passive or active exercises, strengthening exercises, cycling, progressive mobility, or any combination thereof. Studies were included only if a comparator group included either no prescribed mobilization intervention or

Table 1

Electronic search strategy in different databases.

Excerpta Medica Database (EMBASE)					
Title, Abstract, Author keywords	AND	Intensive Care Unit	AND	mobilization	
Cardiac		ICU		mobilisation	
		critical care		physical therapy	
				physiotherapy	
Cumulative Index to Nursing and Allied Health Literature (CINAHL)					
Title (TI)	AND	Abstract (AB)	AND	Abstract (AB)	
Cardiac		intensive care unit		rehabilitation	
Abstract (AB)		ICU		therapy	
Intensive Care Unit		critical care		treatment	
*academic journals only filter applied					
Physiotherapy Evidence Database (PEDro)					
[Title field]	AND	[Therapy Field]	AND	[Method Field]	
cardiac		fitness training		clinical trial	
		strength training			
		stretching, mobilization, manipulation, massage			
Cochrane Library					
Title Abstract Keyword	AND	intensive care	AND	physiotherapy	
cardiac		ICU		mobilization	
*Word variations automatically searched		critical care		physical therapy	
Pubmed					
cardi*	AND	early ambulation	AND	intensive care	
		early mobilization		unit critical care	
		exercise therapy			
		ambulation			
		physiotherapy			
		physical therapy			

* Wildcard operator.
** Clinical trials filter was applied.

delayed intervention (i.e., intervention prescribed after ICU discharge).

Studies which included only a portion of patients admitted for cardiac disease-related events were excluded. Studies including patients admitted for myocardial infarction or other emergency cardiac surgery were excluded as these populations are typically prescribed mobile restriction to reduce cardiac overload. Massage and electro-muscular stimulation studies were not included. Additionally, we excluded studies where intervention was initiated after ICU discharge, or consisted mainly of chest physiotherapy, or other respiratory interventions (i.e., inspiratory training). Likewise, table tilt or vibration-capable bed interventions were excluded. Studies which relied on self-monitored, self-initiated, or self-reported mobility therapy and/or metrics of mobility were excluded. Intervention protocol studies, safety and feasibility studies, editorials, reviews, surveys of practice, retrospective, non-randomized, and non-English studies were also excluded. Studies were excluded if they did not report at minimum the duration of total hospitalization. Finally, studies where comparator included variations in physiotherapy (intensity, frequency, or duration) rather than a true control (delayed or no intervention) group were also excluded.

2.6. Outcomes

Primary outcomes: Hospital length of stay and ICU length of stay.

Secondary outcomes: Physical Function and Adverse Events.

Physical function in this review was defined as any supervised assessment of ambulation or mobility as well as the administration of questionnaires of physical capacity such as the physical portion of the short form (SF-36), a generalized quality of life survey. In this review adverse events were defined as was defined as any occurrence threatening the stability or eligibility for inclusion of the patient including, myocardial infarct, hospital mortality, formation of pressure ulcers/hematomas, etc. Primary outcomes were measured based on hospital admission and discharge records. Due to the variable nature of the intervention, which could be pre-, peri-, or post-operative (ranging from a single session to months of recurring physiotherapy), secondary outcomes were assessed at varying intervals.

2.7. Data synthesis and analysis

Data were extracted by 2 reviewers (XZ and DL) independently using a pre-constructed data extraction form. The data extraction form included the publication information (title, authors, year, etc), participant characteristics (age, gender, etc), intervention details (intervention of experimental group and intervention of control group, frequency, intensity, duration, follow-up), outcomes (primary outcome and secondary outcome, outcome instruments), and study design (randomized, blinded, etc). For continuous data, standard deviation (SD) or standard error (SE) values were extracted. For categorical data, the number of events was extracted.

Review Manager 5.3 (RevMan 5.3) was used for statistical analysis. For all dichotomous variables, relative risks or odds ratios with 95% confidence intervals (CI) were presented. For all continuous variables, mean differences (MDs) or standard MDs with 95% CIs were calculated. Two-sided P value of <.05 was defined as statistical significance. The fixed-effect model was used if data were available and there was no significant heterogeneity.

If heterogeneity was high ($I^2 > 75\%$), the pooled analysis was not considered and a sensitivity analysis was performed. The χ^2 test and Higgins I^2 value were used to assess statistical heterogeneity, with $I^2 > 75\%$ suggesting high statistical heterogeneity.[13] In some evaluations, studies were excluded on the basis of clinical heterogeneity to determine the study's influence on the pooled effect size.

2.8. Participant and public involvement

No patients were involved in this study.

2.9. Ethical consideration

Institutional review board approval was not necessary because all the data were retrieved from public databases.

3. Results

3.1. Study selection

The search among all databases included in this systematic review yielded 1100 and 10 additional studies were identified through other sources. One thousand and fifty studies underwent expedited screening (after removal or duplicates) which included mining summaries and abstracts for compatibility with inclusion/exclusion criteria. After expedited screening, 98 studies were reviewed in full. In 39 studies, the cardiac disease population of interest was either not represented in the pool of critically ill patients or was mixed with patients admitted for non-cardiac critical illness or unspecified. In 35 studies, the intervention did not meet the inclusion criteria, in 13 studies the clinical intervention was not initiated in an ICU, and in 5 studies the comparator group was deemed incompatible with outlined criteria. Ultimately, 5 studies were included in the data synthesis final meta-analysis (Fig. 1).

3.2. Methodological quality

Methodological quality based on the PEDro scale revealed an average study score of 5.8 (Table 2). Three out of 5 included randomized trials included concealment of randomized allocation. All included studies included subjects that were comparable at baseline and outlined specific inclusion criteria for enrollment. Blinding of subjects or therapists could not be confirmed in any of the included studies. Only 1 study reported blinding of the outcome assessors. Four of the 5 studies included an adequate follow-up. Intention to treat analysis was carried out in 4 of the 5 included trials. All studies reported between-group comparisons and point estimates with variability measures for at least 1 key outcome were reported in 2 studies. Based on the PEDro scoring, 4 of the 5 included studies were considered high quality and 1 was considered fair quality based on the fulfillment of a random allocation, concealed assignment, blinding of outcome assessors, adequate follow-up, intention to treat analysis, between-group comparisons, and point estimates and variability.

3.3. Patients

In total, 652 patients were represented across the 5 studies (329 controls and 323 interventions) and 5 countries (Australia, China, Canada, Turkey, and Brazil). They represented patients with cardiac disease awaiting or undergoing mainly coronary artery bypass graft (CABG) surgery, with only 1 study including a fraction undergoing valve replacement surgery, Bentall's procedure, or a combination procedure.[14] Patients represented largely males in their early 60s, which is consistent with the predominant demographics of heart disease patients undergoing similar procedures in the general population.[15] While there are many scoring systems to classify patient acuity in the ICU, the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score is among the more common. The scale ranges from 0 to 71, with score aimed at predicting risk of hospital mortality. In this trial cohort, only 1 study provided an APACHE II score of admitted patients. In this study, the mean score was 17.2 for controls and 16.3 for patients in the intervention group. The range coincides with scores reported for vascular surgery patients admitted to the ICU and is associated with a 22% mortality rate.[16] For the 4 trials which did not report APACHE II scores, 2 provided ejection fraction (EF) at admission, which was taken in this review as a surrogate of risk of mortality at admission. Normal EFs range between 55% and 70% and abnormal scores have been correlated with increased in-hospital mortality.[17,18] EFs reported ranged between <40 and 62%, and, while <40% falls below the "normal" RF rate, this value was used as a threshold for inclusion and did not represent a true average.[19] Two trials provided no assessment of stability or mortality risk upon admission; however, Patman et al excluded patients with post-operative systolic blood pressure <100 or >180 mm Hg, mean arterial pressure <60 or >110 mm Hg, arrhythmias, or subcostal catheter blood loss >100 mL/hour to control for cardiovascular stability. Overall, no statistically significant differences were reported between control and intervention groups at baseline in either of the included trials. Patient demographics are listed in Table 3.

3.4. Interventions

Details of the therapies received are outlined in Table 4. Three studies initiated early mobilization therapy post-operatively, 1 trial initiated intervention pre-operatively, and 1 study reported peri-operative intervention. The pre-operative intervention was administered twice per week for 8 weeks prior to surgery. While the protocol was not detailed, the intervention was supervised, individualized, and multi-dimensional – with an adherence rate of 87.5%.[19] In the peri-operative intervention trial, the experimental groups received twice daily (30-minutes sessions) supervised inspiratory muscle training 5 days prior to and 5 days after surgical procedure in addition to usual care (daily, post-operative progressive mobilization and active exercises of the upper and lower limbs and chest physiotherapy).[20] In one post-operative intervention trial, experimental treatment began during the intubation phase and while physiotherapy was not standardized, techniques included positioning, manual hyperinflation, endotracheal suctioning, thoracic expansion exercises, and upper limb exercises.[14] In that study, post-extubation care included incentive spirometry and continued (non-standardized) physiotherapy management for all subjects. In another post-surgical intervention trial, early mobilization therapy was initiated on post-operative day 1 until discharge. Experimental treatment in this study included daily supervised progressive exercises ranging from Range of Motion active-assistive movements to stair climbing.[21] Usual care in that study included daily supervised deep-breathing exercises beginning on post-operative day 1. In the last included trial, post-operative mobilization
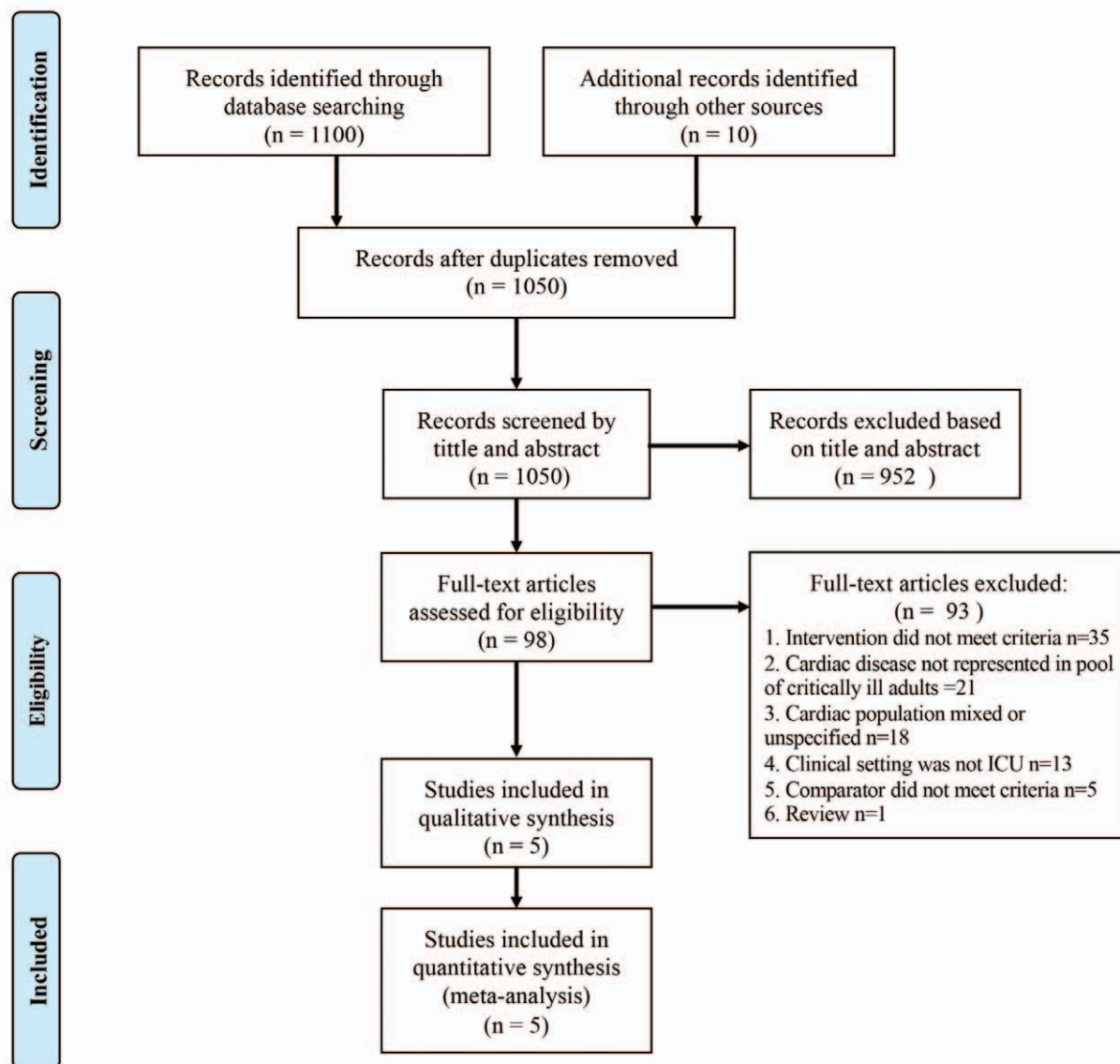
Figure 1. Flowchart for the identification of studies used in the systematic review and meta-analysis of early mobilization interventions in patients undergoing cardiac surgery.

therapy was supervised twice daily. While precise post-operative intervention start date was not specified, intervention recordings were available for at least 19 sessions. The intervention in this study consisted of a 6-step sequence (including supination, sitting up exercises, standing and walking alongside the bed) that was performed progressively, until the patient signaled tiredness or other termination criteria were met. While intervention was personalized to each patient, completion rates for each step and session were available. During the first intervention session, 100% of participants completed step 1 but only 7.5% completed step 2 and 0% completed the subsequent steps. By the 19th

intervention session, 100% of participants were able to complete all 6 intervention steps.[22]

3.5. Comparator treatments

The control group in the pre-operative intervention trial included patients followed by their primary care physicians, cardiologists, or surgeons during the surgery waiting period only (usual care). Usual care (administered to all groups) also included educational intervention at baseline and 1 week prior to surgery, at least 1 nurse/physician phone call during the waiting period, and

Table 2

Quality assessment based on PEDro scale of clinical trials included in the meta-analysis.

	Arthur et al 2000		Patman et al 2001		Mendes et al 2010		Savci et al 2011		Dong et al 2016	
	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
Eligibility criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Randomized allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Concealed allocation	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No
Comparable at baseline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinded subjects	No	No	No	No	No	No	No	No	No	No
Blinded therapists	No	No	No	No	No	No	No	No	No	No
Blinded assessors	Yes	Yes	No	No	No	No	No	No	No	No
Adequate follow-up	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Intention to treat analysis	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Between-group comparisons	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Point estimates and variability	No	No	Yes	Yes	Yes	Yes	No	No	No	No
Total score	6/10	6/10	6/10	6/10	6/10	6/10	6/10	6/10	5/10	5/10

invitation to join cardiac rehabilitation programs post-operatively.[19] Usual care in the peri-operative intervention trial (administered to all groups) consisted of once daily progressive mobilization and active exercises of the upper and lower limbs, as well as chest physiotherapy commencing on the first post-operative day until the fifth post-operative day.[20] One post-operative intervention trial was placed specifically during the intubation phase. In this study, the control group was restricted from any physiotherapy or respiratory therapy until the post-extubation, wherein all patients (usual care) included non-standardized physiotherapy management and incentive spirometry.[14] In the post-operative intervention study by Mendes et al, usual care included no prescribed or supervised inpatient early mobilization, though verbal encouragement for early mobilization was provided. Usual care in this study did included daily supervised deep breathing and coughing exercises beginning from post-operative day 1 for both groups.[21] In the final post-operative intervention study, patients in the control group received the identical 6-step rehabilitation program; however, the intervention was not supervised by clinical staff and was prescribed only after patients had left the ICU.[22]

3.6. Effect on interventions: hospital length of stay

All of the 5 included trials reported hospital length of stay for control and experimental groups. The assessment of hospital length of stay represented 308 patients randomized to the experimental condition and 306 randomized controls. Three studies demonstrated a beneficial effect of early physiotherapy (pooled mean difference −1.63; 95% CI: −3.96 to 0.71, Fig. 2a); however, the overall effect was not significant ($P = .17$). Of the 3 studies reporting a beneficial effect of intervention, the Dong et al study demonstrated a more dramatic effect (7 times greater than the nearest study). For this reason, a sensitivity analysis was

Table 3

Demographic characteristics of patients included in meta-analysis.

Study	Group	Sample size	Age, mean SD	Sex (%) Male	APACHE II, mean SD, or median IQR	Ejection fraction at admission	Admission diagnosis	n (%)
Arthur et al 2000	Control	123	63.8 ± 7.8	82.9	NR	>0.40	Awaiting a first CABG whose surgery dates were at least 10 wk away	246 (100)
	Intervention	123	61.8 ± 8.4	87.8	NR	>0.40		
Patman et al 2001	Control	109	63.9 ± 14.4	77 (70.6)	NR	NR	Coronary artery surgery	139 (64)
	Intervention	101	62.8 ± 12.2	81 (80.2)	NR	NR	valve replacement	47 (21.7)
							Bentall's	3 (1.4)
							combination procedure	21 (9.7)
Mendes et al 2010	Control	23	58 ± 9	87	NR	NR	CAD and clinical indicaton for CABG	47 (100)
	Intervention	24	60 ± 8	66	NR	NR		
Savci et al 2011	Control	21	57.48 ± 11.48	90.4	NR	58 ± 10.4	CAD and scheduled CABG	43 (100)
	Intervention	22	62.82 ± 8.69	86.4	NR	62 ± 9.6		
Dong et al 2016	Control	53	60.2 ± 15.1	22(42)	17.2 ± 4.3	NR	Diagnosed with disease in the left anterior descending artery, circumflex artery, or right coronary artery. Undergoing CAGB	106 (100)
	Intervention	53	62.6 ± 12.8	20(38)	16.3 ± 4.2	NR		

CAD = coronary artery disease, CABG = coronary artery bypass graft.

Table 4

Description of intervention and control groups of included studies.

Study	Design	Clinical setting	Intervention		Usual care (control)
			Pre-operative	**Pre-operative**	**Peri-operative (all groups)**
Arthur et al 2000	Two-group randomized, controlled trial	Hamilton Health Sciences Corporation surgical center, Hamilton, Ontario, Canada	Individualized, prescribed exercise training[*] twice per week in a supervised environment; education and reinforcement; and monthly nurse-initiated telephone calls to answer questions and provide reassurance. Mean adherence was 14 exercise classes over 8.3 wk.	Those assigned to usual care were followed by their primary care physicians, cardiologists, or surgeons.	All patients received the educational interventions (one-on-one and on videotape) at baseline and 1 wk before surgery. All patients received at least 1 home telephone call from a nurse clinician. After surgery, patients in both the treatment and control groups were given the opportunity to join the existing cardiac rehabilitation program.
			Post-operative (intubation)	**Post-operative (post-intubation)**	
Patman et al 2001	Randomized, controlled trial	Royal Perth Hospital, Perth, Australia	Included positioning, manual hyperinflation, endotracheal suctioning, thoracic expansion exercises, and upper limb exercises. Type of physiotherapy was not standardized or controlled. The mean number of physiotherapy interventions provided to subjects of the treatment group was 1.84.	Received no physiotherapy interventions during the intubation period. Once subjects were extubated there were no specific differences in physiotherapy management between those in either group.	
			Post-operative	**Post-operative**	
Mendes et al 2010	Randomized, controlled trial	Irmandade Santa Casa Misericordia Hospital, Araraquara, SP, Brazil	Once-daily supervised (>30 min) post-operative exercise protocol of early mobilization from PO1 until discharge. Protocol consisted of progressive exercises, ROM active-assistive movements to climbing flights of stairs (~2–4 METs). Mean intervention duration not specified.	Usual care with respiratory exercises was routinely prescribed after CABG, no exercise protocol was systematically applied to these patients. Received only verbal encouragement for early mobilization.	
			Peri-operative	**Post-operative**	
Savci et al 2011	Randomized, controlled trial	Ankara, Turkey	Usual care physiotherapy and additionally trained daily, 2 times per day, for 10 d (5 d in pre-operative period, 5 d in post-operative period). Each session consisted of 30+ minutes of inspiratory muscle training and physiotherapy under the supervision of a physical therapist.	Patients were mobilized as early as possible (post-operatively) by the physiotherapist. The patients were instructed to sit out of bed and stand up on the first post-operative day, walk 45 m in the corridor on the second day, walk freely (approximately 150–300 m) on the third and the fourth days, and climb one flight of stairs on the fifth post-operative days. Chest physiotherapy consisted of breathing exercises and coughing techniques.	
			Post-operative	**Post-discharge**	
Dong et al 2016	Randomized, controlled trial	Affiliated Hospital of Qingdao University, China	Education on rehabilitation after CABG was given to all the patients before surgery. Rehabilitation therapy consisted of 6 steps (65+ duration in total) including head up, transferring from supination to sitting, sitting on the edge of the bed, sitting in a chair, transfer-ring from sitting to standing, and walking along the bed. Intervention was supervised and performed twice daily for 10 d. 100% participation for all 19 sessions.	Education on rehabilitation after CABG was given to all the patients before surgery. Received the rehabilitation therapy with the help of family after leaving the ICU.	

CABG = coronary artery bypass graft, PO = post operative day, ROM = range of motion.
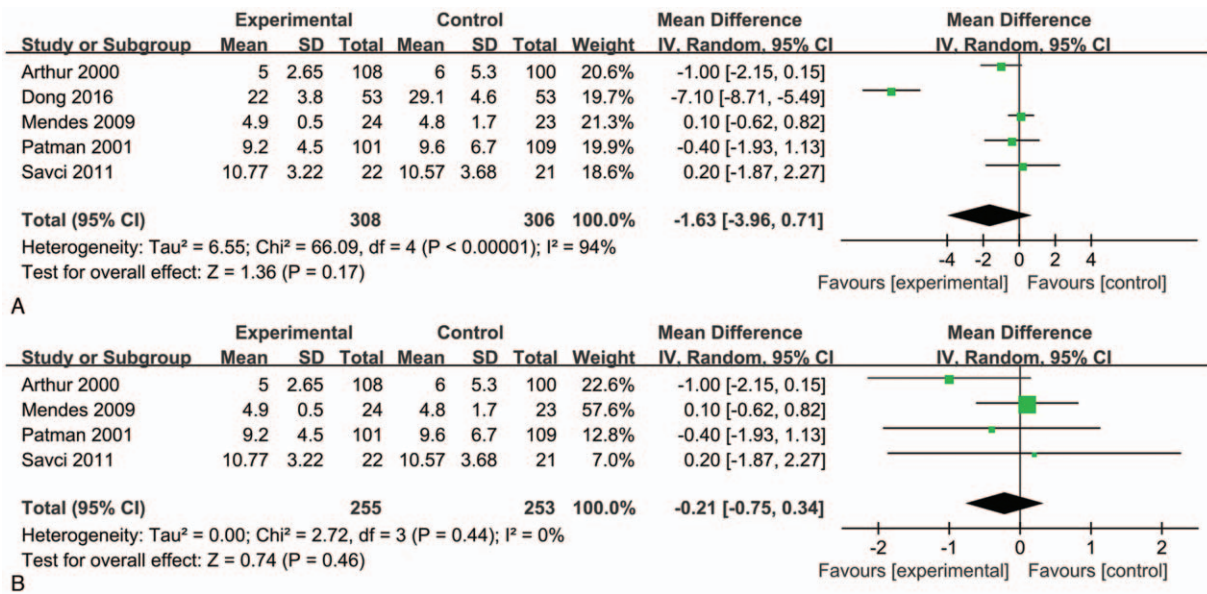
[*] Protocol not specified.

Figure 2. a. Forest plot for length of hospital stay of 5 trials. b. Forest plot of length of hospital stay of 4 trials.

performed excluding Dong et al. In the sensitivity analysis the pooled mean difference was −0.21; 95% CI: −0.75 to 0.34 (Fig. 2b) and the overall effect remained non-significant (P=.46).

3.7. Effect on interventions: ICU length of stay

All of the 5 included trials reported ICU length of stay for control and experimental groups. The assessment of hospital length of stay represented 308 patients randomized to the experimental condition and 306 randomized controls. Three studies demon-

strated a beneficial effect of early physiotherapy (pooled mean difference −0.98; 95% CI: −2.01 to 0.04, Fig. 3a); however, the overall effect was not significant (P=.06). Of the 3 studies reporting a beneficial effect of intervention, the Dong et al study once again demonstrated a severely amplified effect (66 times greater than the nearest study). For this reason, a second analysis was performed excluding Dong et al. In the secondary analysis the pooled mean difference was 0.09; 95% CI: −0.12 to 0.29 (Fig. 3b), actually favoring the control condition; however, the overall effect remained non-significant (P=.41).
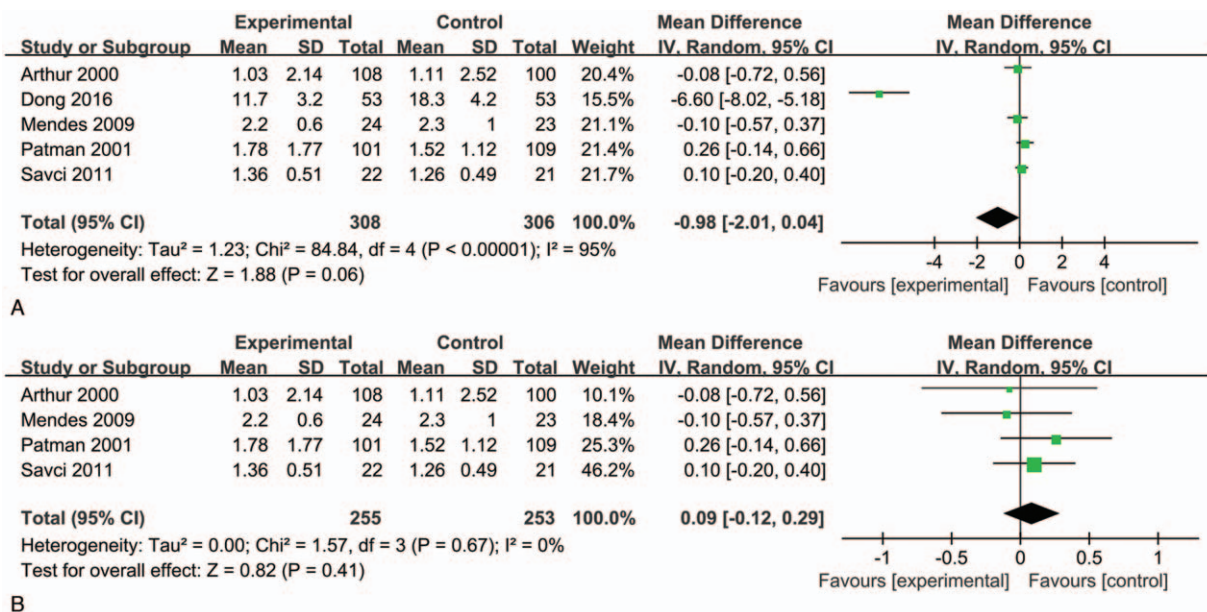

Figure 3. a. Forest plot of length of ICU stay of 5 trials. b. Forest plot of length of ICU stay of 4 trials.

3.8. Qualitative outcomes

The limited number of studies precludes some more commonly reported outcomes and restricts our evaluation to a qualitative nature. Savci et al reported functional changes evaluated by 6 minute walk test (6MWT), specifically changes in meters walked before and after intervention.[20] Arthur et al reported functional outcomes through the evaluation of the Medical Outcomes Study Short Form 36 (SF-36) physical summary score.[19] Additionally, the resting heart rate was assessed as physiological outcome by Mendes et al.[21]

3.9. Adverse events

Only 2 studies reported the adverse effects outcome, which was defined as hospital mortality (reported as percentage of study participants). Dong et al[22] reported a 2% decrease in-hospital mortality and Mendes et al[21] reported a 4.2% decrease in-hospital mortality (specifically due to surgical death), though neither of these decreases were not statistically significant.

4. Discussion

4.1. Key findings

Prolonged hospitalization of patients with cardiac disease increases can put patients at increased risk of developing ICU-acquired weakness and in-hospital mortality. Moreover, shortening the length of hospitalization, specifically, can decrease risk of post-operative complications and reduce medical costs. Thus, various early mobilization interventions have been tested in the ICU in the hopes of improving patient outcomes, though a consensus on the effect of such therapies in critically ill patients remains convoluted by a host of population and methodological-level variation. In this systematic review and meta-analysis, early mobilization therapy was evaluated specifically in cardiac patients undergoing non-emergency procedures in a critical care unit. Individually, 3 of 5 randomized trials demonstrated that intervention favored experimentally treated patients compared to controls. In 1 study in particular, the benefits of ICU intervention were dramatically beneficial relative to the other included studies. However, there was no significant reduction in hospital or ICU length of stay overall. In order to verify the influence of low quality studies on the meta-analysis findings, sensitivity analyses were performed for hospital length of stay and ICU length of stay. The study reported by Dong et al[22] was defined as a low quality according to the PEDro scale (2 reviewers gave a score of 5/10). Therefore, sensitivity analyses required performing the meta-analysis twice: the first time including all studies and a second time excluding the Dong et al study.[22] Overall results and conclusions were not affected by the decisions made during the review of literature process. Thus, the results of the review can be regarded with a high degree of certainty.

4.2. Relationship to other studies

Several studies have systematically evaluated the effect of early mobilization across critically ill patients. For example, a meta-analysis of early mobilization in pneumonia patients in the ICU found a reduction of mean length of stay (hospitalization) by 1.1 days though this study did not exclusively evaluate randomized controlled trials.[23] Moreover, in a recent study of monitored daily ambulation in patients undergoing major surgery, higher step counts on post-operative day 1 were associated with reduced probability of prolonged hospital length of stay.[24] On the other hand, a randomized controlled trial of critically ill patients found no change in ICU or hospital LOS after bedside cycling intervention. Similarly, a study of 104 mechanically ventilated patients found that early exercise and progressive mobilization found no changes in hospital/ICU LOS[25] and a recent review of early mobilization in critically ill patients similarly concluded that while intervention improved functional status, muscle strength, mechanical ventilation, and quality of life, it did not reduce length of stay or ICU-AW.[26]

Some evidence of the effectiveness of early mobilization intervention is available in cardiac populations; however, the majority tend to be focused on high-acuity patients such as those admitted to the ICU for myocardial infarction. In fact, a systematic review of more severe acuity respiratory/cardiac failure patients found that out of 9 studies (none were randomized controlled trials), conclusions were focused on the safety of the intervention rather than efficacy of the intervention.[27]

To the best of our knowledge, early mobilization has only been systematically reviewed in cardiac surgery patients previously by Santos et al, whose meta-analysis attempt was stifled by intervention variability.[28] This review provided crucial preliminary evaluation of the hemodynamically stable cardiac surgery population targeted in the present review and meta-analysis. Of the 9 included randomized controlled trials, Santos et al found that 3 trials reported significant reductions in hospital length of stay and 1 study in ICU length of stay. The trials included in that evaluation were different from the present study in that they included 4 trials which focused on variations of early mobilization "dose" (i.e., intensity, frequency, duration) rather than strict non-intervention or delayed intervention comparators. The advantage of focusing on a physiologically stable critical care population is that variabilities in intervention initiation are not a major factor, allowing a relatively more standardized prescription of early mobilization. Unfortunately, like Santos et al, the present review encountered lack of clarity in the total duration of intervention which was not apparent in 2 trials,[14,21] mainly due to ambiguity in patients' post-operative ability to withstand physiotherapy or discharge date. Moreover, adherence was only explicitly addressed in 3 of the 5 trials.[14,19,22] Additional limitations included that precise mobilization protocols (including session duration and exercise details) were not available for all included trials and that, though best efforts were taken to streamline the control groups, the fact is that usual care largely includes at least some degree of physiotherapy management or encouragement for independent mobilization which has not been quantified or accounted for in the body of literature.

This meta-analysis included interventions initiated up to 8 weeks pre-operatively and as late as post-operative day 1. While mean duration/frequencies could not be derived for all studies, mobilization sessions ranged between 1.84 and 20 sessions. Of the 2 studies which did specify frequency and duration of intervention (both totaling ~20 sessions total), the mean estimated total intervention time was slightly over 600 minutes.[20,22] One advantage of the stringent inclusion/exclusion criteria of this review was that though physiotherapy management or early mobilization was not expressly prohibited, no patients assigned to the control group received supervised or prescribed mobilization intervention during the intervention period, reducing the likelihood of comparator group dilution of mean differences.

4.3. Clinical implications of results

Estimated cost savings associated with early mobilization in the ICU are inherently dependent on presumed reductions in hospital length of stay. Therefore, resource and labor burdens of early mobilization implementation in the ICU may not always translate to cost savings across all ICU populations, as the results of this study suggest. Additionally, while deemed predominantly safe, early mobilization in cardiac surgery patients has been linked to some adverse events, including significant hemodynamic alterations (including blood lactate and central venous saturation) which should be carefully monitored in the ICU.[29] Admittedly, major barriers to safe implementation of early mobilization in the ICU have been reported by physical therapists as insufficient staffing and adequate training.[30] Combined with the findings from a study of 246 cardiac surgery patients undergoing low (once daily) and high-frequency (twice daily) post-operative exercise rehabilitation, which found no differences in the mean hospitalization length of the 2 groups (average 7 day stay),[31] the case for post-surgical cardiac patients may be such that the effects of frequent or high intensity early mobilization protocols may not offset resource constraints or safety concerns. It should be noted however that much evidence has continued to point to short-term benefits such as functional improvements and reductions in all-cause mortality in cardiac patients.[32] At this time, non-standardized protocols for early mobilization, individualized nature of intervention initiation and duration, as well as combined evaluation of diverse critical care populations make it difficult to interpret and extrapolate findings from larger studies. This systematic review and meta-analysis focused on a subset of patients with similar acuity and undergoing very similar surgical conditions as a first step toward eliminating some of the aforementioned confounders. Similarly, broad and common clinical outcomes were selected for meta-analysis, though length of stays may reflect variations in post-surgical complications, functionality, and a wealth of outcomes not covered herein.

5. Conclusions

We found that hospitalization length (ICU and overall) was not significantly impacted by early mobilization therapy. Future studies of this patient population are required to determine additional patient outcomes such as functional capacity, quality of life, long-term survival, etc. Additionally, hospitals should consider means to balance the safety and adequacy of early mobilization intervention with the uniformity required for large-scale evaluation.

Author contributions

BC, GX, and WL designed the study. BC, XY, and WL drafted the protocol and manuscript. DD, XX, XZ, and DL performed the searches and screened the potential studies, extracted the data, assessed the risk of bias, and finished the data synthesis. YL arbitrated any disagreements during the review. All review authors critically reviewed, revised, and approved the subsequent and final version of the manuscript.

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References

[1] Gosselink R, et al. Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. Intensive Care Med 2008;34:1188–99.

[2] Stevens RD, et al. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med 2007;33:1876–91.

[3] Jolley SE, Bunnell AE, Hough CL. ICU-acquired weakness. Chest 2016;150:1129–40.

[4] Cameron S, et al. Early mobilization in the critical care unit: a review of adult and pediatric literature. J Crit Care 2015;30:664–72.

[5] Connolly B, et al. Physical rehabilitation interventions for adult patients with critical illness across the continuum of recovery: an overview of systematic reviews protocol. Syst Rev 2015;4:130.

[6] Castro-Avila AC, et al. Effect of early rehabilitation during intensive care unit stay on functional status: systematic review and meta-analysis. PLoS One 2015;10:e0130722.

[7] Tipping CJ, et al. The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. Intensive Care Med 2017;43:171–83.

[8] Reid JC, et al. Physical rehabilitation interventions in the intensive care unit: a scoping review of 117 studies. J Intensive Care 2018;6:80.

[9] Maher CG, et al. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther 2003;83:713–21.

[10] Macedo LG, et al. There was evidence of convergent and construct validity of physiotherapy evidence database quality scale for physiotherapy trials. J Clin Epidemiol 2010;63:920–5.

[11] Moseley AM, et al. Agreement between the Cochrane risk of bias tool and Physiotherapy Evidence Database (PEDro) scale: a meta-epidemiological study of randomized controlled trials of physical therapy interventions. PLoS One 2019;14:e0222770.

[12] Yamato TP, et al. The PEDro scale had acceptably high convergent validity, construct validity, and interrater reliability in evaluating methodological quality of pharmaceutical trials. J Clin Epidemiol 2017;86:176–81.

[13] Higgins JP, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[14] Patman S, Sanderson D, Blackmore M. Physiotherapy following cardiac surgery: is it necessary during the intubation period? Aust J Physiother 2001;47:7–16.

[15] Lloyd-Jones D, et al. Executive summary: heart disease and stroke statistics – 2010 update: a report from the American Heart Association. Circulation 2010;121:948–54.

[16] Koperna T, Semmler D, Marian F. Risk stratification in emergency surgical patients: is the APACHE II score a reliable marker of physiological impairment? Arch Surg 2001;136:55–9.

[17] Langer NB, et al. Influence of left ventricular ejection fraction on morbidity and mortality after aortic root replacement. J Thorac Cardiovasc Surg 2019;158:984–91.e1.

[18] Paonessa JR, et al. Hyperdynamic left ventricular ejection fraction in the intensive care unit. Crit Care 2015;19:288.

[19] Arthur HM, et al. Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. Ann Intern Med 2000;133:253–62.

[20] Savci S, et al. Short-term effects of inspiratory muscle training in coronary artery bypass graft surgery: a randomized controlled trial. Scand Cardiovasc J 2011;45:286–93.

[21] Mendes RG, et al. Short-term supervised inpatient physiotherapy exercise protocol improves cardiac autonomic function after coronary artery bypass graft surgery – a randomised controlled trial. Disabil Rehabil 2010;32:1320–7.

[22] Dong Z, et al. Early rehabilitation therapy is beneficial for patients with prolonged mechanical ventilation after coronary artery bypass surgery. Int Heart J 2016;57:241–6.

[23] Larsen T, et al. Effect of early mobility as a physiotherapy treatment for pneumonia: a systematic review and meta-analysis. Physiother Can 2019;71:82–9.

[24] Daskivich TJ, et al. Association of wearable activity monitors with assessment of daily ambulation and length of stay among patients undergoing major surgery. JAMA Netw Open 2019;2: e187673.

[25] Schweickert WD, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373:1874–82.

[26] Arias-Fernandez P, et al. Rehabilitation and early mobilization in the critical patient: systematic review. J Phys Ther Sci 2018;30:1193–201.

[27] Polastri M, et al. Physiotherapy for patients on awake extracorporeal membrane oxygenation: a systematic review. Physiother Res Int 2016;21:203–9.

[28] Ramos Dos Santos PM, et al. Effects of early mobilisation in patients after cardiac surgery: a systematic review. Physiotherapy 2017;103:1–2.

[29] Cassina T, et al. Hemodynamic challenge to early mobilization after cardiac surgery: a pilot study. Ann Card Anaesth 2016;19:425–32.

[30] Malone D, et al. Physical therapist practice in the intensive care unit: results of a national survey. Phys Ther 2015;95:1335–44.

[31] van der Peijl ID, et al. Exercise therapy after coronary artery bypass graft surgery: a randomized comparison of a high and low frequency exercise therapy program. Ann Thorac Surg 2004;77:1535–41.

[32] Cortes OL, et al. Early mobilisation for patients following acute myocardiac infarction: a systematic review and meta-analysis of experimental studies. Int J Nurs Stud 2009;46:1496–504.